ON THE ROLE AND NATURE OF RETROACTIVE INTERFERENCE IN ANTEROGRADE AMNESIA

MICHAELA T. DEWAR

BSc (Hons) University of Aberdeen

Thesis submitted in fulfillment of the requirements for the degree of PhD
The University of Edinburgh

Edinburgh
2007

DECLARATION

I declare that this thesis was composed by myself and that the work contained therein is my own, except where explicitly stated otherwise in the text.

The work within this thesis has not been submitted for any other degree or professional qualification.

Michaela T. Dewar

2007

In loving memory of my late grandfather and hero
Albrecht Mütschele, a victim of severe memory loss

CONTENTS

ACKNOWLEDGEMENTS

First and foremost I wish to thank my first supervisor Sergio Della Sala for his wonderful, enthusiastic and excellent supervision and encouragement as well as for all the wonderful opportunities he has given me throughout the last three years. I have gained a wealth of knowledge and experience from Sergio, who has been there for me at all times, whether he was in Edinburgh or on the other side of the world. I could not have asked for a better and nicer first supervisor, and indeed believe that he must be the world's best first supervisor: So, thank you so much Sergio!

Moreover, I would like to thank my second supervisor Sharon Abrahams for her great and wonderful support and encouragement during the last two years. Thanks, Sharon! I could not have asked for a better second supervisor.

A further big thanks goes to Nelson Cowan, my external supervisor across the Atlantic, for all his wonderful support and encouragement in the last three years, as well as for a very fruitful and fun week in his native Columbia, Missouri. I thank his wife, Jean, too, for making me so very welcome.

I would also like to thank Peter Wright for looking after me in the first few months of my PhD before Sergio joined the department.

I am indebted also to Adam Zeman whom I joined at his regular memory clinic during my second PhD year. I thank him greatly for the superb training I received at the memory clinic, for discussing my research with me and for all his help with the recruitment of my research patients.

Furthermore I would like to thank Jon Stone, Adam's successor, for allowing me to continue to sit in and participate in the memory clinic and for helping with recruitment of patients.

I am further very grateful to Nicoletta Beschin, for recruiting and testing patients with me in Italy and for looking after me so kindly during my research visit. Moreover, I would like to thank Yuriem Garcia, my Cuban collaborator, all the researchers at the Cuban Neuroscience Centre, and last but not least my Cuban host family for making my research semester in Havana such a very memorable one.

I further thank my own family, especially my two grannies who have encouraged me all the way and my parents who have both supported and encouraged me from the start, and who looked after me in such a loving way during my PhD write up. Thank you so much, Mama and Dad!

I thank all my friends and my office mate Marian for keeping me a happy girl during the last few years and for dragging me out when I needed some vital PhD distraction. I would like to thank Tristram Rees in particular.

I thank the members of HCN (University of Edinburgh) for their fruitful comments and feedback regarding my PhD research and for their encouragement during the last years. Moreover, I am indebted to the University of Edinburgh for funding the last two years of my PhD and the European Commission for sponsoring my research fellowship in Cuba.

A very very big thank you also goes to all the patients and control participants who kindly volunteered to participate in my PhD research, sometimes for long durations. I would not have been able to conduct this research without their support.

Last but not least, I would like to thank my dad for introducing a very young curious Micha to the wonderful world of science, for explaining science to me so beautifully (to the present day!) and more latterly for discussing my own scientific research with me.

Abstract

Recent research has elucidated significantly improved delayed recall in patients with severe anterograde amnesia following an *unfilled* as opposed to a *filled* retention interval. Such findings are of great interest as they suggest that some anterograde amnesiacs are able to retain material for much longer than usual when *Retroactive Interference* is kept *minimal*. The research thus provides a novel cognitive hypothesis for the severe forgetting in anterograde amnesia, namely a greatly *heightened susceptibility* to *Retroactive Interference*.

The aim of this thesis was to further examine such phenomenon and hypothesis. More specifically the main aim was to (a) investigate which cognitive conditions are required for a *benefit* of minimal Retroactive Interference to emerge in anterograde amnesiacs; and thus how specific their susceptibility to Retroactive Interference is, and (b) which cognitive processes underlie the *benefit* of minimal Retroactive Interference in such patients. A secondary aim was to review and further explore Müller and Pilzecker's (1900) original research and theory of Retroactive Interference in forgetting in healthy people, to investigate the effects of Retroactive Interference on age related memory decline as well as to examine potential neural correlates of the benefit of minimal Retroactive Interference. Various samples of anterograde amnesia patients (Focal injury and MCI) and healthy participants were tested by means of a range of experimental manipulations in order to explore these questions. The research elucidated that *any material or distraction* ('diversion Retroactive Interference') had to be removed during the delay interval for anterograde amnesiacs to show improved delayed recall. Moreover the results of this thesis strongly suggest that minimal Retroactive Interference allows for improved *Long Term Memory* formation in at least some anterograde amnesia patients. These two main findings were also made for the healthy participants, albeit to a greatly reduced extent.

In conclusion, the present research provides further and novel detailed evidence for a 'diversion' Retroactive Interference hypothesis of forgetting in pathological and normal forgetting alike.

Chapter 1: General Introduction

1.1 Introduction – Anterograde Amnesia

It is relatively straightforward to identify the presence of *anterograde amnesia* in a patient presenting with a *severe difficulty* or even *inability* to explicitly *remember events* and *information* experienced only moments before.

Neuropsychologically speaking, such patients perform very poorly on tests assessing *delayed* recall of verbal information, such as prose or word lists, and delayed recall of non verbal material such as a previously copied figure.

In contrast to the severe memory deficits following a delay interval, patients with anterograde amnesia invariably show normal *immediate* memory for the aforementioned types of material. Hence, performance at immediate verbal recall, including digit span, as well as non-verbal recall including visual and visuospatial span, is usually in the normal range in such patients.

Thus, a clear *dichotomy* is usually present between tests of *immediate* and *delayed* recall in a typical patient with anterograde amnesia.

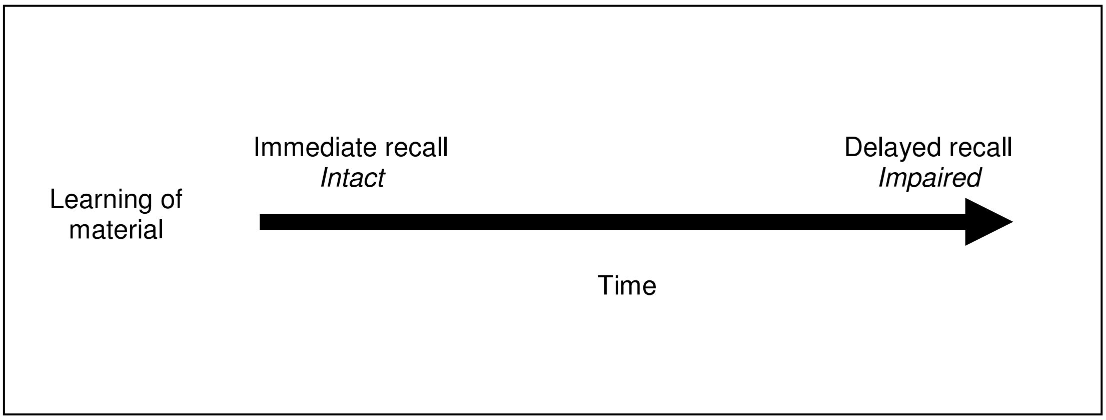


Figure 1.1. Memory in a patient with anterograde amnesia: Newly learned material is typically recalled normally immediately after learning. However, delayed recall is very poor, often non-existent.

Moreover, the majority of patients presenting with anterograde amnesia also show some *temporally graded retrograde amnesia* (Ribot, 1892); that is amnesia for the most recent months or years preceding the event causing the amnesia. However, the more remote retrograde memory is usually spared (this is illustrated in Figure 1.2 below). The patients' other cognitive functioning and ability are also usually in the normal range (Wilson, 1987).

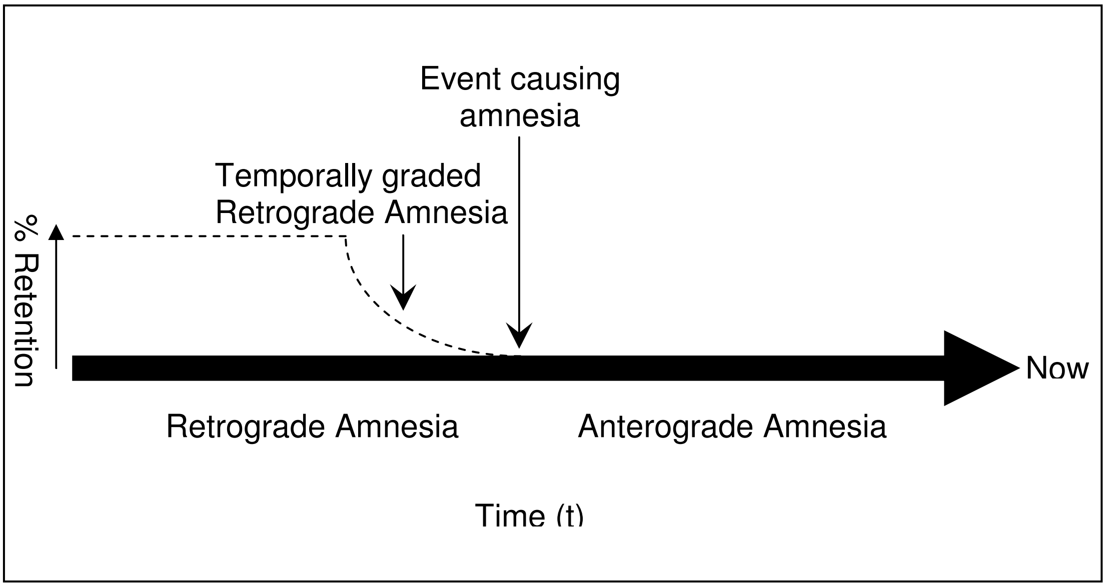


Figure 1.2. Anterograde amnesia depicts amnesia for all events and information experienced *following* the event causing the amnesia. Retrograde amnesia on the other hand depicts amnesia for all events and information experienced *prior* to the event causing the amnesia. The majority of patients with anterograde amnesia also show some retrograde amnesia, however, this is usually temporally graded in that the remote premorbid memories are better than the more recent ones.

1.2 <u>Cognitive hypotheses for anterograde amnesia</u>

In striking contrast to the somewhat straightforward identification of anterograde amnesia itself, identification of the *faulty cognitive process(es)* underlying such memory deficit has proven to be rather more challenging. Indeed, while it is generally agreed that there exists a large discrepancy between immediate and delayed recall in patients with anterograde amnesia, and thus that the deficit is one of Long Term Memory (LTM) as opposed to Short Term Memory (STM), the precise locus and nature of such LTM deficit has not been established to date. A number of differing LTM hypotheses have been put forward to offer (potential) cognitive explanations for the presence of anterograde amnesia (see for example Kopelman, 2002; Wilson, 1987). The list of theories is wide-ranging (see Kopelman, 2002, for a thorough review) but can be broadly categorized into hypotheses relating to (a) LTM encoding, (b) LTM storage and (c) LTM retrieval, the three main postulated cognitive stages of the LTM process (Kopelman, 2002; Wilson, 1987) (see Figure 1.3).

Encoding → Storage → Retrieval

Figure 1.3. The three main postulated cognitive stages of LTM

1.2.1 Faulty Encoding

A somewhat dated theory (see Kopelman, 2000 for a review) posits that the prime deficit in anterograde amnesia is the product of faulty *encoding*, i.e. a fault in the registration stage, during which an initial *representation* of the incoming information is formed for further LTM processing (Mayes et al., 1997). While some research has suggested that such may be the case for patients with Korsakoff's Syndrome, who show diencephalic lesions (c.f. Huppert and Piercy, 1977; Huppert and Piercy, 1978; Mayes et al., 1997; Wetzel and Squire, 1980), there is very little evidence for such notion in patients with other underlying causes of anterograde amnesia (c.f. Huppert and Piercy, 1979). Huppert and Piercy (1979) for example found that patients with Korsakoffs's syndrome showed normal rates of forgetting when the duration of exposure time of to-be-retained pictures was increased from that of neurologically intact controls (4 or 8 seconds for Korsakoffs's syndrome and 1 second for controls). However, while the famous anterograde amnesia patient HM, who has bilateral medial temporal damage, showed a similar degree of initial retention of to-be-retained pictures following an exposure time of 15 seconds, he showed highly accelerated forgetting over a longer delay interval, thus demonstrating that his deficit was not merely an impairment of initial acquisition of memories.

Moreover, Mayes et al. (1997) for example argue that if patients with anterograde amnesia had problems with the encoding of semantic information, they should have great difficulties in answering questions about the semantic content of such information immediately following stimuli presentation. Mayes et al. (1993) tested this prediction by presenting patients with anterograde amnesia and controls with line drawings for a duration of six seconds and subsequently asking them questions about the drawings. No group difference in performance was obtained, which was taken as evidence against an encoding hypothesis of anterograde amnesia. Moreover, Baddeley and Wilson (2002) have recently reported intact immediate prose recall in patients with anterograde amnesia due to focal injury, a finding that has been replicated by Gooding et al., (2005), Cowan et al. (2004) and Della Sala et al. (2005), and a finding that provides further evidence that material can indeed be encoded by patients with anterograde amnesia. Further evidence against an encoding deficit hypothesis of anterograde amnesia comes from the presence of some temporally graded retrograde amnesia in almost all patients with anterograde amnesia (Wilson, 1987). Indeed, if the underlying cause of anterograde amnesia were a deficit at encoding, no retrograde amnesia should be present in such patients as the encoding process would have been intact prior to the event causing the amnesia. Thus, on the whole, it appears unlikely that an encoding deficit can explain (all of) the severe memory impairment seen in patients with anterograde amnesia, in particularly those with non-diencephalic lesions. Indeed, it appears that the cognitive culprit is more likely to be found in a later LTM stage.

1.2.2 Faulty Retrieval

A further cognitive theory of anterograde amnesia posits that the deficit occurs at the *retrieval* stage as opposed to the encoding stage of declarative LTM (Warrington and Weiskrantz, 1970, Warrington and Weiskrantz, 1978). Such theory assumes that material is not only *encoded*, but also *stored* in LTM.

Initial evidence for such theory came from studies elucidating that patients with anterograde amnesia showed some retention of previously learned verbal and pictorial stimuli when given cues such as (a) the first three letters of previously presented words or (b) fragmented words or pictures (Warrington and Weiskrantz, 1968; Warrington and Weiskrantz, 1970). Further evidence for a retrieval hypothesis of anterograde amnesia has come from studies showing greatly increased performance in anterograde amnesiacs when prompts are provided (Marslen-Wilson and Teuber, 1975). Indeed, even patient HM is said to have been able to benefit from prompts in a famous faces naming test based on faces of people who became famous *after* his surgery (Marslen-Wilson and Teuber, 1975).

The improved retention following cued recall or prompts has been taken as evidence that these patients *do* have access to previously presented stimuli but cannot access these normally. According to Warrington and Weiskrantz (1970; 1974) the alleged impairment in accessing to-be-retained material is the cause of a vulnerability to proactive interference (PI). Initial evidence for their PI hypothesis came from studies that revealed apparent deficits in the inhibition of prior learned material at recall of subsequent material in patients with amnesia. Indeed, Warrington and Weiskrantz (1974) reported that while amnesic patients were able to perform as well as controls at cued recall of a 10-word list using semantic category cues (e.g. 'yellow flower','shellfish') following a filled delay interval of 60 seconds, their performance dropped greatly when they were presented with a second word list, which contained the same categories as the first list. However, such PI hypothesis for anterograde amnesia was later rejected by Warrington and Weiskrantz themselves following later research (Warrington and Weiskrantz, 1978; Weiskrantz, 1982, see also Kopelman, 2002): Both patients and controls were firstly presented with a list consisting of 15 words and tested immediately via cued recall with the first three letters of every word. Such cued recall was followed by presentation of a second list of 15 words, each of which shared the same first three letters with one of the first list words. Participants were subsequently given four cued recall trials of the second list, again by presenting the first three letters of each word. Thus the cues were the same for both list one and list two. While proactive interference did emerge in the first recall trial of list two, there was *no* difference between the controls and patients in the amount of PI. Indeed, group differences only emerged during the subsequent three recall trials of list two. If a high susceptibility to PI were one of the prime causes underlying the apparent retrieval deficit and thus anterograde amnesia, a large group difference should have emerged in *all* of the second list recall trials. As stated by Warrington and Weiskrantz (1978) themselves then, a PI hypothesis of anterograde amnesia appears somewhat unlikely.

Moreover, as argued by Squire (1982), intrusion errors such as those demonstrated by Warrington and Weiskrantz (1970; 1974) (following the first trial), have mainly been limited to patients with Korsakoff's who also show frontal pathology. Given more recent findings of PI susceptibility in patients with frontal lobe lesions and/or executive deficits (c.f. Shimamura et al., 1995; Baldo and Shimamura, 2002), it is possible that a susceptibility to PI could be a *secondary* deficit in amnesic patients presenting with lesions that include the frontal lobes.

While a specific PI retrieval hypothesis of anterograde amnesia appears unlikely, the aforementioned studies revealing improved retention following cued recall and prompts nonetheless indicate a possible retrieval deficit. However, one has to be careful when interpreting the apparent improvement in retention following cued recall and prompting. Indeed, such retrieval cues and prompts very rarely lead to normal or even near-to normal *explicit* memories in patients with anterograde amnesia (Warrington and Weiskrantz, 1970; Squire, 2004; Squire, 2006). Warrington and Weiskrantz (1968) for example presented their amnesic patients with fragmented pictures and words that gradually became more complete and asked the patients to identify such stimuli. It was found that on subsequent identification trials of the same stimuli patients required less complete versions of the stimuli for correct identification, yet had no recollection of having been exposed to the pictures on a previous occasion. Indeed Warrington and Weiskrantz (1968) state that their patients treated the memory test with fragmented pictures and words as a 'guessing game' (Warrington and Weiskrantz, 1968, p. 974). Moreover Graf et al. (1984) showed that while their sample of anterograde amnesiacs were able to benefit from presentation of the first three letters of previously presented words when instructed to 'write the first word that comes to mind' (Graf et al., 1984, p.172), they showed no improvement in retention when requested 'to think of a word from the cards with the same beginning letters' (Graf et al., 1984, p.172). Thus, even though the actual 'cues' were identical in both conditions, the patients only benefited when the task instructions were such that participants could guess, i.e. when the task was framed as a non-memory task. Given the absence of any actual memory instructions in the studies by Warrington and Weiskrantz (1968) and Warrington and Weiskrantz (1970), it is likely then that their patients were indeed able to benefit due to 'guessing'.

The apparent inability of anterograde amnesiacs to retrieve explicit memories even when aided by cues strongly indicates that the patients' severe memory deficit cannot be simply explained by a retrieval deficit (Squire, 2006). Thus, while retrieval of such information does indicate that information has reached a form of LTM storage, such findings cannot be translated into a *retrieval hypothesis of* anterograde amnesia. Indeed, what is revealed is now assumed to be *priming* (Tulving and Schacter, 1990), a form of implicit memory that is spared in this patient group (Tulving and Schacter, 1990, see Squire, 2006 and Squire, 2004 for a review).

Further apparent evidence for a retrieval hypothesis of anterograde amnesia has come from studies showing greatly increased performance in anterograde amnesiacs in recognition tasks (c.f. Hirst et al., 1986, Hirst et al. 1988, Aggleton and Saw, 1996, Baddeley and Vharga-Khadem, 2001). However, such 'spared' recognition memory is rare (Aggleton and Shaw, 1996) and appears to be limited to those anterograde amnesiacs with focal lesions of the hippocampus, diencephalon, fornix or thalamus (Aggleton and Shaw, 1996, see also Baddeley and Vharga-Khadem, 2001). However, as with cued recall, recognition paradigms do not appear to elicit explicit LTM retention. Indeed, it is assumed that such recognition underlies a sense of (implicit) familiarity with the correct material as opposed to an explicit recollection (c.f. Baddeley and Vharga-Khadem, 2001).

In fact, anecdotal evidence for such spared familiarity in anterograde amnesia dates back to 1911, when Clarapède, a French Neurologist, made an interesting observation: He noted that one of his anterograde amnesic patients, whom he had shaken hands with the previous day while secretly holding a pin in his hand, refused to shake his hand the next day, even though she had no explicit memory of the event that led to such avoidance.

It appears then from both such old anecdotal evidence as well as the more recent experimental work, that anterograde amnesiacs are most probably able to perform better when cued or prompted, not because this facilitates *retrieval* of *explicit* LTM, but because their *implicit* memory has remained *intact*.

It should be further highlighted that neurologically intact individuals *also* benefit from simpler recall measures such as recognition and prompts (Kopelman, 2002). In fact a study by Haist et al. (1992) indicated that the benefits occurring when recognition, as opposed to free recall, is utilized are proportional for amnesiacs and neurologically intact individuals. If a retrieval deficit was to blame for the severe memory impairment observed in anterograde amnesia, patients should show greatly heightened benefits from cues, prompts and recognition paradigms. However, as is revealed above, such is not the case.

Moreover, as argued by many opponents of the retrieval deficit hypothesis, if anterograde amnesia were explained by a retrieval deficit, one would predict patients with anterograde amnesia to also have retrieval difficulties for retrograde memory (c.f. Squire, 1980, Squire, 1982, Curran and Schacter, 2000; Squire 2006, Wilson, 1987). While many patients with anterograde amnesia do indeed also show some retrograde amnesia, it is normally temporally graded. Thus, unless retrieval of very remote material is somehow unaffected or spared by the hypothesized retrieval deficit, it appears very unlikely that such deficit can account for (all) of the severe amnesia that such patients present with.

When considering the above evidence for and against a retrieval deficit hypothesis of anterograde amnesia, it becomes apparent that such hypothesis is a somewhat unlikely candidate.

1.2.3 Faulty Storage

The rather weak evidence for either an encoding or retrieval deficit hypothesis of anterograde amnesia turns the search for a cognitive deficit of anterograde amnesia to a stage *in between* LTM encoding and LTM retrieval.
As stated above, such stage is generally referred to as the ‘storage’ stage of LTM within cognitive psychology. Nonetheless, very little is actually known about such a LTM stage in cognitive psychology, rendering any specific storage deficit hypothesis somewhat difficult.

Indeed, within cognitive psychology it is often simply assumed that LTM storage is faulty, without providing further detail as to how such deficit occurs. According to the ‘modal’ model of amnesia, patients with anterograde amnesia can retain information for as long as their attention is not diverted from to be-retained material, i.e. within their intact STM. Indeed, even H.M., the famous anterograde amnesiac, was able to retain material within his span capacity if he was allowed to rehearse such material (Milner, 1968; Odgen, 1996). However, once the attention of such patients is diverted, the-to-be-retained material is alleged to fall prey to the time limitations of their intact STM and thus to decay rapidly as a function of time (decay theory of forgetting). See Figure 1.4 below.

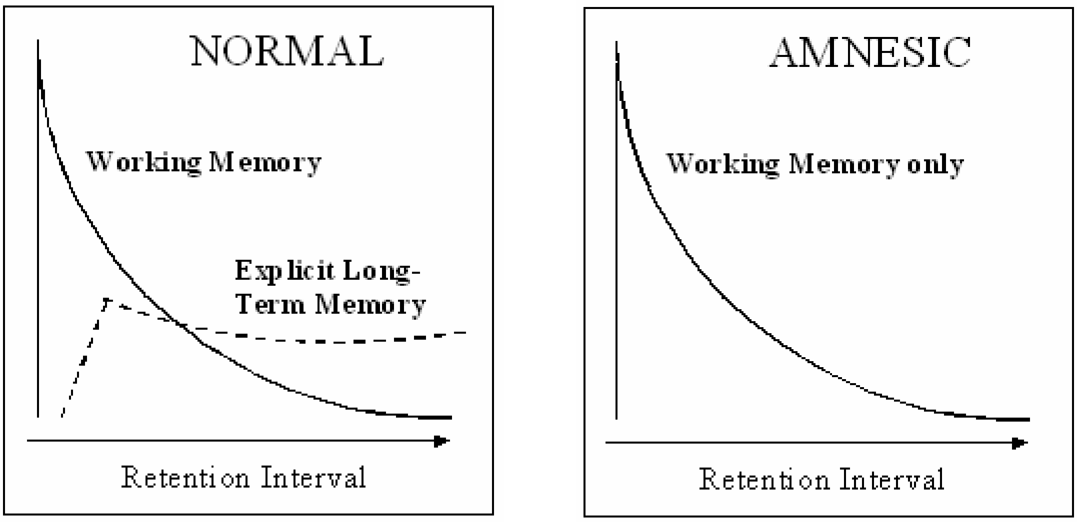


Figure 1.4. The ‘modal’ model of anterograde amnesia

However, there are at least two pitfalls regarding this somewhat simplistic 'storage' deficit hypothesis of anterograde amnesia. Firstly, it does not provide sufficient details as to the precise locus of the cognitive deficit within the LTM storage stage. Given the mix of impaired anterograde amnesia, a temporally graded retrograde amnesia and *intact* remote retrograde memory, it is important to specify precisely the locus of the hypothesized storage deficit. For example, damage to the LTM store itself cannot be assumed as anterograde amnesia and temporally graded retrograde amnesia should be coupled with a full blown retrograde amnesia, i.e. all LTM, premorbid and new should be greatly impaired. A specific deficit at LTM store input also appears unlikely as such deficit should not lead to temporally graded retrograde amnesia. Thus, it is important to further investigate the precise cognitive deficit within LTM storage in order to adequately model anterograde amnesia within a theoretical frame of reference.

A second drawback to the simple modal model of amnesia is the assumption that forgetting occurs due to decay within time limited STM once the patient's attention is diverted from the to-be-retained material (see Figure 1.4). While such could indeed be the underlying cause of the severe forgetting seen in anterograde amnesiacs, there is also the possibility that (at least some) capacity for new LTM storage exists, but that (a) new LTM decays very rapidly, i.e. accelerated forgetting (Wilson, 1987; see Kopelman, 2002 for a review), or (b) new LTM is displaced by the post-learning distraction hypothesized to disrupt STM (see Figure 1.5 below). Indeed, given the near-to-constant presence of such post-learning distraction in the day to day life of a patient with anterograde amnesia, one cannot in fact tell whether forgetting occurs due to decay or displacement from STM or LTM. Indeed, both types of hypothetical forgetting from STM or LTM would be predicted to lead to greatly impaired delayed recall. Such argument also applies to the standard neuropsychological assessment of memory in this patient population: Delayed recall in the standard tests of anterograde memory function, e.g. the Wechsler Memory Scale and the Rivermead Behavioural Memory Test, *always* follows a delay interval containing *further neuropsychological testing.*

Thus, while such tests are undoubtedly clear indicators of impaired LTM, they do not provide precise information as to whether the patient's severe forgetting over a period of time is the product of decay or displacement from STM or LTM.

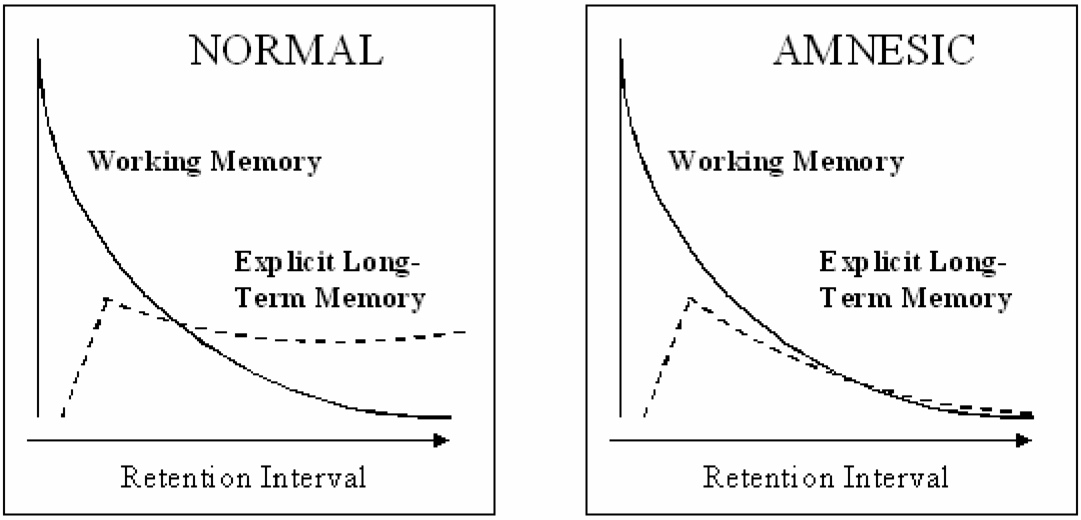


Figure 1.5. An alternative model of anterograde amnesia

While some studies do suggest that accelerated forgetting may be the prime cognitive culprit in anterograde amnesia, the evidence for such theory does not appear to be very strong (c.f. Kopelman, 2002). Moreover, it would be difficult to explain why, once within the LTM store, the new but not the old memories should be subject to such accelerated forgetting. The same argument applies to the possibility of displacement from the LTM store: Indeed, if the severe forgetting underlay displacement from the LTM store, one would expect both recent *and* premorbid LTM to fall prey to such displacement, and thus to be severely impaired. However, this is not the case.

While such arguments suggest that it is unlikely that the forgetting seen in anterograde amnesia could be the product of information loss from the LTM store per se, there is the possibility that such forgetting could nevertheless occur during LTM processing, however, not within the actual LTM store itself, but during the *formation* of LTM.

Indeed, given the aforementioned presence of a temporally graded retrograde amnesia in the vast majority of anterograde amnesia cases examined to date, it appears necessary to fractionate LTM storage further - into a *LTM store*, as well as an *intermediate LTM formation* stage, i.e. consolidation.

There are some subtle hints for a 'consolidation deficit' hypothesis in the psychology literature on anterograde amnesia (Milner, 1966; Wilson, 1987; Pallar, 1997; Kopelman, 2002), however these are only tentative and in fact rejected in the case of Wilson (1987). Indeed, Wilson (1987) rejects a consolidation deficit hypothesis of anterograde amnesia on the basis of Weiskrantz' (1978) claims that consolidation can take place as allegedly evinced by anterograde amnesiacs' intact implicit recall (see above). However, the findings of intact implicit learning and memory are not necessarily strong evidence against a *declarative* LTM consolidation deficit hypothesis of anterograde amnesia. Nonetheless, such consolidation hypothesis of anterograde amnesia has not received much attention in more recent years within the field of psychology. In fact this also applies to the very concept of consolidation itself. Indeed, while consolidation has not only been researched extensively but also integrated fully into the LTM model as well as the amnesia model within neuroscience, such cannot be largely said for the field of psychology (Wixted, 2004; Dewar et al., in press, see also Chapter 2). Such neglect of consolidation per se has obvious implications when attempting to hypothesize a potential 'cognitive' consolidation deficit of anterograde amnesia. Thus, prior to further discussing whether or not the forgetting seen in patients with anterograde amnesia underlies decay from STM or displacement from LTM consolidation, it is important to consider and understand such LTM consolidation process in more detail.

Seeing as neuroscientists and psychopharmacologists have already done a great deal of highly interesting and informative research on consolidation as well as on a consolidation hypothesis of anterograde amnesia, it makes sense to first explore such existing findings and theories.

1.3 A glance at neuroscience's 'consolidation' theory of memory and Anterograde Amnesia

First researched and described by Müller and Pilzecker in 1900 (Wixted, 2004; Dewar et al., in press, see also Chapter 2), 'consolidation' (*consolidare* = Latin for 'to make solid', from *cum* + *solidus* 'solid') has been a popular and widely researched process within neuroscience and psychopharmacology. It is defined by Dudai (2004) as *'the progressive postaquisition stabilization of long-term memory'* as well as *'the memory phase(s) during which such presumed stabilization takes place'* (Dudai, 2004, p. 52).

The first clinical evidence for consolidation comes from observations made by Ribot (1881, 1882) who reported that brain injury had a more detrimental effect on recent than remote premorbid memories (Wixted, 2004). Such finding has been replicated extensively during the last century and today is known as 'temporally graded retrograde amnesia'. One of the first explanations for such temporally graded retrograde amnesia can be gleaned from Burnham (1903):

'*The fixing of an impression depends upon a physiological process. It takes time for an impression to become so fixed that it can be reproduced after a long time interval; for it to become part of a permanent store of memory considerable time may be necessary. This we may suppose is not merely a process of making a permanent impression upon the nerve cells, but also a process of association, of organization of the new impressions with the old ones…Now suppose a shock occurs which arrests these physiological processes in the nervous tissue. What will be the result? Not only will the mind be a blank for the period of insensibility following the shock, but no impressions will be remembered which were not already at the time of the accident sufficiently well organized to make their persistence for a considerable interval possible. Hence the amnesia will be 'retroactive''*

(Burnham, 1903, pp.128-129)

He goes on to state: *'The essential characteristic of these cases of retroactive amnesia is that the memory is lost because it was never fully organized.'* (Burnham, 1903, p. 129)

With respect to the cognitive modeling of human memory, the findings of a temporally graded retrograde amnesia as well as the hypothesis put forward by Burnham (1903) strongly suggests that the formation of LTM takes time and cannot be compared to the instantaneous long term 'memorizing' of files by a computer. Thus, while a personal computer is capable of 'memorizing' documents such as this very thesis within milliseconds, our brains require time, up to many years, to process, organize and memorize the often highly complex information and episodes, which we encode.

Burnham (1903) concludes his highly interesting paper by stating: '*There must be time for nature to do her part. Without appealing to any mystical form of mental or cerebral activity it is clear that a night's sleep may be more effective in fixing a lesson in the memory than continued repetition. Hurry defeats its own end.' (Burnham, 1903, p. 131)*

As argued by Dudai (2004), Burnham's (1906) 'time' actually refers to two different kinds of consolidation, a fast kind of consolidation (as initially proposed by Müller and Pilzecker (1900), see Chapter 2) as well as a slow kind of consolidation as revealed by patients presenting with temporally graded retrograde amnesia. Evidence for such two types of consolidation has been provided via computational neural networks (c.f. Alvarez and Squire, 1994; Squire and Alvarez, 1995; McClelland et al., 1995). Dudai (2004) refers to such fast and slow kinds of consolidation as *'synaptic'* and *'systems'* consolidation respectively.

In short, *synaptic consolidation*, which has been the focus of molecular research, refers to a fast and short strengthening process, taking place in synapses and neurons immediately following encoding (Dudai and Morris, 2000, Dudai, 2004). Such consolidation is as Dudai (2004) puts it 'universal' (Dudai, 2004, p. 56) in that it has been identified in all species. Synaptic consolidation is alleged to render new memories *resistant to interference* by distraction, drugs, seizures and lesions within a matter of seconds to hours (Dudai, 2004). Moreover it is frequently associated with a physiological process taking place within the hippocampus termed Long Term Potentiation (LTP) (Bliss and Lomo (1973)) (see Morris 2003; Lynch 2004 for reviews), which is a long-lasting strengthening of the synapses (i.e. the connections) between two neurons that are simultaneously active.

Systems consolidation on the other hand refers to a much slower type of memory strengthening; a 'progressive reorganisation of memory traces throughout the brain' (Dudai and Morris, 2000, p. 149) that can last years (Dudai, 2004). Such process is assumed to take place between the Medial Temporal Lobe (MTL)/hippocampus and the neocortex, slowly rendering the memory trace dependent on LTM storage in the neocortex and independent from the hippocampus, which is hypothesised to act as a *temporary* storage of new memory traces (c.f. Squire and Alvarez, 1995). To date it is not known whether systems consolidation occurs in parallel to or as a consequence of synaptic consolidation (Dudai, 2004).

It appears that neuroscientists have not (yet) differentiated substantially between such two different kinds of consolidation when theorising about the consolidation deficit giving rise to anterograde amnesia. It appears that both kinds are assumed to be faulty to some extent. Such assumption does not come as a surprise given that anterograde amnesia very rarely occurs without at least a slight temporally graded retrograde amnesia. Interestingly however, recent research on patients with epilepsy has revealed an apparent intact anterograde memory in such patients following a delay interval of < 30 min, yet a significantly impaired anterograde memory when tested following longer delay intervals (Kapur et al., 1997; O'Connor et al., 1997; Zeman et al., 1998; Blake et al., 2000; Mayes, 2003, Manes et al., 2005). Such findings are suggestive of the aforementioned *accelerated forgetting* (c.f. Kopelman, 2000) in the cognitive neuropsychology literature on anterograde amnesia. With respect to the aforementioned two kinds of consolidation, such findings tentatively indicate that in some patients with anterograde amnesia the *synaptic* consolidation process may function while the *systems* consolidation process does not (Blake et al., 2000). Thus, anterograde amnesia could have two types of causes at the consolidation level: Firstly, it could be the product of a deficit in both synaptic and systems consolidation, secondly it could also be the product of a more focal deficit of systems consolidation only. Both would predict anterograde amnesia as well as some retrograde amnesia. Interestingly Meeter and Murre (2005), who developed the TraceLink Model, predict anterograde amnesia to arise from a lesion in a synaptic consolidation type mechanism or from a systems consolidation type lesion, the former leading to an isolated anterograde amnesia.

1.4 Introducing a consolidation hypothesis of anterograde amnesia to Psychology

The somewhat strong neuroscience evidence for (a) a consolidation stage within LTM as well as (b) a consolidation deficit hypothesis of anterograde amnesia, strongly suggests that both should also be considered in the search for a *cognitive* hypothesis of forgetting in anterograde amnesia. Indeed, in doing so the presence of anterograde amnesia coupled with a temporally graded retrograde amnesia yet intact remote retrograde memory could be easily explained within a cognitive framework. Moreover, inclusion of such consolidation stage also facilitates both appliance and testing of the aforementioned LTM RI hypotheses of anterograde amnesia. Hence, rather than positing an RI effect within the modal model's LTM store per se, an RI deficit could be posited at LTM consolidation. Such in turn would allow for the testing of a specific RI effect at consolidation, thus leaving remote premorbid memories spared, as is the case in the typical patient presenting with anterograde amnesia.

With respect to the aforementioned 'modal' model of amnesia at least two plausible specific types of forgetting can be predicted when one considers a deficit at LTM consolidation: Firstly, it may be the case that newly encoded information can be retained in STM, but cannot be consolidated as such process can no longer take place under any conditions. In such a case there would not be much deviation from the modal 'model' of amnesia (see Figure 1.6(a) below), i.e. the actual forgetting would still occur due to rapid temporal decay from time limited STM due to the patient's diversion of attention from the to-be-retained material: Hence, forgetting in such patients would occur as a consequence of interference by new material/tasks with *overt* maintenance of to-be-retained material within time limited STM.

Importantly, however, the 'attention diverting' new material and activity could also interfere with covert maintenance of to-be-retained material during consolidation. Thus, it may be the case that newly encoded information can be retained in STM and *can also* enter the consolidation stage, but that the material/activities interposed between Immediate recall and Delayed recall interferes with such consolidation (see Figure 1.6(b)).

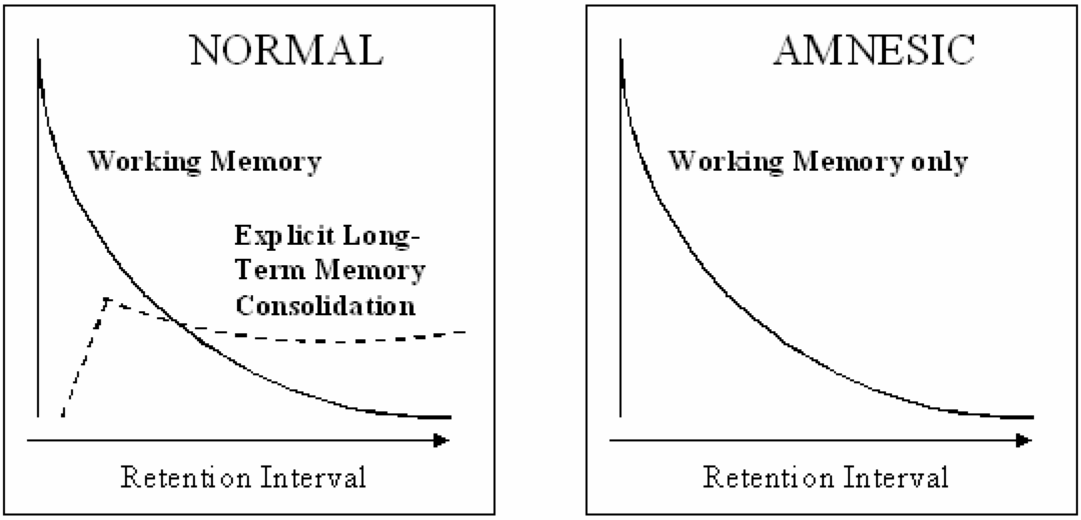


Figure 1.6(a). The 'modal' model of anterograde amnesia

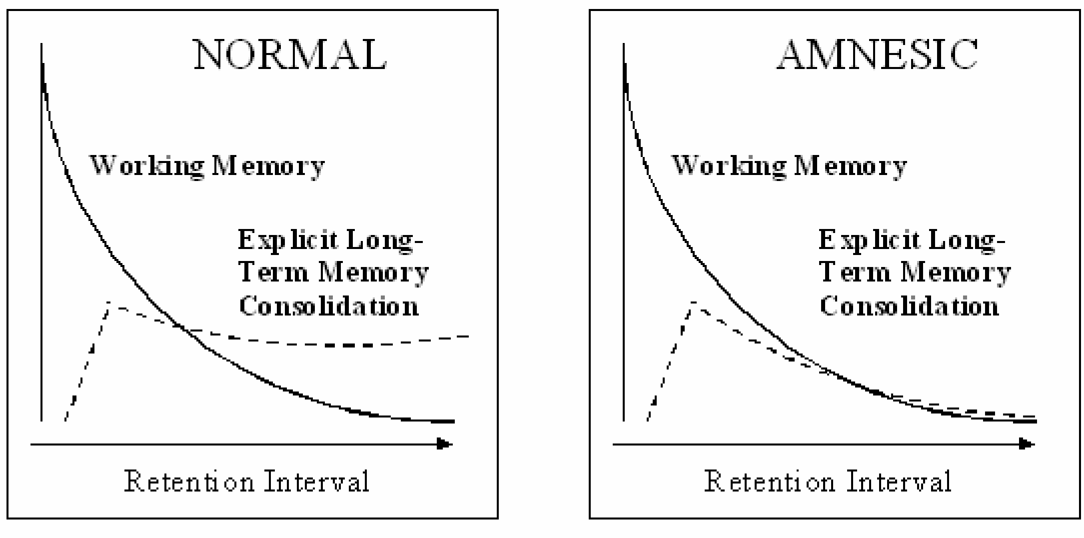


Figure 1.6(b) An alternative model of anterograde amnesia

1.5 <u>Cowan et al. (2004) and Della Sala et al. (2005): A new *cognitive* hypothesis of forgetting in anterograde amnesia: Increased susceptibility to Retroactive Interference</u>

The question of whether or not the material/activity present during the standard delay interval affects time limited STM or LTM (consolidation) in anterograde amnesia was recently examined by Cowan et al. (2004) and Della Sala et al. (2005). In the first study reported by Cowan et al. (2004) patients with anterograde amnesia due to focal lesions were verbally presented with several wordlists (containing 15 words), each of which were followed by immediate recall (see Figure 1.7). Such immediate recall was followed by a 10 minute delay interval during which the critical manipulation took place:

Either the patients were engaged in *further neuropsychological testing* (as would be the case in a standard neuropsychological assessment of anterograde amnesia, see above) *('Retroactive Interference' Condition*), or they were asked to *rest alone in the darkened, quite room* (*'Minimal Retroactive Interference Condition',* a condition that shall henceforth be referred to as 'Minimal RI' or

'MinRI' for short in this thesis). It should be underlined that the study was a repeated measures design. Thus, each patient underwent both Delay Conditions. Following the 10 minute delay interval, the patients and controls were requested to recall as many words as they could from the previously presented word list. Participants were never pre-warned about the delayed recall.

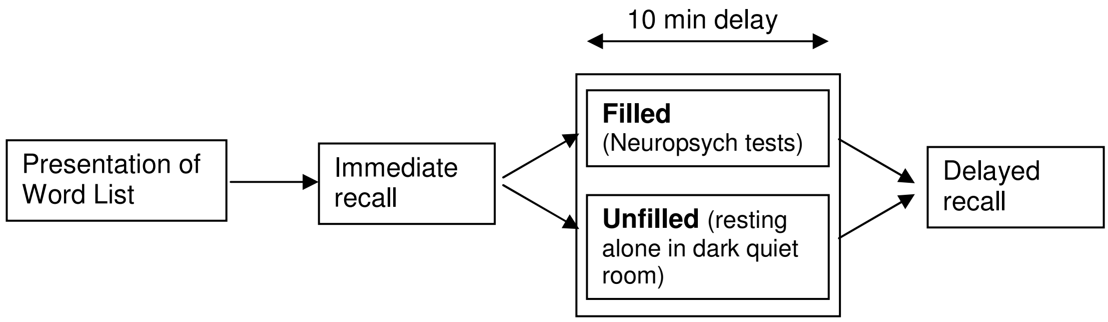


Figure 1.7. Procedure of the first study by Cowan et al. (2004)

Given the equal delay interval duration in the two conditions, the prediction was that there should be *no* differences in delayed recall following the two conditions if the *passage of time* were *the only or at least prime cause* of forgetting, i.e. if forgetting simply occurred due to *decay* from time *limited STM*. If on the other hand, forgetting occurred due to displacement from LTM (consolidation) following interpolation of new material, it was hypothesized that the removal of such material may have beneficial effects at delayed recall in patients with anterograde amnesia.

The study revealed that indeed four out of the six patients tested benefited significantly from the unfilled interval. More precisely, mean proportion retention for these four patients went from 14% following the filled delay interval to 49% following the unfilled interval (age and education matched controls went from a retention of 46% in the filled to a retention of 74% respectively). Such substantial improvement in the four patients following the 10 minute unfilled interval indicates that at least some patients with anterograde amnesiac can in fact retain information for much longer than previously assumed when *Retroactive Interference* is kept *minimal*.

In order to examine whether or not such findings would also be elucidated following a longer delay, Cowan et al. (2004) replicated the experiment on the same participants but using a one hour delay interval. Moreover, they used prose passages as opposed to word lists as to-be-retained material (see Figure 1.8).

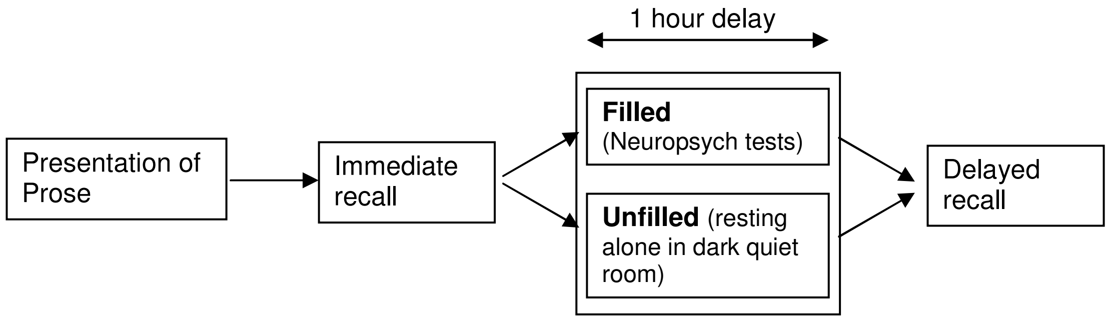


Figure 1.8. Procedure of the second study by Cowan et al. (2004)

As in the first experiment four of the six (the same as previously) patients benefited significantly from the unfilled one hour delay interval, the group mean percentage retention being 7% following the filled interval and 79% following the unfilled delay interval (the control group mean percentage retention was 79% and 89% following the filled and unfilled delays respectively). The patient mean of 79% retention following a *one hour* unfilled delay interval was indeed highly remarkable given the usual forgetting of to-be-retained material within seconds or minutes in such population.

With respect to the main prediction of the study then, the findings provide strong evidence that the severe amnesia in the four patients who benefited from the unfilled interval, cannot simply be explained by temporal decay, i.e. by the ‘modal’ model of amnesia. Nonetheless, it was not clear why two patients did not show any benefit following the unfilled delay interval. Cowan et al. (2004) speculate whether or not the particular lesion site of these two patients (hippocampal) may have led to the observed differences in performance between these two patients and the remaining four.

Nevertheless, the findings of a significant benefit of an unfilled delay interval in four patients strongly suggest that such patients may present with a greatly *heightened susceptibility to Retroactive Interference*.

Further strong evidence for such a cognitive hypothesis of anterograde amnesia comes from a third study by the same authors (Della Sala et al., 2005). In order to minimize individual differences in lesion loci, Della Sala et al. (2005) replicated the second of the two Cowan et al. (2004) studies (i.e. the one with a one hour delay interval and prose passages) with a sample of patients diagnosed with amnestic Mild Cognitive Impairment (aMCI) (Petersen et al., 1999).
As in the study by Cowan et al. (2004) a significant improvement was found in the patient group in percentage retention following the unfilled than the filled delay interval: The patient mean percentage correct retention following the filled interval was 20%, while that following the unfilled interval was 55% (age and education matched controls showed a group mean percentage retention of 80% following the filled and 89% following the unfilled condition).

It should be noted that it is highly unlikely that the remarkable benefit of Minimal RI can be explained by explicit STM rehearsal. Firstly the initial delayed recall came as surprise, meaning that participants had little if no incentive to consciously rehearse the material for up to an hour, yet did not lead to poorer recall than later trials. Furthermore, the to-be-retained information in Della Sala et al.'s (2005) study and Cowan et al.'s (2004) second experiment was a prose passage consisting of a much larger quantity of information than can be rehearsed within the traditional time limited working memory. If rehearsal were the only cognitive process underlying the benefit, patients should have only recalled as much information as can be actively rehearsed in working memory. Finally, two patients were observed to be sleeping (identified by loud snoring, a state in which conscious rehearsal would be carried out with some difficulty) during some hour-long retention intervals with Minimal RI, yet benefited from Minimal RI as much as on other trials, and as much as other patients did.

Overall, the three studies thus strongly suggest that the passage of time per se cannot explain (all of) the severe memory difficulties experienced by patients presenting with anterograde amnesia. Indeed, if the passage of time, were the only factor, no differences in retention should have been observed following the two Delay Conditions as time itself was constant. It should further be noted that these patients were typically unable to remember anything after 30 seconds and hence that the improvement observed in these experiments by minimizing Retroactive Interference was indeed remarkable.

Contrary to previously postulated theories then, the reported findings demonstrate that at least some anterograde amnesia patients do not inevitably forget to-be-retained information within seconds but that they can retain it for at least one hour under conditions of Minimal RI. It thus appears that a high susceptibility to RI is likely to be at least one of the underlying cognitive deficits of anterograde amnesia.

Overall then, the studies by Cowan et al., (2004) and Della Sala et al., (2005) provide strong evidence for a *new* cognitive theory of forgetting in anterograde amnesia: namely, a

'***Retroactive Interference hypothesis of forgetting in anterograde amnesia***'.

1.6 Aims of the thesis

The aim of the present thesis was to further examine such new hypothesis and to test its predictions in more detail.

More specifically the main aim was to (a) investigate which cognitive conditions are required for a *benefit* of Minimal RI to emerge in anterograde amnesiacs; and thus how specific their susceptibility to Retroactive Interference is (Chapter 4) and (b) which cognitive processes underlie the *benefit* of Minimal RI in such patients (Chapters 5 and 6).

A further aim was to review Müller and Pilzecker's (1900) pioneer RI research (Chapter 2), to investigate the role and nature of Retroactive Interference in forgetting in healthy people (Chapters 3 and 7), to investigate the effects of Retroactive Interference on age related memory decline (Chapter 7) as well as to examine potential neural correlates of the benefit of Minimal RI (Chapter 8).

Chapter 2: A trip down memory lane – The origins of the Retroactive Interference theory of forgetting[1]

Müller GE. and Pilzecker A. Experimentelle Beiträge zur Lehre vom Gedächtniss. Zeitschrift für Psychologie. Ergänzungsband 1: 1–300, 1900.

2.1 Introduction

Ebbinghaus' seminal work suggested that forgetting occurred as a function of time. However, it raised a number of fundamental theoretical issues that still have not been resolved in the literature. Müller and Pilzecker (1900), who coined both memory 'consolidation' as well as 'retroactive interference' addressed some of these issues in a remarkable manner. However, their observations have been mostly ignored in recent years and are not as yet available in English. The following chapter will thus provide a review and discussion of their early pioneer work on and theory of retroactive interference.

2.2 Setting the scene

2.2.1 Müller and Pilzecker

The seminal work on RI by Georg Elias Müller (1850 – 1934) (Figure 2.1) and his student Alfons Pilzecker took place during 1892 and 1900 at the Psychology Institute of the University of Göttingen (Germany).

[1] This chapter is part of an article in press in a Cortex special section on the history of memory: Dewar, M.T., Cowan, N. & Della Sala, S. (in press). Forgetting due to retroactive interference: A fusion of Müller and Pilzecker's (1900) early insights into forgetting and recent research on anterograde amnesia. *Cortex*. www.cortex-online.org
A published conference abstract on the chapter material as well as additional material also exists: Dewar, M.T., Della Sala, S. & Cowan, N. (2006). Forgetting due to retroactive interference: A fuse of Müller and Pilzecker's (1900) early insights into forgetting and recent research on anterograde amnesia. Abstract of paper presented at the 16th annual meeting of Theoretical & Experimental Neuropsychology (TENNET 16). Symposium IV – History of memory. *Brain and Cognition*, *60*, 333-334.

Figure 2.1. Photo of Georg Elias Müller

The Institute, which in fact was founded by Müller himself in1887, still bears his name today (‘Georg-Elias-Müller Institut für Psychologie’). It was the second Psychology Institute to be established worldwide and it is said that this institute quickly turned into a Mecca of experimental psychology renowned for its significant research in the areas of psychophysics, sensory psychology and memory function. One of the research projects conducted within the Institute’s memory function area was an extensive study on associative memory by Müller and Pilzecker. It was this research that led to their ‘discovery’ of RI.

The aim of Müller and Pilzecker’s (1900) research was to present participants with nonsense syllable pairs to investigate (a) the amount of learning repetition required for the participants to be able to recall the second (unemphasised) syllable when cued with the first (emphasised) syllable and (b) the percentage of correctly recalled syllables as well as time required for recall when repetitions were kept constant.

2.2.2 Müller and Pilzecker's (1900) methods

2.2.2.1 Materials

In order to investigate this in a controlled fashion Müller developed an ingenious apparatus for presentation and recall of to be remembered stimuli (see Figure 2.2):

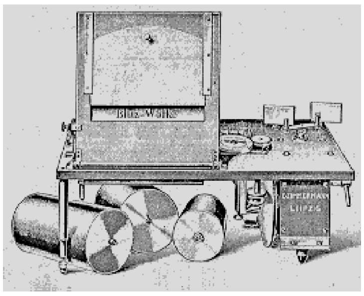


Figure 2.2. The memory drum utilised by Müller

A prism drum (Figure 2.3) consisting of 12 sides, which could be turned around via a horizontal axis served as the main display unit of the stimuli. Numerous nonsense syllable pair lists were printed on paper, each pair being displayed in a vertical fashion leaving sufficient space between pairs for each pair to take over one of the 12 sides of the prism (the maximum syllable pairs was 12).

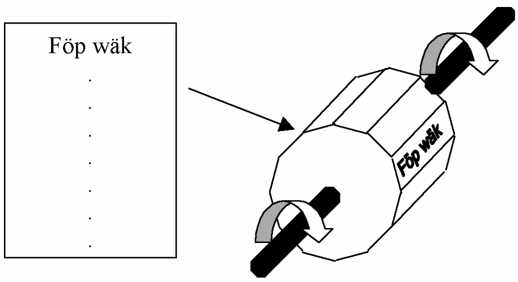


Figure 2.3. The prism drum

The prism drum was situated behind a wall, which contained a small slot that matched the size of one prism drum side (see Figure 2.4).

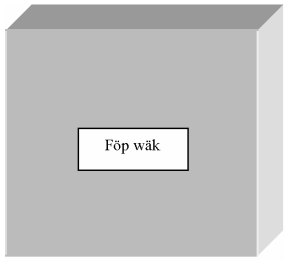


Figure 2.4. The prism drum behind the wall

2.2.2.2 Procedure

The participant sat in front of this wall so that he/she could only ever see one prism side and therefore only one syllable pair. During the learning phase the prism drum was rotated at a constant speed so that presentation time for all syllable pairs was constant across lists. Participants were asked to emphasize the odd (the first) syllable of every pair during the reading of the presented material. Drum rotation time as well as repetitions of main lists differed across experiments. During recall a shield, which was held in position via an electromagnet, covered the peek hole prior to presentation of the first syllable (see Figure 2.5). The experimenter then opened an electrical circuit, which resulted in the shield falling down and thereby enabling the participant to see the first stimuli (the emphasized syllable). The falling of the shield furthermore led to the opening of a contact resulting in a disruption of a current, which flowed through a Hipp's chronoscope. This in turn activated a clock, which measured recall time. The clock circuit was closed again as soon as the participant made a verbalization, which was picked up by a funnel during the first experiments. Later experiments were undertaken with a lip key (on which the participant purses his/her lips, then breaking a circuit by speaking). Having provided a response the participant lifted the shield up to its starting position (the circuit required for the electromagnet to hold the shield in position was closed by the experimenter just prior to the participant lifting the shield). The participant then turned the prism drum so that the next syllable would be positioned behind the shield. A special lock enabled the participant to only turn the drum by a certain degree (i.e. by one side). Participants were actively engaged in helping out in this way so that any thoughts about the syllables could be minimized.

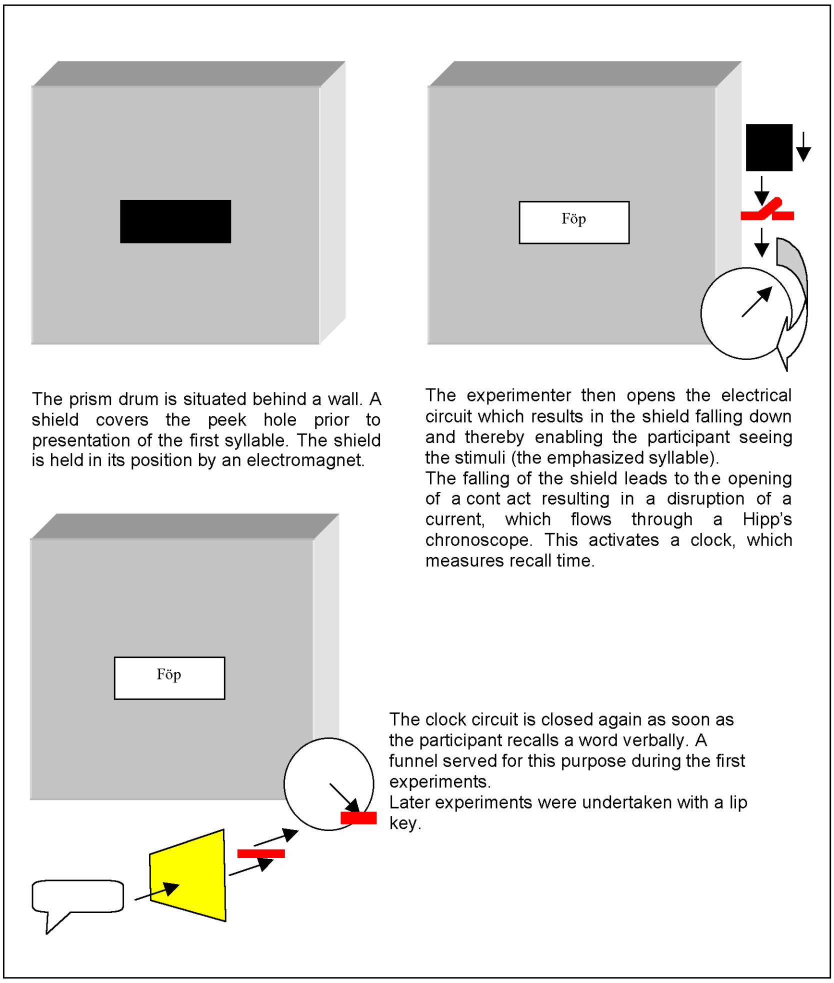


Figure 2.5. Recall procedure

2.3 Müller and Pilzecker's (1900) experiments on associative memory – summary of topics in their book

Müller and Pilzecker's (1900) book contains various chapters, all of which focus on varying aspects of associative memory. (Chapter 1 – experimental procedure, Chapter 2 – The relationship between reproduction time and association strength and other factors, Chapter 3 – The perseveration tendencies of stimuli, Chapter 4 – The interaction and competition of simultaneous reproduction tendencies, Chapter 5 – Retroactive Inhibition, Chapter 6 – The initial reproduction tendency, Chapter 7 – About the various types of reproduction tendencies, which are triggered by trochaic reading of syllable lists. Analysis of false memory, Chapter 8 – Various). The chapters that are most interesting and relevant to the present discussion are chapter 3 (The perseveration tendencies of stimuli) and 5 (Retroactive Inhibition).

2.4 Reproductive tendencies and the birth of consolidation theory

Chapter 3 concerns the reproductive tendencies of recently learned verbal material and introduces the concept of memory consolidation to psychological research. The authors state: '*Every stimulus owns a perseveration tendency following its appearance in consciousness. This is a rapidly declining tendency to reappear in consciousness'*[2] (Müller and Pilzecker, 1900, p. 58). The authors provide the following everyday life example: If a scientist spends hours attending to an interesting phenomenon, such a phenomenon may suddenly reappear as a visual image if the scientist is not doing any effortful task afterwards. Müller and Pilzecker (1900) explain that the origin of their term 'perseveration' tendency comes from the field of Neurology and Psychiatry where this term is used to describe '*disruptions in the formal procedure of a cerebral action, which manifests itself as a tendency to repeat an already undertaken function (either centrifugal or centripetal direction) straight after or shortly after and also at unsuitable locations/moments*' (p.60).

The authors cite Von Söldner (1894) who argued that perserveration could also appear in healthy people but to a lesser degree. Müller and Pilzecker (1900) therefore decided to adopt this term for their finding. They provide further everyday examples such as the all too familiar phenomenon of the earworm or the tendency for prior images and thoughts to enter consciousness against one's will and in a random manner if (a) one has the ability to concentrate mentally on such images and thoughts in the first instance and (b) 'consciousness' is not being used for any other subsequent effortful task. In light of the current discussion on RI, point b in

[2] Original German text*: 'Jede Vorstellung besitzt nach ihrem Auftreten im Bewußtsein eine Perseverationstendenz, d.h. eine im Allgemeinen schnell abklingende Tendenz, frei ins Bewußtsein zu steigen'.*

particular is of special interest as the authors tentatively mention the requirement of an 'empty mind' for stimuli to reappear in consciousness.

The authors predict from the above reported everyday experiences that the perseveration tendencies of a given stimulus list can be weakened by strongly diverting one's attention to another stimulus. And indeed various experiments such as their Experiment 6 elucidated a dampening of the reappearance of the to-be-learned syllables during a delay interval by the reading of a subsequent syllable list. However, the authors raise the critical issue that this *effortful task* may not actually lead to poorer results due to a decline in the frequency of reappearances of the presented stimuli in consciousness per se but that this task may actually hinder *consolidation* of the previous association. Hence Müller and Pilzecker (1900) state that the perseveration tendency may in fact be useful for consolidating the associations between the syllables. This is followed by their revelation that such early speculations were indeed true. They state: '*We will see in Chapter 5 that the above hinted hypothesis is applicable and that indeed the associations between syllables of a list do not only depend on the number of readings and the behaviour of the participant during reading, but also on the degree to which the participant is engaged mentally following the end of reading*.' (p.68).

Despite revealing such confirmation of earlier speculations in this chapter it is important to note that the authors do not appear to have planned research into RI but were seemingly motivated to do so after obtaining some interesting data in one of their earlier experiments (Experiment 29) on reproduction tendencies.

2.5 Retroactive Interference (RI)

2.5.1 The discovery of RI

The aim of this experiment (Experiment 29), which lasted 25 days, was to investigate whether there was a difference between the reproduction times (time taken between recognition of the presented stimuli and reproduction of the associated stimuli) between associations that were learned 24 hours or 11 minutes before recall.

The participant was firstly presented with list 1, which was followed by a 36 second unfilled interval that was followed by list 2. There were five further repetitions of this sequence, which was followed by a 10 minute delay interval. The participant was then presented with the odd syllables and asked to recall the associated even syllables. Having recalled lists 1 and 2 the participant was given a relaxation interval. This was followed by presentation of lists 3 and 4, which were separated by 6 minutes. Recall of these two lists took place 24 hours after the learning phase. No difference was found between recall of lists 1 and 2 and that for lists 3 and 4 with respect to reproduction time. However some interesting findings emerged with respect to recall percentage (see Table 2.1).

List	Percentage correct
1	58
2	58
3	61
4	39

Table 2.1. Recall percentage

Interestingly the percentage correct was identical for list 1 and 2. The authors pointed out that this was indeed intriguing because Mrs. Müller, the participant, stated that the very short time period between reading of list 1 and list 2 (36 seconds) led to the *wiping out* of list 1 by list 2. The authors speculate whether reading of list 2 did indeed impede list 1 but that the participant was fatigued by the time list 2 was read, leading to the participant performing poorly on list 2, which consequently resulted in a balance of scores. In other words there could have been a *hidden* detrimental effect of list 2 reading on list 1. The authors stated that the reading of list 4 could not have resulted in such a detrimental effect on list 3 as list 2 did on list 1 due to the relatively long interval between list 3 and 4 (six minutes). In a replication study (Experiment 30) a further participant stated that immediate reading of a second list was detrimental for the first list. However this participant showed increased recall for list 2, which was therefore in line with the participant's subjective feedback. These two studies gave rise to Müller and Pilzecker's (1900) prediction that '*the processes, which serve the production of a read syllable list also continue for a certain time after the reading of such syllables, but that they can be weakened via a different mentally effortful task during this time resulting in an inhibition (more specifically a developmental inhibition) of the read syllable lists via this mental effort'* (p. 179). They subsequently stated: ' *In the absence of any other short name we want to term this type of inhibition retroactive inhibition because it relates to a process which has already terminated externally; to the already accomplished reading of a syllable list'* (p.179).

The better performance in list 2 recall than list 1 recall in Experiment 30 provides evidence that the data in Experiment 29 did possibly result from a compensation of the RI effect by fatigue. However, the authors acknowledged that the advantage of lists 2 and 4 in Experiment 30 may have been triggered by the participant attending to the first lists with lesser degree than to the later lists. Hence they claim that critics could in fact argue that the improved performance in lists 2 and 4 were not due to their newly coined RI but simply to a rise in attention to the second lists at presentation. In order to verify the existence of RI the authors ran seven experiments (Experiments 31 – 37), which were designed to exclude the possibility of the above stated alternative hypothesis. A selection of these experiments will be described and discussed subsequently.

2.5.2 In search of evidence for the existence of RI…

2.5.2.1 Experiment 32:

'Die Rückwirkende Hemmung bei nachfolgendem Lesen einer anderen Silbenreihe'
('Retroactive Inhibition during subsequent reading of a different syllable list')

The aim of this experiment was to investigate whether an interval filled with a second syllable list would lead to lower recall than an unfilled interval. The participant in this study was presented with a list of six syllable pairs and asked to read each pair aloud (emphasizing the second syllable). This was repeated 12 times, after which there appeared an 18 second gap (required for changing the paper on the prism drum). This gap was either followed by a filled delay, in which the participant was presented with a second list of syllable pairs to learn, or an unfilled delay (in which no second syllable list was presented). After 8 minutes the participant was presented with the first syllables of each pair and asked to recall the corresponding second syllables. In the filled condition the participant was also asked to recall 3 of the second list syllables to ensure that she fully attended to this list. This experiment clearly showed that the filled delay period led to a lower recall performance than the unfilled delay period. This is illustrated in Figure 2.6.

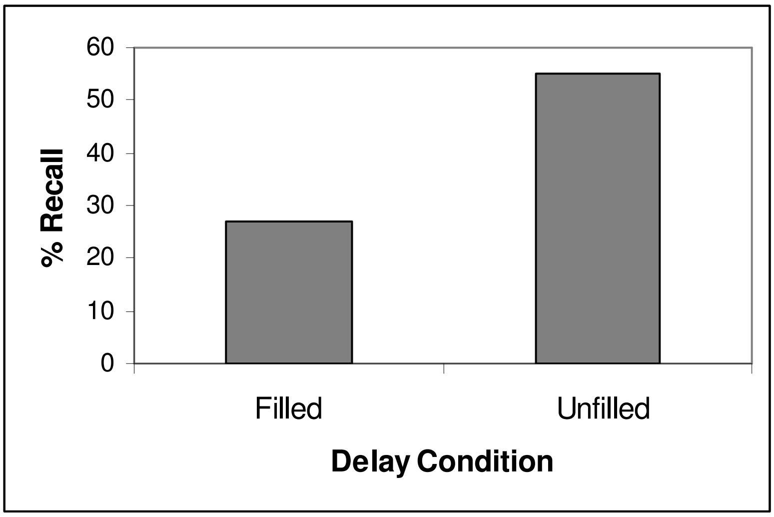


Figure 2.6. Delayed recall as a function of Delay Condition

2.5.3 Retroactive interference – material specificity or general mental effort?

Even though Müller and Pilzecker's (1900) first RI study did demonstrate that an interpolated second syllable list impeded recall of the to-be-retained list, it did not elucidate whether the detrimental effect of the interpolated list was directly related to material similarity (i.e. both lists containing nonsense syllables) or to a more general interference (i.e. any subsequent material or task).

It appears that Müller and Pilzecker (1900) may have been working under the material similarity assumption initially as they told participants that they could read a newspaper during the unfilled period in order to avoid thinking about the to-be-recalled syllable lists. They therefore cannot have thought that the reading of new material would have a detrimental effect on later recall. Nevertheless it appeared that many of the participants were skeptical about reading a newspaper during the unfilled period. Dr Behrens in Experiment 32, for example, spontaneously stated that she preferred not to see these newspapers because '*the pictures and jokes within these newspapers occupied her intensively meaning that she would forget the newly read syllables'* (p. 183). Her preferred method was to walk up and down the room while thinking her own thoughts. She also stated that none of the read syllable lists appeared in consciousness during this time. It appears that such subjective comments may have triggered a curiosity in Müller and Pilzecker (1900) to investigate whether the observed drop in recall was indeed associated with material specific interference or more general mental effort.

2.5.3.1 Experiment 35:

'Die rueckwirkende Hemmung bei nachfolgeneden Bilderversuchen'
('Retroactive interference in experiments containing subsequent pictorial stimuli')

In order to investigate this issue Müller and Pilzecker (1900) tested the same participant as for Experiment 32. The participant was asked to read the nonsense syllable pairs (8 times) and then to look at a set of 3 landscape paintings (10 seconds per picture), which had to be described to the experimenter in detail straight after. The picture task was always brought to an end after 2 minutes (i.e. 30 seconds of observing and 90 seconds of describing) in order to reduce any tiredness at later recall of the main lists.

As in the previous experiment an unfilled delay interval was also included in this study. If the 'benefit' following the unfilled delay period had been merely induced by a lack of new syllables (i.e. material specific stimuli) both Delay Conditions in Experiment 35 should have proven beneficial. However, recall for main lists, which had been followed by the secondary picture task was worse (24% correct) than recall for the main lists that had not been followed by the picture task (56% correct). This is illustrated in Figure 2.7.

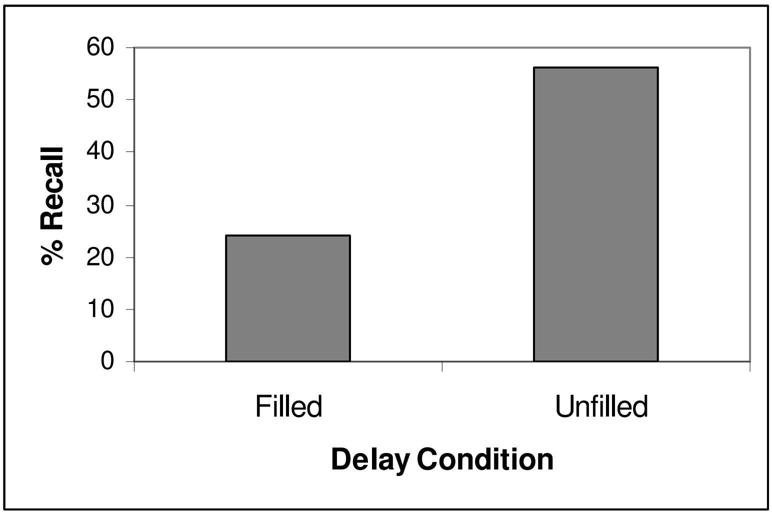


Figure 2.7. Delayed recall as a function of Delay Condition

When comparing the two experiments (Experiments 32 and 35) it can be seen that recall was almost identical after the two interpolated tasks (27% correct following syllables and 24% correct following pictures) and that the detrimental effect of the interpolated task cannot be accounted for purely by the similarity of the to be remembered stimuli and the interpolated material. Müller and Pilzecker (1900) consequently used this finding to provide quantitative evidence for their notion of RI being interference by a subsequent <u>mentally effortful</u> task (rather than material specific interference).

However as stated above, diversion RI as a theory of forgetting has been largely ignored in modern Psychology. The little that has remained of RI since Müller and Pilzecker (1900) is not greatly akin to the original definition. Indeed, the general consensus on RI in more modern times has undeniably been that this is interference of the-to-be learned material by **learning of new similar material**, see for example the Oxford Dictionary of Psychology: '*Impairment of memory for previously learnt information, or performance of a previously learnt task, caused by subsequent learning of similar information or a similar task'* (p.638). Such definition for RI can also be found in Psychology textbooks (e.g. Gleitman et al. 1999; Carlson et al. 2004; Kosslyn and Rosenberg, 2004) and recent articles published in Psychology journals (e.g. Tendolkar et al. 1997; Blank, 2002; Mottron et al. 1998).

2.5.4 RI – item similarity and/or mental effort?

The obvious question is therefore: Where did this theory come from and why has it taken the place of a well proven initial theory? An extensive article on RI by Robinson (1920) suggests that a number of researchers (De Camp; Webb; Brockbank; all cited in Robinson, 1920) began to criticise and dismiss diversion RI theory due to a failure to replicate Müller and Pilzecker (1900) findings of non-specific RI. Instead they began to argue that similarity, previously rejected by Müller and Pilzecker (1900) as an account for RI induced forgetting, was the major cause of forgetting.

Two of these researchers were McGeoch and MacDonald (1931) who studied the effect of similarity between to-be-retained material (10 adjectives) and interpolated stimuli (synonyms, antonyms, unrelated adjectives, syllables and 3 digit numbers) using a modernised version of Müller's memory drum (see Figure 2.8).

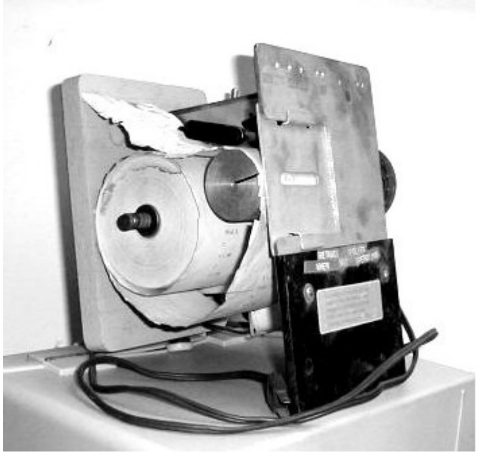


Figure 2.8. An early apparatus for studying verbal learning at the University of Missouri - Columbia, where John A. McGeoch was Chairman from 1930 to 1935. An electric motor advanced the paper roll at preset intervals so that the current trial's stimuli were visible through the slot-shaped window in the metal plate shown here on the right. McGeoch (1932) advanced the idea that forgetting cannot be attributed to the passage of time per se.

Unfortunately the authors did not employ an unfilled condition. Even though their control condition was defined as 'rest' participants in this study were asked to read 'College Humour under instruction to select and mark the three best jokes on each page' (p.582), a condition more in line with a verbal interference task than 'rest'. Nevertheless participants performed better following this interpolated task than following any of the others. Furthermore, it was found that recall following the other conditions declined with increasing similarity between to-be-recalled stimuli and interpolated stimuli in the following manner: 3 digits (38.5% - 3.85 adjectives), nonsense syllables (25.8% - 2.58 adjectives), unrelated adjectives (21.7% - 2.17 adjectives), antonyms (18.3% - 1.83 adjectives) and synonyms (12.5% - 1.25 adjectives). Further evidence for a similarity-based account of RI was later voiced by Dey (1969) who showed that recall dropped with increasing synonymity ratings between the to-be-retained adjectives and the interpolated adjectives.

However neither McGeoch and McDonald's (1931) nor Dey's (1969) study contained non-material-specific interpolated tasks. Hence while the authors provide strong evidence for interference effects by highly similar interpolated tasks, such evidence cannot be used to reject diversion RI theory. In order to do so the authors would have had to compare recall following a highly similar interpolated task and a more general interpolated task. It may of course be argued that the 'rest' interval, which did lead to higher recall than the similar tasks, was akin to diversion RI and therefore that this provides possible evidence against diversion RI and for similarity RI (i.e. RI by items similar to the to-be-retained material). In fact Robinson (1920) did include similar and general interpolated conditions and found that the similar condition led to the lowest recall while all general interpolated tasks led to higher and equal recall. Robinson's (1920) findings led Skaggs (1925), a supporter of Müller and Pilzecker's (1900) RI theory, to investigate the effect of similarity and diversion RI on delayed recall. Participants in his study were asked to memorize the position of chessmen on a chessboard and were subsequently engaged in one of four conditions: (1) memorizing a new chessman formation (similar), (2) memorizing the positions of non-chess items on the board (intermediate), (3) multiplication (dissimilar) and (4) studying post card pictures of scenery (dissimilar). This was followed by recall of the original chessman positions.

Even though individual data were not clear-cut, group averages suggest a relationship between error rate and degree of similarity of the interpolated task. Closer inspection of the data elucidates that the similar task led to the highest error rate while differences between the intermediate and dissimilar conditions were not substantial. It was further found that performance was better in a syllable recall task when the interpolated task contained reasoning problems (dissimilar) as opposed to new syllables (similar). In light of such findings one can appreciate how diversion RI may have been pushed further and further away from the spotlight. However it is important to note that none of these studies contained an unfilled delayed condition. Participants were asked to read (McGeoch and McDonald, 1931; Robinson, 1920) or talk to the experimenter (Dey, 1969) during the 'rest' interval and Skaggs' (1925) study did not contain a rest period at all. Therefore while there is no doubt that similarity effects did emerge in these studies, there is no evidence that similarity is the **only** contributing RI factor of forgetting. Hence it is possible that the more general interpolated tasks also affected recall but with no unfilled condition to compare such recall to, such hypothesis is speculative only. In order to reject diversion RI as an underlying cause of forgetting the authors would have also had to include an unfilled delay interval and shown that recall following the unfilled and 'rest' interval was ***equally*** better than that following the similar conditions.

2.6 Which processes does RI affect?

2.6.1 Müller and Pilzecker's (1900) research into RI and consolidation

Müller and Pilzecker (1900) not only investigated the nature of RI but also sought to explain **how** RI led to forgetting. Their early theories of consolidation led Müller and Pilzecker (1900) to make the prediction that 'the associations of a read syllable list are less and less affected by the reading of a subsequent syllable list the later the reading of the subsequent list occurs' (p. 184).

Experiment 34:'Die rückwirkende Hemmung ist um so stärker, je früher die nachfolgende Reihe gelesen wird'
('Retroactive Inhibition increases in strength as the proximity between main list and second list decreases')

In order to test such hypothesis Müller and Pilzecker (1900) presented a participant with a list of syllables. This was followed by one of two delay intervals and subsequent delayed recall. The crucial difference between the two delay interval conditions was the onset time of the reading of the second syllable list, which was either presented after 17 seconds (time required to change the drum) or six minutes after presentation. As predicted it was found that recall was higher following the late onset Delay Condition (after six minutes) than the immediate onset Delay Condition (49% and 28% respectively). This led Müller and Pilzecker (1900) to conclude that the first syllable list could be strengthened (i.e. consolidated) during the six minute interval, resulting in the syllable list being less susceptible to the interfering effects of the second syllable list.

Skaggs (1925) provided further evidence for such a *temporal gradient of RI* (Wixted, 2004) following a more extensive experiment, which included 4 conditions, in which a period of ‘simple equation problems’ (p.21) was interpolated at varying onset times within a five minute delay interval. The to-be-retained information in this case was a reconstruction test, in which the participant was presented with a chess board containing five chessmen, whose positions the participant had to remember during the recall period.

Skaggs’ (1925) data revealed that the group average number of errors was highest following immediate onset of the algebra task and levelled thereafter (i.e. even one minute of rest prior to RI was sufficient for the number of errors to drop largely) thus supporting Müller and Pilzecker’s (1900) notion of a detrimental effect of (diversion) RI on consolidation and their perseveration theory.

2.6.2 Opposing views – Consolidation versus the Transfer theory

Such notion was challenged by opponents of the perseveration theory such as McGeoch and Nolen (1933) and Robinson (1920) (see Wixted, 2004 for a full review) who found that the detrimental effects of RI were identical whether RI was positioned immediately after item presentation or immediately before item recall. These researchers argued that such findings supported the so-called transfer theory of retroaction. McGeoch and Nolen (1933) provided the following definition of transfer theory: ‘*The theory holds that the decrement in measurable retention which follows interpolated learning occurs because of a confusion between the original and interpolated materials, a confusion which results from the transfer of parts or aspects of one to the other*’ (p.414). The same authors also state that the theory is based on a major requirement, which is that *‘the interpolated material be learned* *before the original material has been forgotten and that it bear at least a minimum similarity to the original material'* (p.414).

However, Skaggs (1933) argued that the studies leading to such a theory were flawed in that they contained inappropriate rest intervals e.g. looking at pictures or counting beans which he believes introduces *'a complicating mental activity which is far from the state of passivity demanded by a crucial test of temporal position and the perseveration view'* (p.413). Indeed considering that the delay intervals were long (23-24 hours in McGeoch and Nolen's (1933) case) and anything but unfilled (i.e. introducing enduring RI) in most cases, it is not surprising that recall was equally bad following immediate or delayed similarity RI.

A further criticism voiced by Skaggs (1933) is the inclusion of highly similar to-be-retained and interference material (e.g. two mazes in McGeoch and Nolen's 1933 study) and the presentation of highly similar interference material immediately prior to recall of the to-be-retained stimuli. Having considered similarity based RI himself in his 1925 paper, Skaggs (1933) strongly argued that one would expect that the learning of very similar information immediately prior to recall of A would 'introduce confusion into the recall of A' (p.412). He went on to make an important point namely that 'this would not be retroactive inhibition at all but a simple case of ***reproductive inhibition***' (p.412), hence a case of inhibition at retrieval as opposed to consolidation. Indeed similar material is likely to lead to the same amount of similarity RI if placed at the very start and the very end of the delay interval for this very reason. Hence while such material is likely to interfere with consolidation and retrieval when placed immediately following presentation of the to-be-retained information, it is also likely to interfere with the retrieval of such information if placed immediately prior to recall. This in turn would overshadow at least some of the benefits of delayed RI.

Skaggs (1933) extends his above-mentioned theory of coexisting similarity and diversion RI (Skaggs, 1925) and makes the crucial proposition that these two forms of RI act at different stages in the memory process. He stated: '*there are two factors causing what is now called retroactive inhibitory effects. In one case a strong mental-neural activity cuts in an organized and on-going mental-neural process, a process of neural inertia. This is true for retroactive inhibition since a second activity interferes with a fixing process on the part of an earlier initiated activity. There is considerable (at least indirect) evidence for such fixating processes. In the other case there is a matter of the establishment of wrong associative tendencies which operate at the time of recall. This is due to the mixture of like and unlike elements in the two learning situations. Whether we wish to call the detrimental influence on later recall retroactive inhibition or plain reproductive inhibition depends entirely on whether the original learning is actually weakened as such at the time of the interpolated activity or whether it is a matter of confusion and blocking in the actual recall'* (p.413).

This statement forms a plausible answer to both above raised questions, namely that of similarity versus mental effort and that of the cognitive processes affected by RI.

These two questions will form the core part of the research to be reported in this thesis.

.

Chapter 3: Material specificity of Retroactive Interference (1) Healthy volunteers[3]

3.1 Experiment 1: A modern Müller and Pilzecker – like experiment on healthy volunteers

3.1.1 Introduction

Even though Müller and Pilzecker (1900) provided some evidence that RI encompasses interference by a subsequent mentally effortful task, they did not try to reject all possible alternative explanations or indeed be more specific when defining *mental exertion*. It is important to highlight that even though the main interpolated task in Experiment 35 involved pictures, the participant had to *verbally* describe the three pictures in the subsequent recall period. Even though such verbal description would have not been highly similar to the to-be-retained syllable pairs, it could have directly interfered with such syllables due to its verbal content (i.e. being identical in modality and verbal coding). For this reason Müller and Pilzecker's (1900) experiment cannot be used to fully reject the notion of material specific interference. In order to elucidate recall decline in the absence of material specific interference one requires an interpolated task, which is absent of any verbal content.

Furthermore both interpolated activities (Experiment 32 and 35) required the participant to learn the interpolated material (syllables or pictures) as recall followed. Hence even though one common factor of the interpolated tasks of Experiment 32 and 35 is 'mental effort' they also share an **intentional memory** factor. Even though Müller and Pilzecker's (1900) work clearly illustrates that forgetting is not simply caused by interference by highly similar material, the task of having to learn new

[3] This chapter is part of Dewar et al. (in press). *Cortex*. www.cortex-online.org
A published conference abstract on the chapter material as well as additional material also exists: Dewar, M.T., Della Sala, S. & Cowan, N. (2006). Forgetting due to retroactive interference: A fuse of Müller and Pilzecker's (1900) early insights into forgetting and recent research on anterograde amnesia. Abstract of paper presented at the 16th annual meeting of Theoretical & Experimental Neuropsychology (TENNET 16). Symposium IV – History of memory. *Brain and Cognition*, *60*, 333-334.

material in both interpolated tasks means that this factor, as opposed to (or in addition to) more general mental effort, could have been the culprit. In order to reject such a notion one requires an interpolated task that is mentally effortful yet does not require the participant to intentionally learn any new information of any sort (e.g. looking at the picture but not actively trying to remember it).

One may also question whether merely observing something without actively trying to remember it could be enough to lead to interference (e.g. initial *incidental* encoding of information). Hence another common factor evolves: both tasks contained new material (irrespective of the fact that this material had to be remembered). In order to investigate whether mental effort **per se** can really be the culprit one requires a condition in which the participant has to do an effortful task that does not include **any** new information.

3.1.2 Aims of Experiment 1

Prompted by Müller and Pilzecker's (1900) work, the aim of this experiment was to investigate material specificity not in terms of interpolated tasks that exactly matched the to-be-retained material (i.e. word lists) but in terms of more general similarity/dissimilarity as well as mental effort.

3.1.3 Method

144 volunteers (59m/85f, mean age = 21.08 years, SD = 1.76; mean years of education = 15.82 years, SD = 1.65) took part in a between subjects study, in which presented verbal material had to be recalled following one of six Delay Conditions. Each participant was allocated to one of six groups (N = 24 per group), each of which was presented with the same to-be-retained stimuli. In contrast to Müller and Pilzecker (1900) but in line with some more modern memory research the to-be-retained stimuli on each trial comprised a list of 15 verbally presented nouns (1 per second), which were selected from the MRC Psycholinguistic Database and matched

for familiarity, imaginability, concreteness and frequency (word frequency was taken from the British National Corpus) (see Appendix A). Depending on which group the participant had been assigned to he/she then undertook one of six interpolated tasks during an eight-minute interval (identical to Müller and Pilzecker's delay period).

The experiment was set up to include one purely verbal interpolated task (group 1) in order to investigate whether interpolated verbal material would result in a different effect than non-verbal material. Participants in this verbal task were required to listen to a radio recording for the duration of the eight-minute interval and asked to attend carefully as questions would follow delayed list recall. In order to compare this condition to nonverbal 'interference', a visual analog was created (group 2). As with the verbal task the visual task consisted of real life material (visual clips of scenes around the University campus) that had to be attended to in order to be recalled subsequently after list recall. Hence both tasks contained an intentional memory factor and therefore some level of effort and differed only in modality. A further visual task was included, in which participants were asked to detect differences between pairs of visually presented pictures and to highlight these by circling them (i.e. spot the difference) (group 3). No new memories had to be formed during this visual attention task. The same applied to a mathematics task, in which participants were given short mathematical problems, and asked to solve them as fast as possible (group 4). Even though these two tasks did not contain an intentional memory factor, they both contained new meaningful material. Hence the visual attention task most certainly could not interfere due to item similarity but it could interfere due to the introduction of new general information

Moreover, if RI is characterized by material or modality specific interference or interference by new meaningful material then a task that is solely mentally effortful without containing new meaningful material should not have a detrimental effect on later recall of the lists. In order to test this, a tone detection paradigm (TDP) was utilized in which participants were required to detect piano notes of various decibels, which were embedded in brown noise (group 5). The task was mentally demanding yet did not contain any new meaningful information (cf. Reitman, 1974).

In order to make any subsequent inferences about the nature of RI, a control condition was also added (group 6). Participants in this condition were asked to merely sit in a comfortable chair and rest. They were further asked to try not to think of the presented wordlists. All groups were subsequently asked to freely recall as many of the presented words verbally. Each participant performed a total of three presentation-delay-recall trials, each of which consisted of a different wordlist. While the interpolated task remained the same across the three trials (e.g. attending to videos for those assigned to the video group), the stimuli within such task differed across trials (e.g. video 1, video 2 and video 3). The order of the three wordlists and three interpolated stimuli was counterbalanced across participants. Word list presentation, the delay interval and word list recall were all undertaken in the same laboratory and by the same experimenter to minimize any external contextual change.

3.1.4 Results and discussion

Percentage recall means were computed for every participant. Descriptive data revealed three outliers whose performance fell out-with two standard deviations from the mean; data from these participants were consequently excluded from the main analysis. A one way ANOVA revealed a significant difference in recall following the six interpolated tasks ($F(5, 140) = 5.519$, $p < 0.001$). Newman-Keuls post-hoc tests (alpha level = 0.05) revealed that this was the result of higher recall following the control condition than any of the five other conditions (i.e., all interference conditions). No differences in recall were found between these five interference conditions (see Figure 3.1).

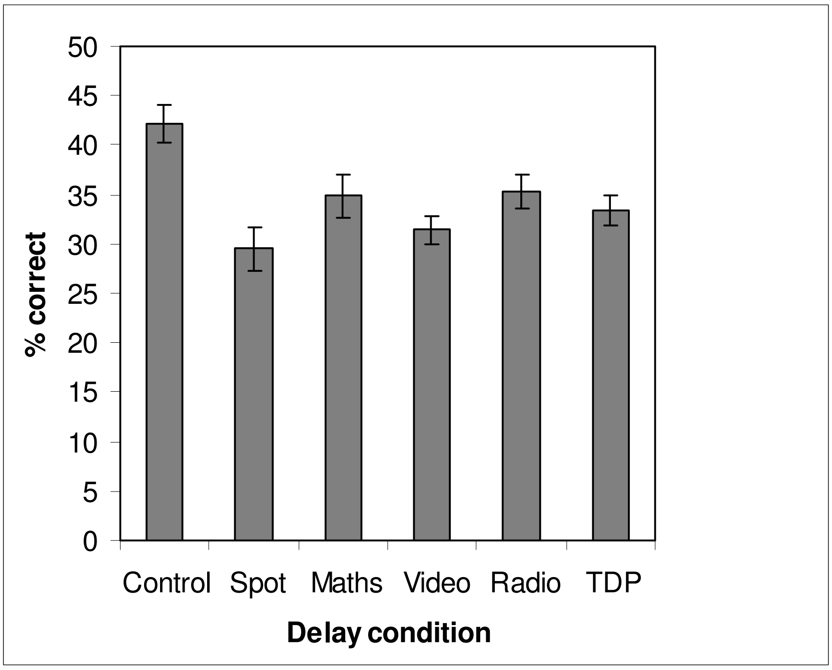


Figure 3.1. Percentage correct delayed recall as a function of RI Delay Condition. Error bars = SEM.

These data allow the following conclusions:

(a) With respect to the criticism of a verbal component embedded in Müller and Pilzecker's (1900) visual RI task, the current study elucidates that a verbal component is ***not*** necessary for a drop in word list recall to emerge.

(b) Mathematics, Spot-the-difference and tone detection interpolated tasks all led to a significant drop in recall when compared to the control condition highlighting that an intentional learning factor is **not** required for the drop in recall to emerge.

(c) Most importantly however is the finding that tone detection, the task assumed to be mentally effortful without containing new meaningful material, resulted in a significant drop in recall when compared to the control condition. This provides some evidence that indeed mental effort is **sufficient** to lead to a reduction in delayed recall.

This highly suggests that, as proposed by Müller and Pilzecker more than a century ago, subsequent ‘diversion’ RI (i.e. RI caused by any interpolated mental effort) is a key factor for forgetting to occur. However, if mental effort (and level of mental effort) is the main factor with respect to RI, why did McGeoch and MacDonald’s (1931) participants perform worse following highly similar interference stimuli than less similar (yet still verbal) stimuli? Furthermore, if stimulus similarity is indeed a highly important factor with respect to RI then why is there no difference between recall following Müller and Pilzecker’s (1900) visual and syllable conditions? Why did the present experiment not lead to poorest recall following the verbal task? Even though this task did not contain wordlists it nevertheless contained verbal information, which should have interfered more with the wordlists than the tone detection or the Spot-the-difference task.

With respect to the former question it may be argued that differences in recall following McGeoch and MacDonald’s (1931) various tasks may be explained by differences in mental effort required for the tasks. However it seems unlikely that synonyms require more effort to learn than unrelated adjectives or nonsense syllables, thus making it difficult to explain such findings in terms of diversion RI.

With respect to the second question one may argue that similarity effects are confined to specific processes or material rather than occurring at a modality level. In other words being of the same modality (i.e. wordlists and story) may not be specific enough for similarity interference effects to emerge. Indeed Robinson (1920) provides evidence for such speculation. He found that recall for a list of eight four place numbers was much lower following the learning of another list of eight four place numbers than following multiplication of four place numbers or learning of a string of 32 numbers. In fact the latter tasks led to very similar recall as the other interpolated tasks (e.g. observing pictures or reading a passage of text). This is indeed interesting as it suggests that even highly similar material (4 place digits in the multiplication) or tasks (learning a series of single digits) may not necessarily have a detrimental effect on recall of 4 digit numbers! It appears that as Robinson

(1920) puts it ‘unless the two sets of material are presented in highly similar form there may be no high degree of inhibition’ (p.53).

While such evidence may explain why our verbal interpolated task did not lead to lower recall than the nonverbal tasks, it does not explain why our verbal task did nevertheless lead to lower delayed recall than the control task and why Müller and Pilzecker’s (1900) verbal interpolated task, which was highly similar to the to-be-retained material and its presentation, did not interfere more with recall than their visual task. As the visual task did contain verbal content thus making it more similar to the syllable interpolated task in terms of modality a possible argument could be that both conditions interfered due to being similar to the to-be-retained information. However such hypothesis appears very unlikely in light of the above reported work by Robinson (1920) who would certainly deem the verbal content within the visual task ‘dissimilar’. It appears then that it is virtually impossible to explain diversion RI in terms of similarity RI or vice versa which suggests that both types may in fact affect memory.

In fact Skaggs (1925), also confronted with the contradictory finding of both similarity and diversion RI, proposed an interesting theory of RI that encompasses both similarity **and** diversion RI (see Figure 3.2): He states that when interpolated material is identical or highly similar to the to-be-retained material there is no inhibition but repetition and therefore reinforcement (see Figure 3.2). He goes on to theorise that as the interpolated material decreases in degree of similarity so do the reinforcement factors while the interfering factors increase. This would occur until interference reaches a maximum, after which interference decreases. Skaggs (1925) stated that it is after this maximum that ‘*we can say that the more dissimilar the materials the LESS the detrimental influence’* (p.57). It is however Skaggs’ (1925) last point that is the most crucial with respect to the similarity – general effort ‘debate’. Skaggs (1925) stated: ‘*However, the curve of detrimental influence never reaches zero because after the work and learning are as different as can possibly be made there is still a demanding influence exerted by work’* (p.57).

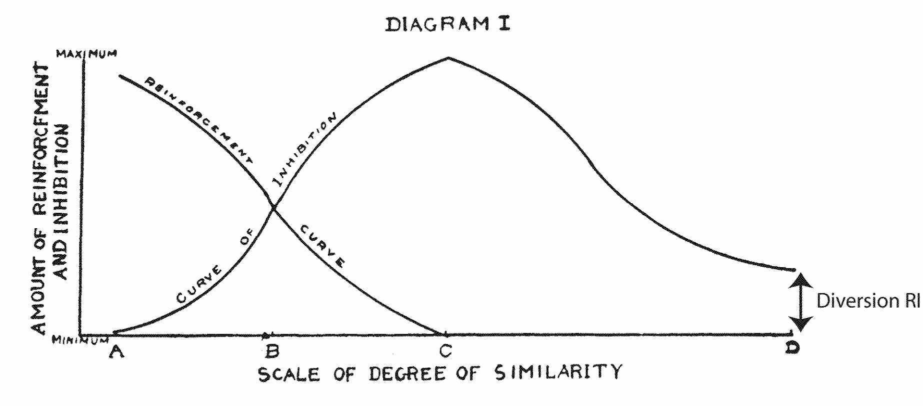


Figure 3.2. Skaggs' (1925) diagram of reinforcement and inhibition

Caption quoted from Skaggs (1925): *'Explanatory Note. – The above diagram is merely theoretical in its outline. Possibly the curves may be drawn with some mathematical precision in the future. The scale on the left vertical represents the amount of reinforcement and retroaction – two opposed processes. The horizontal scale represents the degree of similarity between the original learning and the interpolated work. Beginning at A where learning and work are identical, as we go to the right there is greater and greater dissimilarity until at D the two are as dissimilar in content and method as possible. At A inhibition is at a minimum and reinforcement at a maximum (mere repetition); at C the situation is reversed. At D the inhibition curve has fallen but never to the original minimum'* (p. 32).

Skaggs' (1925) research and theory therefore suggests that similarity AND general mental effort both can have an effect on subsequent recall and that both can in fact go hand in hand as opposed to being two mutually exclusive entities and theories. Indeed Skaggs (1925) makes the important point that any interpolated material/task, be it mental effort per se or similar material, causes diversion RI, and that similar material simply adds further interference (i.e. similarity RI) due to its similarity with the to-be-retained material.

3.1.5 Conclusion

In conclusion, the present study, which was set up to tackle the alternative hypotheses that were left open following Müller and Pilzecker's (1900) pioneer research on RI, strongly suggests that, in neurologically intact individuals RI need not be material or even modality specific to have a detrimental effect of retention of to-be-retained material. Thus, the study provides strong evidence that all *diversion RI* must be minimised in order for neurologically intact individuals to benefit from minimal RI.

The present findings thus suggests that, as proposed by Müller and Pilzecker (1900), *'diversion'* RI is a key factor for forgetting to occur in the neurologically intact population. Nonetheless, as argued by Skaggs (1925) such does not mean to say that similarity RI does not play a part in forgetting; both are likely to play a role. However, while any interpolated mental effort is likely to cause diversion RI, only highly similar material causes similarity RI

Chapter 4: Material specificity of Retroactive Interference (II) Neurological Patients

4.1 Experiment 2: Material specificity of RI - Mental effort versus Minimal RI

4.1.1 Introduction

The findings reviewed and reported in Chapters 2 and 3 of a highly likely role of *diversion* RI on forgetting in the neurologically intact population are of great interest with respect to Cowan et al.'s (2004) and Della Sala et al.'s (2005) recent findings of a *non-material specific* RI effect on memory in some patients with anterograde amnesia.

Indeed, in parallel to the modern RI research on the neurologically intact population, previous research on interference effects in the memory-impaired population has focused exclusively on interference of the *material specific* type. As discussed in Chapter 1 such research has elucidated a particular susceptibility to *PI* in some patients with frontal lesions (e.g. Shimamura et al., 1995; Baldo and Shimamura, 2002). Shimamura et al. (1995) further tentatively suggest possible (similarity based) effects of RI in their frontal lobe patients. While such particular patients (i.e. frontal/dysexecutive patients) may benefit substantially from the sole removal of *similarity RI,* this argument cannot be made for the amnesic patients who benefited from Minimal RI in the studies by Cowan et al. (2004) and Della Sala et al. (2005). Indeed, given that the RI imposed during the delay interval was non-material specific, and thus *not* akin to similarity RI, the patients should have 'benefited' from the absence of similarity RI in both the Minimal RI as well as the RI conditions if they were highly susceptible to similarity RI. Thus performance following the two conditions would have been predicted to be equally well. However, firstly, the results clearly elucidate that all examined patients performed very poorly, the majority retaining 0, following the non-material specific RI delay interval which strongly suggests that such patients were not merely susceptible to similarity RI. Moreover, the majority of patients showed somewhat improved retention following the Minimal RI interval, a finding that strongly suggests that (a) the sole removal of similarity RI was not sufficient for such patients to show memory improvement and thus (b) that these patients' RI susceptibility must encompass more than merely similarity RI.

A study on similarity RI by Mayes et al. (1994) provides further tentative evidence that the sole removal of similarity RI during the delay interval may not lead to a benefit in non-frontal/executive patients with amnesia. Participants in their study were asked to remember sets of ten photos of faces. This was then followed by the Interference condition, during which the participants were presented with a further set of photos of faces or the standard condition, during which the participants were 'engaged in conversation and other activities (not involving faces)' (p.549). The authors found a significant main effect of Group, the basis of which was lower delayed recall in the patients than the controls. However no significant group x condition interaction was shown leading them to conclude that '*there was no evidence that the amnesic group as a whole was more susceptible to the type of sustained retroactive interference that was built into the present experimental design*' (p. 558).

While an unfilled interval would have been necessary in order to examine whether or not this particular sample of amnesiacs may have been susceptible to non-material specific RI, the study clearly showed that this group of patients did not benefit from the removal of similarity RI only.

Moreover, assuming that similarity RI does not occur on a constant basis in every day life, one would expect an amnesic patient with a particular susceptibility to similarity RI to show islands of anterograde memory in everyday life.

However, the patients tested in the two studies by Della Sala et al. (2005) and Cowan et al. (2004) showed very severe anterograde amnesia, both in everyday life as well as in objective clinical testing.

Given the findings of a small, yet significant effect of diversion RI on memory in the neurologically intact population (Müller and Pilzecker, 1900, Skaggs, 1925 and Experiment 1), it could thus be hypothesised whether the apparent susceptibility to non-material specific RI in some anterograde amnesiacs may in fact embody a greatly heightened susceptibility to such *diversion RI*.

While the findings by Cowan et al. (2004) and Della Sala et al. (2005) do indicate that the RI susceptibility in some anterograde amnesiacs extends beyond the realms of similarity RI, their findings alone do not provide sufficient evidence for a *diversion* RI hypothesis of anterograde amnesia.

Indeed, their RI comprised not only mental effort, but also *new verbal* and *new meaningful material*. While no intentional learning of such material was required, one cannot exclude the possibility that the nevertheless encoded new verbal material and/or new meaningful material, as opposed to the mental effort associated with such materials and tasks, could have had a direct effect on processing of the to-be-retained material. Thus, one plausible alternative to a diversion RI hypothesis could be that some patients with anterograde amnesia may be highly susceptible to *modality specific* RI. However, if RI susceptibility in anterograde amnesiacs were modality specific, the amnesic patients tested by Mayes et al. (1994) should have performed better following the conversation-filled delay interval (non-modality specific RI) than the interval containing further visual material (modality specific RI). However, such was not found. Nonetheless, seeing as it is not known if this sample would have shown a benefit of Minimal RI, such potential evidence against a modality specific RI hypothesis in anterograde amnesia is tentative only and cannot be utilized to reject such hypothesis with particular regard to the findings by Cowan et al. (2004) and Della Sala et al. (2005).

In line with the aforementioned presence of new meaningful material during Cowan et al.'s (2004) and Della Sala et al.'s (2005) delay intervals, a second plausible alternative to a diversion RI hypothesis of forgetting in anterograde amnesia could be that some patients with anterograde amnesia may be highly susceptible to any new meaningful material, irrespective of its modality.

The possibility of such two alternative hypotheses for the non-material specific RI effect in anterograde amnesia highlights the necessity to examine and reject such hypotheses before a specific *diversion* RI hypothesis can be postulated.

As discussed in Chapter 3, a way of examining whether or not the non-material specific RI susceptibility in some anterograde amnesiacs represents a susceptibility to diversion RI, as opposed to modality specific RI or to any new meaningful RI, is to investigate proportion retention following a delay interval which contains only mental effort (i.e. a task that is mentally effortful yet lacks any new meaningful or modality specific material).

The underlying reasoning for such method is that if patients are indeed susceptible to diversion RI, a delay interval containing mental effort only should be greatly detrimental to later retention, i.e. retention should be poorer following such RI than Minimal RI. If on the other hand patients are susceptible to modality specific RI or to any new meaningful material, the interpolation of mental effort only should *not* affect memory processing in such patients, i.e. no substantial differences would be predicted between retention following such RI delay and a Minimal RI delay.

4.2 <u>Experiment 2(a)</u>

4.2.1 Aims of Experiment 2 (a)

The aim of the present Experiment was thus to examine whether or not a delay interval containing a solely mentally effortful task with *no* new modality specific or meaningful material would lead to a lower proportion retention than a delay interval consisting of Minimal RI in patients with anterograde amnesia.

4.2.2 Method

4.2.2.1 Participants

11 patients diagnosed with anterograde amnesia (7m/4f, mean age = 40.72, age range = 20 – 72; mean education = 11.8 years, education range = 8 - 18) and 11 age and education matched controls (6m/5f, mean age = 42.45, age range = 21 – 74; mean education = 14.55, education range = 8 – 20) volunteered to take part in the present study.

Four of the patients (PA, PB, PC and PD) were recruited through the Department of Clinical Neurosciences, Western General Hospital, Edinburgh (via Consultant Neurologists Dr Zeman and Dr Stone). The other 7 patients (PE, PF, PG, PH, PI, PJ and PK) were recruited through the Dipartimento di Rihabilitazione, Ospedale Somma Lombardo, Italy, via Dr Beschin. Full ethical approval for the study was granted by the NHS Lothian Local Research Ethics Committee. All participants gave their consent to take part in the study. All patients except PC were outpatients. PC was an inpatient at the time of neuropsychological and experimental testing. None of the patients had any known pre-morbid psychiatric or neurological histories. Five of the patients had closed-head injuries (PE, PG, PH, PI and PJ), two had been affected by anoxia following cardiac arrest (PF and PK), one had been affected by probable birth asphyxia and subsequent childhood epilepsy (PD), one had suffered from a stroke (PA), one from limbic encephalitis (PB) and the other from probable limbic encephalitis (PC). CT or MRI scans indicated probable lesion sites (these will be discussed in Experiment 7). Patients PE and PH had previously taken part in the study by Cowan et al. (2004) (PH = Patient 4 in Cowan et al.'s (2004) paper, PE was not included in their final paper).

All patients underwent extensive neuropsychological assessment[4] (see Table 4.1a, Scottish patient sample and Table 4.1b, Italian patient sample, below) and were

[4] *Neuropsychological assessment of Patients PA, PB and PC was conducted by Michaela Dewar. Neuropsychological assessment of Patient PD was undertaken by Dr Abrahams (Clinical Neuropsychologist and second supervisor, Edinburgh University). The neuropsychological assessment of the 7 Italian patients PE-PK was undertaken by Dr Beschin*

selected according to most of the following *inclusion criteria*, which were the same as for the study by Cowan et al. (2004):

(1) Complaints by family members of an abrupt onset of memory loss as the main symptom; (2) classification as amnesic according to the Rivermead Behavioural Memory Test (Baddeley et al., 1991, Brazzelli et al., 1993); (3) performance below cut-off score for normality in verbal delayed recall according to the Selective Verbal Learning Test (Buschke, 1975; Spinnler & Tognoni, 1987) and non-verbal delayed recall according to the Rey Osterrieth Figure delayed recall (Caffarra et al., 2002); (4) normal performance in short term memory tasks, i.e. digit span (WAIS III, Wechsler, 1997; Novelli et al., 1986) and corsi span (WMS-III, Wechsler, 1998; Novelli et al., 1986); (5) score within the normal range on an aphasia test including comprehension (Token Test, De Renzi and Faglioni, 1978; Boston Naming Test, Kaplan et al., 1983; Frenchay Aphasia Screening Test (FAST), Enderby et al., 1987); (6) Scores above cut-off in a test of verbal reasoning (Verbal Judgement Test, Spinnler & Tognoni, 1987; WAIS III, Wechsler, 1997), (6) Scores above cut-off in the Raven Progressive Coloured Matrices (Raven, 1965).

Testing session

It should be noted that for patients *PE – PK* (the Italian sample) Experiment 2(a) formed the first part of a series of experiments, which were conducted during the same testing session. This was done in order to minimize patient travel. Adequate breaks (including a long 25 minute break), and refreshments were provided during the testing session, which lasted approximately 2.5 hours including breaks. The testing session (for patients PE – PK) consisted of the following, in chronological order:

1.) Experiment 2(a)

2.) Experiment 4(a)

3.) Break (25 min)

4.) Experiment 2(b)

5.) Experiment 4(b)

Patients PA – PD (the Scottish sample), who were seen prior to the Italian sample, only took part in Experiment 2(a), except for patient PB who participated in an extended version of Experiment 2(a) (see Experiment 3).

Measure		Patients (Scottish sample)			
	cut-off	PA	PB	PC	PD
Age		67	72	49	30
YoE		10	17	12	11
Gender		m	m	m	f
No of years(y)/months(m) since damage		1y	2y 2m	<1m	since birth
Rivermead screening	9	0	/	0	/
Rivermead classification*	/	vs	/	vs	/
Frenchay Aphasia Screening Test	25	28	30	30	/
Similarities (WAIS-III) scaled score (raw score)	4	3(5)	17(30)	6(12)	6
Raven Matrices	18	31	35	32	/
Digit span (WAIS-III) raw score	/	6	5	6	6
Word span#	/	3	3	3	/
Corsi span scaled score (raw score)	4	12(6)	7(4)	13(6)	/
Word list recall immediate scaled score (WMS-III)	4	/	/	/	5
Word list recall total immediate (SRT)	/	34	53	58	/
Word list recall total immediate, individual cut -offs (SRT)	/	83.91	72.6	101.5	/
Word list recall delayed scaled score (WMS-III)	4	/	/	/	5
Word list recall delayed (SRT)	/	1	1	0	/
Word list recall delayed, individual cut -offs (SRT)	/	4.76	3.92	8.23	/
Paired associates test total immediate recall, scaled score (raw score) (WMS-III)	4	4(0)	5(0)	5(3)	/
Paired associates test delayed, scaled score (raw score) (WMS-III)	4	4(0)	5(0)	5(1)	/
Rey Figure copy corrected	<28.87	25.4	34	29.58	35
Rey Figure delayed corrected	<9.46	10.53	0	0	0
Trail Making A, Raw	/	84	131	38	44
Trail Making A, Individual Cut-offs	/	>56	>71	>50	>40
Trail Making B, Raw	/	207	402	91	99
Trail Making B, Individual Cut-offs	/	>137	>112	>84	>67
Trail Making, Raw (B-A)	/	123	271	53	55

All scores are age and education adjusted unless otherwise stated, *Rivermead classification: n = normal, s = severe, vs = very severe, PD was tested on a different test battery than PA-PC, Cut-offs for SRT = 2SD cut-off, Cut-off for Trail Making = 10^{th} percentile, #Word span test designed by Michaela Dewar and Sergio Della Sala, pilot version, no norms are available yet.

Table 4.1a. Selected characteristics of tests and amnesic patient performance (Scottish patient sample)

Measure	Normal cut-off	Patients (Italian sample)						
		PE	PF	PG	PH	PI	PJ#	PK
Age		29	43	25	32	20	34	47
Education (years)		10	8	15	16	11	12	8
Gender		f	f	m	m	m	m	f
No of years(y)/months(m) since damage		4y 2m	8m	1y 8 m	6y 1m	2y 2m	6y 4m	1y 2m
MMSE	< 23.8	27.59	27	21.07	24.19	/	23.75	23.62
Rivermead screening	<9	9	2	2	2	2	3	3
Rivermead classification*		n	vs	vs	vs	vs	s	s
Boston naming test	<43	54	42	49	51	45	49	53
Token Test	<29	32	35	36	36	32	35	33
Phonological fluency	<16	19	29.1	5.5	18	15.2	26	7.5
Category fluency	<9	9.5	28	16	13	27	11.5	8
Verbal judgement	<32	46.25	52.5	49.25	49.25	52.6	42.25	44.5
Raven Matrices	<18	47.75	23	23	24	39.2	24	27
Weigl card sorting	< 4.25	15	5.75	15	3.75	7.25	8.25	5
Digit span	< 3.5	5.75	4	4	5.25	5.25	5.5	4
Corsi span	< 3.25	5.5	4	3.25	3.25	3.25	2.5	4
Word list recall immediate	< 36	56	44	31	46	45	52	48
Word list recall delayed	< 2	0	0	1.05	0	0	/	0
Rey figure copy	< 28.87	36	36	36	36	36	/	36
Rey figure delayed	< 9.46	0	3.75	1.75	0	2.5	/	0
Trail Making A	>93	58	58	54	60	110	/	75
Trail Making B	>282	136	703	210	159	152	/	161
Trail Making (B-A)	>186	78	644	157	99	42	/	86

All scores are age and education adjusted, *Rivermead classification: n = normal, s = severe, vs = very severe, # PJ was unable to perform the Rey Figure Test and the Trail Making test due to a motor deficit

Table 4.1b. Selected characteristics of tests and amnesic patient performance (Italian patient sample)

Mini Mental State Examination (MMSE) (Folstein et al., 1975); Rivermead Behavioural Memory Test, Scottish sample: (Baddeley et al., 1991), Italian sample: (Brazzeli et al., 1993); Frenchay Aphasia Screening Test (FAST) (Enderby et al., 1987); Similarities, WAIS-III (Wechsler, 1997); Raven's Coloured Progressive Matrices (Raven, 1965); Digit span, Scottish sample: WAIS-III (Wechsler, 1997), Italian sample: (Novelli et al., 1986); Corsi span, Scottish sample: WMS-III (Wechsler, 1997), Italian sample: (Novelli et al., 1986); Word list recall, Scottish sample: WMS-III (Wechsler, 1997) and Selective Reminding Test (SRT) (Buschke, 1975), Italian sample: (Spinnler and Tognoni, 1987); Paired Associates, Scottish sample: WMS-III (Wechsler, 1997), Italian sample: (Novelli et al., 1986); Rey Figure (Caffarra, 2002); Trail Making Test, Scottish sample: (Tombaugh, 2004), Italian sample: (Giovagnoli, 1996); Boston Test (Kaplan et al., 1983); Token Test (De Renzi and Fagliono, 1978); Weigl Test (Spinnler and Tognoni, 1987), Verbal Judgement (Spinnler & Tognoni, 1987).

4.2.2.2 Procedure

All participants were presented with four prose passages verbally by the Experimenter which they were asked to try and remember for subsequent immediate recall. The prose passages were taken from the Rivermead Behavioural memory Test (Baddeley et al., 1991; Brazelli et al., 1993) (see Appendix B) and contained 21 'ideas' each. Prose presentation was followed by free immediate verbal recall in each of the four conditions. The end of immediate recall marked the start of a ten minute delay interval, which was always followed by delayed recall.

The critical manipulation in the present Experiment lay in the delay interval condition (Minimal RI vs. RI). This is illustrated in Figure 4.1.
In the Minimal RI interval the participant was left alone in the darkened quiet room (Minimal RI). In the RI delay interval the participant engaged in a longer variation of the Tone Detection Paradigm (TDP) that was previously used in Experiment 1 (see stimulus description in Chapter 3). The TDP stimuli consisted of a sound track of brown noise, within which a piano note was randomly embedded on 50 occasions. While the note remained the same throughout the ten minute track, its loudness varied (its decibel level was reduced by either 13db, 22db, 24db or 36db). The track was played back digitally on a laptop via the E-prime (Psychology Software Tools, Inc.) and presented to the participants via headphones. Participants were given a PC mouse and asked to press the left mouse button whenever they detected the piano note. Number of mouse presses were recorded by E-prime.

In trial 1 the participants were told that they would be presented with a prose passage, which they should attend to carefully as they would be asked to recall as much as they could immediately following story presentation. Following Immediate recall Participants were asked to rest in the room for a short duration while the Experimenters left the room to set up the next part of the study. The Experimenter subsequently left the room and dimmed the lights (having previously informed the participants that they would do so).

On re-entering the room following 10 minutes the Experimenter switched on the lights. She then apologized to the participant telling him/her that there had been a problem with the tape recorder during the previous recall of the story and asked the participant to try and recall as much of the story as they could once more. Such deception was required in order to minimize any suspicion in the participant regarding delayed recall in the next trial (i.e. the participant should be under the impression that delayed recall was not ‘usually’ required).

Prior to Trial 2 the participant was given instructions on the tone detection paradigm and asked to do a one minute practice trial. This trial (a) served as a practice trial for the later tone detection paradigm, (b) allowed for minimization of later tone detection instructions, and thus minimization of extra interference and (c) further aided in making the participants believe that the Experimenters had in fact gone away to prepare another task.

In trial 2 the participant was once again instructed to listen and attend to a prose passage and informed that that he/she would be requested to recall as much as they could immediately following story presentation.

Following immediate recall the participant was given very brief instructions on the subsequent tone detection paradigm while the Experimenter placed the headphones over the participant’s ears.

The participant then engaged in the tone detection paradigm for a period of 10 minutes while the examiner remained in the room out of the participant’s sight. Two of the patients (PB and PC) had to be tested in a very small room on the hospital ward. In this case the Experimenter was unable to remain in the room without being seen by the patient. The Experimenter thus left the room standing in front of the door and taped the tone detection delay for these two patients for later checking of the tape recordings for activities other than tone detection.

Following tone detection the Experimenter removed the participants' headphones and asked the participant to try and recall as much from the immediately preceding prose as he/she could.

After trials 1 and 2 patients and controls may suspect that delayed recall would also occur during the subsequent trials meaning that at least some patients and controls would try to explicitly maintain the prose material over the duration of the 10 minute delay. In the Cowan et al. (2004) and Della Sala et al. (2005) studies participants were asked whether they had rehearsed, and only 2 patients responded that they had tried to rehearse. These patients may have been more able to remember delayed recall in previous trials or at least suspected it for future trials. However, given the severe memory impairment in such patients it is possible that some patients simply cannot remember whether or not they tried to rehearse during the various trials when asked following such experiment. Hence, reliance on post experimental feedback may not be a highly reliable measure of presence/absence of rehearsal. In order to minimize any variance in proportion retention that could result from the use of rehearsal in some but not other participants due to varying degrees of insight into the Experiment, all participants were explicitly informed that delayed recall would follow the delay interval in the subsequent Minimal RI trial (trial 3) and tone detection trial (trial 4). These two trials were otherwise identical to trial 1 and trial 2 respectively.

It was further reasoned that such procedure would allow for an examination of delayed recall following Minimal RI as well as tone detection under both 'incidental' conditions (when explicit rehearsal would be assumed to be unlikely) as well as 'intentional' conditions (when explicit rehearsal would be assumed to be likely). The procedure is depicted in Figure 4.1.

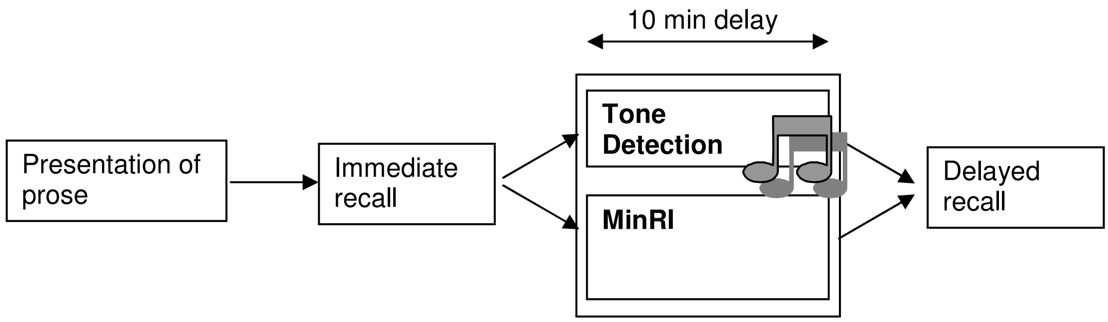


Figure 4.1. Procedure of the Experiment

The testing of the 4 Scottish patients (PA – PD) and controls (CA – CD) was undertaken by Michaela Dewar. The testing of the Italian patients (PE – PJ) and controls (CE – CJ) was undertaken by Dr Beschin under the guidance of Michaela Dewar.

4.2.2.3 Counterbalancing

The order of trials was kept constant across participants in order to avoid convolution of potential behavioural differences that could arise due to varying lesion loci and size.

Due to the small sample size of the initial Scottish patient sample (N = 4), order of prose passages was also kept constant for patients PA - PD. The order of prose passages was *A – B – C – D*.

In the Italian leg of the study, for which the sample size was larger, it was however decided to counterbalance order of prose passages to avoid any potential confounding among condition type and prose passage number. Four participants in each group (PE, PF, PG, PJ and CE, CF, CG, CJ) were presented with the prose passages in the order *A – B – C – D*, while the remaining three participants (PH, PI, PJ and CH, CI and CJ) in each group were presented with the prose passages in the order *B – A – D – C*.

4.2.2.4 Prose scoring

Only story ideas that were recalled verbatim or close synonyms were scored as correct. Scoring took place during testing and was subsequently checked against a tape recording after testing had been completed.

4.2.3 Results

Individual participant data from trial 1 and 3 (Minimal RI) and 2 and 4 (tone detection) was initially collapsed to compute individual participant means for proportion retention (number of story ideas recalled/total number of story ideas within presented story) at immediate recall and delayed recall for the Minimal RI as well as the tone detection condition respectively. These means are illustrated in Figures 4.2 – 4.5 below:

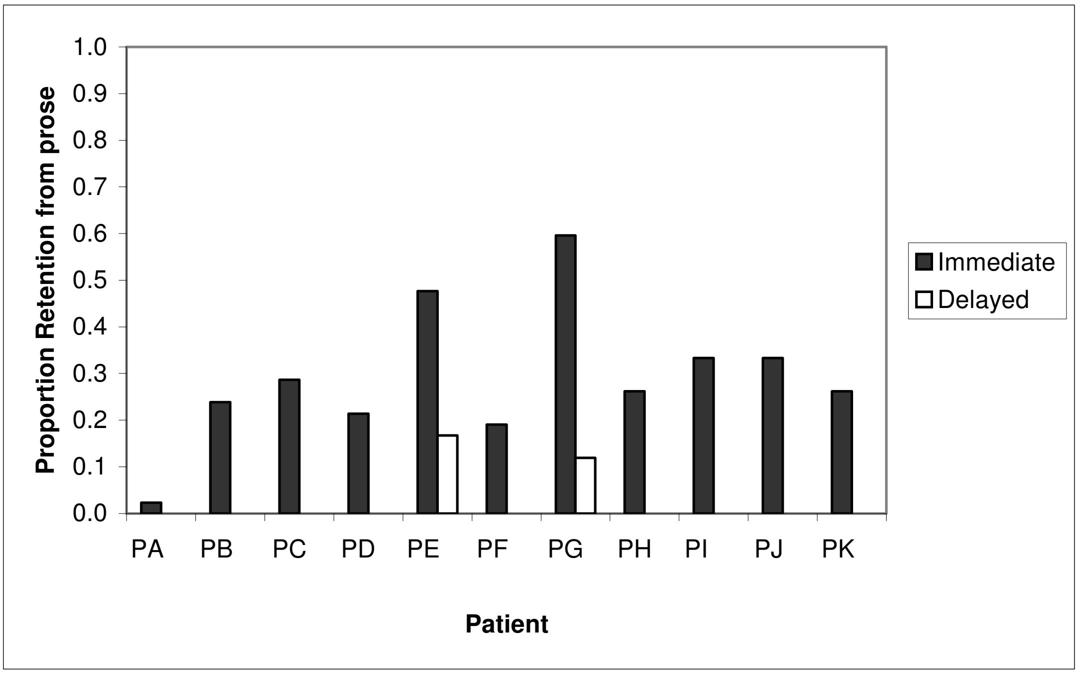


Figure 4.2. Patient proportion retention of prose material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the tone detection condition.

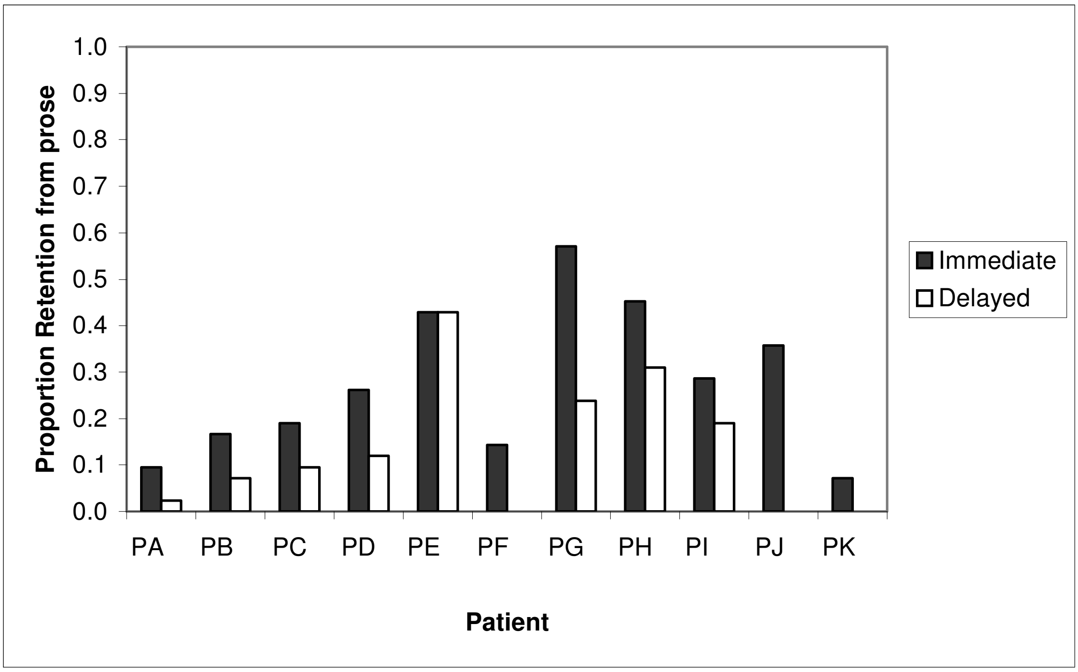


Figure 4.3. Patient proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the Minimal RI Condition.

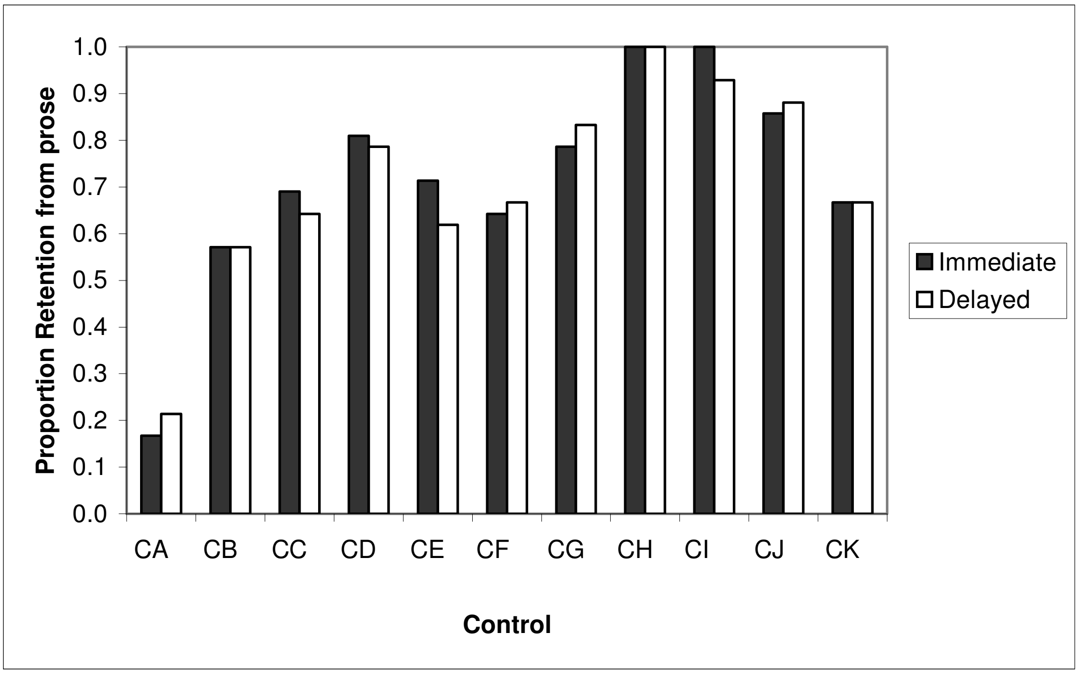


Figure 4.4. Control proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the tone detection condition.

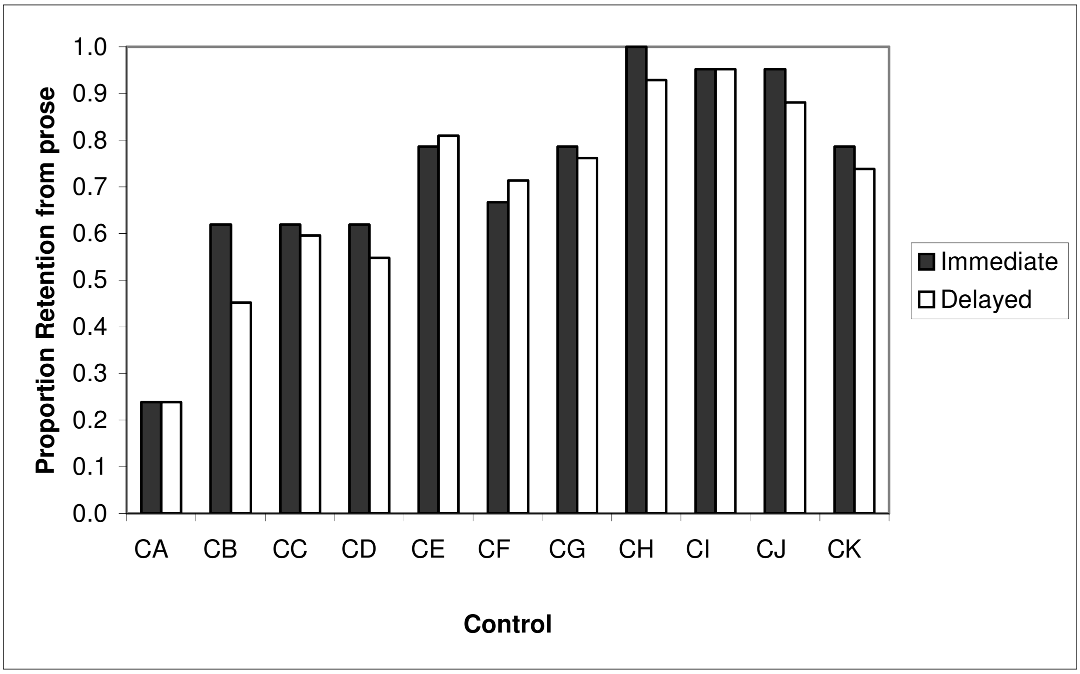


Figure 4.5. Control proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the Minimal RI Condition.

A mixed factors ANOVA on proportion correct at immediate recall with within subjects factor Delay Condition (Minimal RI vs. tone detection) and between subjects factor Group (Patients vs. Controls) was initially run to assess the state of memory before a delay was imposed. The ANOVA revealed that proportion correct at immediate recall did not differ significantly across the two conditions for either group. However, a main effect of group was obtained, with the control group performing significantly better at immediate recall than the patient group, $F(1, 20) = 30.851$, $p < 0.001$. Group mean immediate proportion correct and SD was 0.284 (0.147) and 0.724 (0.218) for the patients and the controls respectively. No Delay Condition x Group interaction was found.

As in the previous studies on RI in amnesia (Della Sala et al., 2005; Cowan et al. 2004) proportion retention at delayed recall was further measured as the number of correct story ideas recalled at delayed recall divided by the number of correct story ideas recalled at immediate recall in the same trial (i.e. Delayed Recall/Immediate Recall; DR/IR).

Participant mean proportion retention (DR/IR) for the Minimal RI and tone detection Delay Conditions are shown in Figures 4.6 and 4.7.

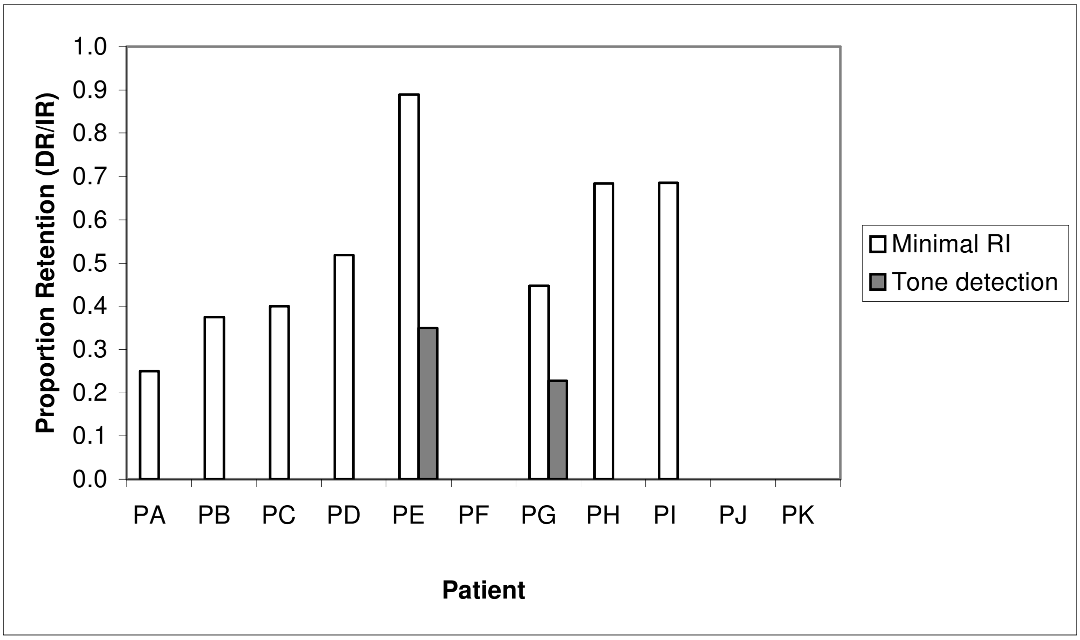


Figure 4.6. Patient proportion retention of story material (Delayed Recall/Immediate Recall) following Minimal RI and tone detection.

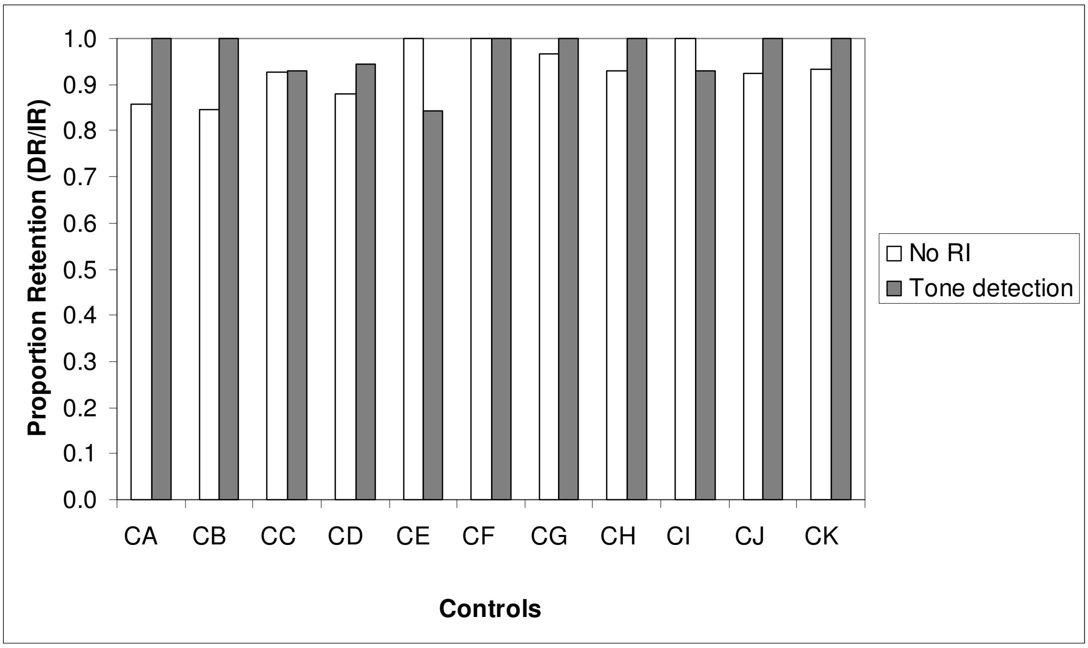


Figure 4.7. Control proportion retention of story material (Delayed Recall/Immediate Recall) following Minimal RI and tone detection.

A mixed factor ANOVA with within subjects factor Delay Condition (Minimal RI vs. tone detection) and between subjects factor Group (Patients vs. Controls) revealed a significant Delay Condition main effect, $F(1, 20) = 12.882$, $p < 0.01$, a highly significant Group main effect, $F(1, 20) = 159.519$, $p < 0.001$ as well as a highly significant Delay Condition x Group interaction, $F(1, 20) = 19.607$, $p < 0.001$. Group means and SEMs are depicted in Figure 4.8 below. A simple main effects analysis on Delay Condition for each group separately showed that while proportion retention was significantly better following the Minimal RI than the tone detection Delay Condition in the patient group, $F(1, 10) = 17.959$, $p < 0.01$, proportion retention did not differ significantly between the two Delay Conditions in the control group, which performed at ceiling in both conditions.

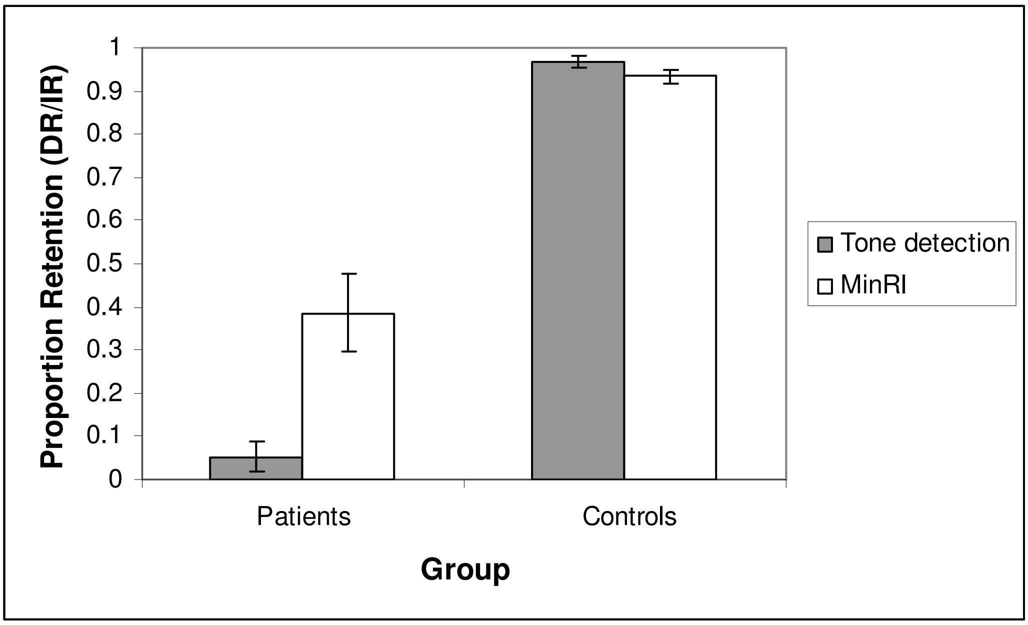


Figure 4.8. Mean Group proportion retention of story material (Delayed Recall/Immediate Recall) following Minimal RI and tone detection.

Figure 4.6 above shows that three of the patients did not show any retention following the Minimal RI Delay Condition. It was thus decided to re-run the above ANOVA following exclusion of these three patients. The results of this ANOVA did not deviate from those of the ANOVA including all 11 patients (a Delay Condition main effect, $F(1, 17) = 22.467$, $p < 0.001$; a Group main effect, $F(1, 17) = 31.640$, p

< 0.001; a Delay Condition x Group interaction, $F(1, 17) = 145.450$, $p < 0.001$). However, as indicated in Figure 4.9, the patient group mean for proportion retention following the Minimal RI delay was elevated slightly following exclusion of the three patients who scored 0 in this condition.

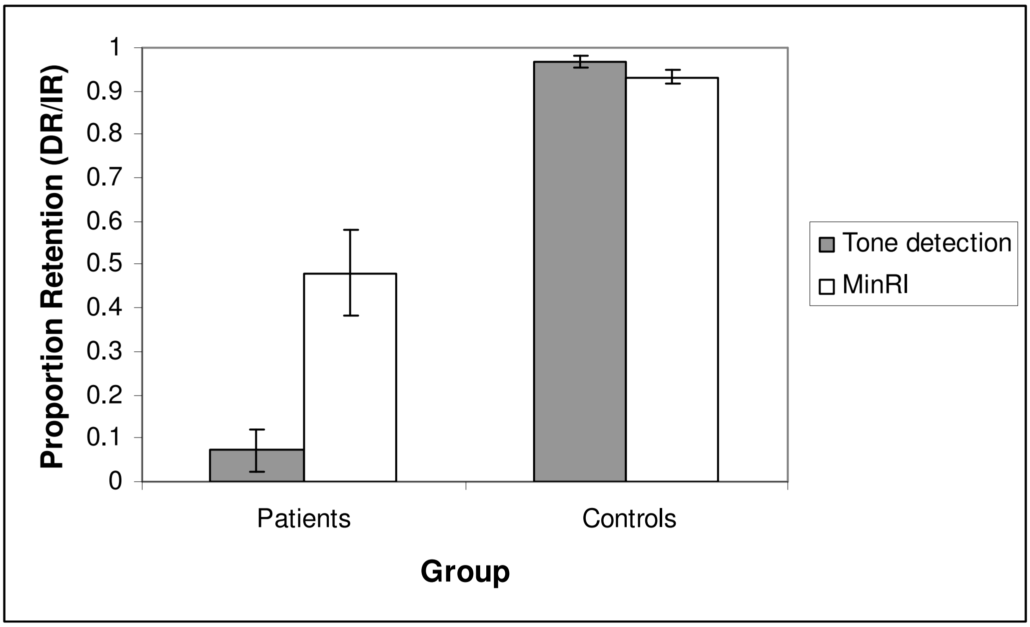


Figure 4.9. Mean Group proportion retention of story material (Delayed Recall/Immediate Recall) following Minimal RI and tone detection (after exclusion of three patients who whose proportion retention following Minimal RI was 0)

4.2.3.1 <u>Performance at tone detection</u>

In order to examine whether or not the two groups differed in performance at tone detection, a tone detection mean score (i.e. number of mouse presses) was computed for each participant from the two tone detection trials.

Due to complications with E-prime data was lost for three patients: data for both tone detection trials for patient PB, and data for one of the two tone detection trials for patients PE and PG. Given that tone detection performance was highly consistent for the two trials for the other participants (Cronbach's alpha = 0.884 for all participants and Cronbach's alpha = 0.836 for the patient sample only), the existing tone detection score from one trial was utilized as the mean tone detection score for patients PE and PG. Patient PB was however excluded from the data set for the analysis of tone detection data.

A one-way ANOVA with between subjects factor Group (Patients vs. Controls) revealed no significant difference in the tone detection mean score between the two groups. Moreover, no significant correlations were obtained between tone detection mean score and proportion retention following tone detection for the two groups overall, nor for the two separate groups.

4.2.3.2 <u>Incidental versus Intentional?</u>

In order to examine whether or not the forewarning of subsequent delayed recall in trials 3 and 4 led to any changes in proportion retention (DR/IR) in the participants, a mixed factors ANOVA with between subjects factor Group (Patients vs. Controls) and within subjects factors Delay Condition (Minimal RI vs. tone detection) and Delayed Recall Instruction (Incidental vs. Intentional) was run on proportion retention. Besides the previously elucidated significant Delay Condition main effect, $F(1, 20) = 13.277$, $p < 0.01$, significant Group main effect, $F (1, 20) = 150.563$, $p < 0.001$ and Group x Delay Condition interaction, $F(1, 20) = 18.824$, $p < 0.001$ no significant effects were obtained.

Figure 4.10 shows Group mean proportion retention as a function of Delay Condition and Delayed Recall Instruction.

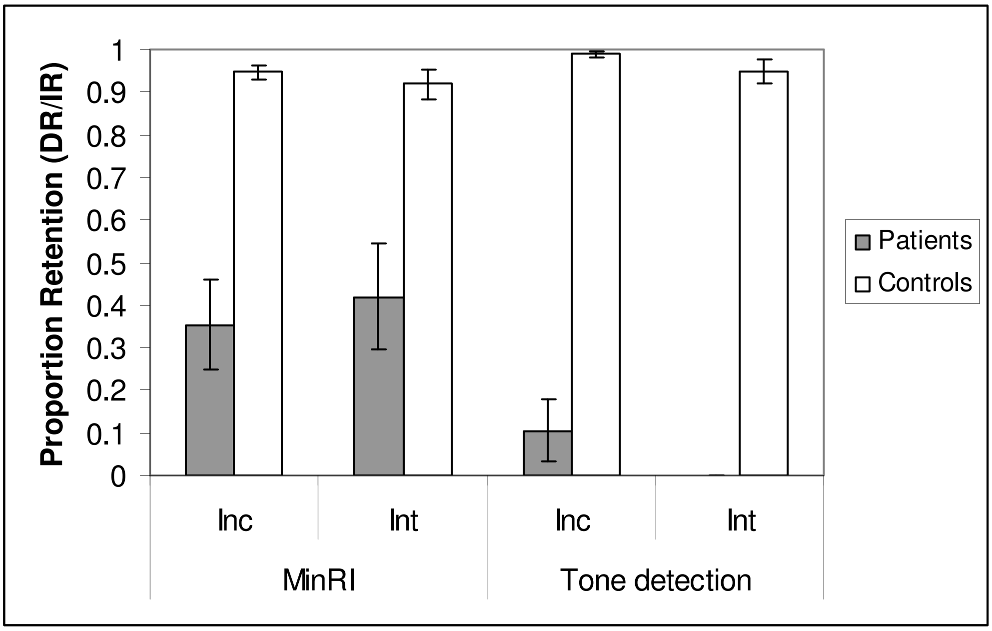


Figure 4.10. Group mean proportion retention (Delayed Recall/Immediate Recall) as a function of Delay Condition and Delayed Recall Instruction.

Given that three patients did not perform > 0 following either Minimal RI or tone detection, the above ANOVA was re-run following exclusion of these three patients. However, the results did not deviate greatly from those of the ANOVA including all patients.

4.2.3.3 <u>Rehearsal or explicit maintenance of prose during Minimal RI</u>

Debriefing of all participants revealed that five out of the 11 patients and 8 of the 11 controls tried to explicitly maintain the prose material during Minimal RI (via ‘repeating’ the material) while the residual patients and controls did not reveal any such rehearsal.

	PA	PB	PC	PD	PE	PF	PG	PH	PI	PJ	PK
Benefit	*Yes*	***Yes***	*Yes*	*Yes*	*Yes*	No	*Yes*	***Yes***	***Yes***	No	No
Rehearsal MinRI	Yes	**No**	No	Yes	Yes	No	Yes	**No**	**No**	No	Yes
Int>Inc	No	**No**	Yes	Yes	Yes	No	Yes	**No**	**No**	No	No

	CA	CB	CC	CD	CE	CF	CG	CH	CI	CJ	CK
Benefit	*No*	*No*	*No*	*No*	*Yes*	Yes	*No*	*No*	*Yes*	No	No
Rehearsal MinRI	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Int>Inc	No	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes

Table 4.2. The table indicates which participants showed a benefit of Minimal RI, which participants tried to explicitly rehearse story material during Minimal RI and which participants 'benefited' from the warning that delayed recall would follow Minimal RI (i.e. the intentional MinRI trial). Patients marked in **bold** are patients who showed a benefit in the absence of apparent rehearsal and in the absence of a benefit of intentional MinRI.

4.2.4 Discussion

The aim of the present Experiment was to examine whether or not a delay interval containing a solely mentally effortful task with *no* new modality specific or meaningful material would lead to lower proportion of prose retention than a delay interval consisting of Minimal RI in patients with anterograde amnesia.

A prerequisite for the current investigation was that at least some patients should show the previously elucidated benefit of Minimal RI (Cowan et al., 2004; Della Sala et al., 2005).
Such prerequisite was clearly met in the present experiment, which revealed that eight out of the eleven patients who participated in the experiment showed a benefit of Minimal RI. Such replication of the original findings by Della Sala et al. (2005) and Cowan et al. (2004) is of great interest in itself as it provides further strong support for improved retention following a condition, which involves Minimal RI.

With particular respect to the main aim of the present experiment, the core data showed that indeed on average the patient sample's proportion retention was significantly lower following tone detection, which contained no new modality specific or meaningful material, than following Minimal RI. In fact, Figure 4.6 shows that out of the eight patients who showed > 0 proportion retention following Minimal RI, only two patients (PE and PG) actually showed any prose retention following tone detection, and even these two patients showed a substantial benefit of Minimal RI. Indeed, out of the remaining six patients who showed > 0 proportion retention following Minimal RI, some patients could not even remember that a story had been read out to them prior to tone detection. For example, on being asked to recall the story presented prior to tone detection Patient PH responded 'What story?' and stated that he could not remember that there had been a story. In striking contrast however, this patient showed a mean proportion retention score of 0.68 following Minimal RI, a clear demonstration of the highly detrimental effect of a solely mentally effortful task on memory processes in such a patient with anterograde amnesia.

Overall, the present results strongly suggest that removal of modality specific RI or meaningful new material was *not* sufficient to allow for substantial memory improvement in this sample of anterograde amnesiacs. Hence, it appears that mental effort, too, had to be removed for a benefit of Minimal RI to emerge in the eight patients who showed > 0 proportion retention following Minimal RI.

Such findings are relevant for several reasons:

Firstly, they add further evidence to the notion by Cowan et al. (2004) and Della Sala et al. (2005), that in contrast to previous research findings of PI and similarity RI in memory-impaired patients with executive function deficits (e.g. Shimamura et al., 1995; Baldo and Shimamura, 2002), materials/activity interpolated between the learning and delayed recall of to-be-retained material need *not* be highly similar for interference to occur in some anterograde amnesiacs. Moreover however, the present findings strongly suggest that interpolated material/activity need *not* even be similar in modality or semantically meaningful for substantial interference to occur in such cases. Thus, any mentally effortful interpolated activity appears to affect such patients' memory processing.

Given the apparent small, albeit significant effect of *diversion RI* on memory processing in the *neurologically intact population* (see Chapter 2 and Experiment 1 in Chapter 3), the present findings indicate that at least some of the severe memory impairment in some anterograde amnesiacs may be the product of a greatly heightened susceptibility to the *diversion RI* that affects memory in the neurologically intact population to a small extent.

Given the near-to constant presence of such diversion RI in both clinical testing as well as everyday life, one would predict a patient with a severely heightened susceptibility to diversion RI to show a dense anterograde amnesia, as is indeed the case in the patients tested in this Experiment.

It remains to be examined however why two of the patients (PE and PG), who both benefited from Minimal RI, were able to retain some prose material following tone detection while the remainder of the patients who benefited from Minimal RI were not.

It is possible that such differences among the patients who benefited from Minimal RI may reflect qualitative differences in RI susceptibility. Thus, patients PE and PG may present with a more specific RI susceptibility than the other patients. However, seeing as no modality or material specific RI Delay Condition was included in the present study, this hypothesis cannot be further examined via the current data. It is further plausible that these two patients are simply less susceptible to RI overall, meaning that they may also be able to retain some prose material following, for example, the RI utilized by Della Sala et al. (2005) and Cowan et al. (2004).

Patient PE's neuropsychological assessment data indicates that her amnesia may be less severe than that of the other patients. Indeed, out of the patients tested on the Rivermead Behavioural Memory Test, she was the only patient to have scored at cut-off and thus just within the normal range on this test of every day memory. It may thus be plausible that PE's RI susceptibility is less profound than that of others. However, the neuropsychological data does not allow for any more specific inferences concerning the nature of such potentially lesser susceptibility to RI, i.e.

whether it may be due to a more specific RI or a reduced susceptibility to diversion RI. The underlying reason for PG's apparent lesser susceptibility to RI appears even less clear. Indeed, PG's Rivermead Behavioural Memory test classification was 'very severe', a classification that was supported by below cut-off scores on all tests of learning and delayed recall.

Nonetheless, it is plausible that he may have been able to retain some prose material following tone detection due to explicit rehearsal. Indeed, he, as well as in fact PE indicated that they had tried to rehearse some of the prose material at some points during tone detection. Whether or not these two patients 'merely' retained some material following tone detection due to such explicit rehearsal or whether they do indeed differ from the other patients with respect to RI susceptibility remains to be tested empirically via future research. Such future research could initially involve delayed recall following (a) tone detection, (b) psychometric testing as in Cowan et al. (2004) and Della Sala et al. (2005) and (c) Minimal RI. If patients PE and PG are indeed less susceptible to RI overall, one would expect them to be able to retain some prose material after tone detection as well as after psychometric testing. If they scored 0 following psychometric testing, one could go on to assess their delayed recall following tone detection and concurrent rehearsal blocking task such as shadowing of a non-word. The underlying prediction would be that if these patients simply showed some retention following tone detection due to explicit verbal rehearsal, they should perform at floor following the tone detection + rehearsal blocker Delay Condition. If on the other hand they were able to show some prose retention following tone detection due to a less specific RI susceptibility, they should be able to retain some prose material following the tone detection + shadowing task as well.

It also remains to be examined why three patients (PF, PJ and PK) did not show any delayed recall after either Delay Condition. This question will be returned to in subsequent chapters.

4.2.4.1 A matter of explicit rehearsal?

It might be argued that the elucidated difference in proportion retention following Minimal RI and tone detection could simply underlie the ability to explicitly rehearse the prose material during Minimal RI but not during tone detection.

While such a hypothesis cannot be fully excluded, it appears highly unlikely that all eight patients who showed a benefit of Minimal RI did so merely due to explicit rehearsal during Minimal RI. Indeed, four out of these eight patients reported during post experimental feedback that they had *not* attempted to rehearse the material in any of the delay intervals. However, given the patients' anterograde amnesia, the post experimental feedback may not be entirely reliable. Hence, some patients may have not in fact remembered whether or not they had attempted to rehearse the prose material during the unfilled delay intervals. However, seeing as all participants were warned about delayed recall in the second Minimal RI trials ('intentional'), it was postulated that the probability of rehearsal would be highest within this trial, and hence that participants would possibly perform better following this 'intentional' Minimal RI trial than the first 'incidental' Minimal RI trial. However, the analysis on this data revealed no such results. Moreover, Table 4.2 shows that out of the four patients who showed a benefit of Minimal RI yet stated that they had not rehearsed the material, three did *not* show higher performance following the intentional than the incidental Minimal RI trial, a finding that strengthens the evidence against a rehearsal account of the benefit of Minimal RI in at least these three patients.

It should also be noted that while the tone detection paradigm applied in the current study was attention demanding, pilot work on neurologically intact individuals demonstrated that verbal material could be rehearsed while doing the task. And indeed, some of the controls in the present study stated that they had rehearsed the story material while doing the tone detection task.

Thus, if patients had been very motivated to explicitly maintain the material during the delay intervals they should have been able to do so during both Minimal RI as well as tone detection. It could of course be argued that anterograde amnesiacs differ from neurologically intact individuals in their ability to rehearse and detect tones concurrently. If this were the case the patients in the current study may have been unable to do both tasks concurrently, thus leading to 0 proportion retention at delayed recall. However, if the present patients had indeed tried to rehearse the story material during tone detection, yet failed to do so due great difficulties in dual tasking, one would have expected the patients' tone detection performance to have suffered as a consequence.

However, as evinced by the analysis of the tone detection data, the patient sample and control sample did not differ in terms of their performance at the tone detection task.

Thus, it appears very unlikely that the highly detrimental effect of tone detection, and thus diversion RI, on memory in this patient sample could have been the sole consequence of a blocking of explicit STM rehearsal.
The issue of STM rehearsal will be returned to in Chapter 5 and 6.

4.2.4.2 Mental effort of tone detection stimuli itself?

While the detrimental effect of tone detection on memory in the present patient sample has so far been explained in terms of Müller and Pilzecker's (1900) 'mental effort', and thus diversion RI, there is the possibility that the tone detection stimuli per se, i.e. irrespective of the detection task, may have been sufficient to interfere with memory processing in the patients. Hence, it cannot be excluded that any RI, not only mental effort, had to be removed for these patients to show memory improvement. This possibility will be further examined in Experiment 2(b).

4.2.4.3 Control data

Turning to the control data of the present study, it was of interest that no detrimental effect of tone detection on proportion retention was elucidated in the present sample of neurologically intact controls. Indeed, given the findings of significantly lower delayed recall following tone detection than Minimal RI in the neurologically intact participants in Experiment 1, it was predicted that proportion retention would be slightly lower following tone detection than Minimal RI in the current sample of neurologically intact participants as well.

However, the lack of a detrimental effect of tone detection on retention in the present control sample does not necessarily conflict with the presence of such an effect in Experiment 1. Indeed, given the ceiling effect in proportion retention in the current control sample, it is possible that such effect simply did not show. It is possible for example that retention in both Delay Conditions was augmented in the control group by explicit rehearsal. Indeed the majority of controls stated that they had tried to rehearse the prose material occasionally during both Minimal RI and tone detection.

Moreover, it could also be postulated that at least some of the discrepancy in the findings between the current experiment and Experiment 1 could be explained by the difference in the type of to-be-retained material used in the two studies. Indeed, while to-be-retained material in Experiment 1 consisted of lists of unrelated words, the participants in the current experiment were asked to remember prose passages. It is plausible that the retention of prose material is easier than that of unrelated words, at least in neurologically intact individuals, so that diversion RI may not have any substantial effect on retention of such prose material. Thus, performance at delayed prose recall may not be greatly improved under conditions of Minimal RI due to ceiling effects in performance under conditions of RI.

In fact, some potential evidence for a greater RI effect on word list than prose retention in neurologically intact people can be gleaned from Cowan et al.'s (2004) control data: They found that controls' mean proportion retention of prose material dropped from 0.89 under conditions of Minimal RI to 0.79 under conditions of RI. In contrast, the same controls' mean proportion retention of word list material dropped from 0.74 under conditions of Minimal RI to 0.46 under conditions of RI.

It is thus possible that potential ceiling effects due to explicit rehearsal coupled with a lesser effect of RI on retention of prose material may have occluded the predicted detrimental effect of diversion RI on memory in the present control sample.

4.2.5 Conclusion

The results of the present Experiment elucidate that in eight patients who were able to retain some prose material following a Minimal RI delay interval, the interpolation of mental effort only (i.e. without any new modality specific or semantically meaningful material) was sufficient to lead to very poor delayed recall. These findings strongly suggest that at least some patients with anterograde amnesia are highly susceptible to *diversion RI*, i.e. the type of *non*-material–or-modality specific RI that appears to play a small, yet significant role in forgetting in the neurologically intact population.

Nonetheless, future research is necessary in order to establish whether all anterograde amnesiacs who are susceptible to RI present with a susceptibility to diversion RI or whether some may show more specific RI susceptibility, e.g. a susceptibility to modality specific RI. Furthermore, it remains to be established whether the detrimental effect on memory by tone detection is the product of mental effort (i.e. Müller and Pilzecker's (1900) definition of RI) or whether it may in fact be the consequence of the tone detection stimuli per se. The latter will be the focus of Experiment 2(b).

4.3 Experiment 2 (b)

4.3.1 Aims of Experiment 2 (b)

The previous Experiment *2(a)* was set up to examine whether or not a delay interval containing a solely mentally effortful task with no new modality-specific or meaningful material would lead to a lower proportion retention than a delay interval containing no RI in anterograde amnesiacs.

The aim of the present Experiment was to tease apart such mental effort and non-modality-specific and non-meaningful material in order to investigate whether a delay interval containing mental effort + non-modality-specific and non-meaningful material would lead to lower proportion retention than non-modality-specific and non-meaningful material only. Thus the question was whether only *mentally effortful* interpolated material/activity or *all* interpolated material/activity need to be removed during the delay interval for a benefit of Minimal RI to emerge in anterograde amnesiacs?

4.3.2 Method

4.3.2.1 Participants

The seven Italian anterograde amnesiacs (PE-PK; 4m/3f, mean age = 32.857, age range = 20 – 47; mean education = 11.43, education range = 8 – 16) and seven Italian age and education matched controls (CE-CK; 4m/3f, mean age = 33.43, age range = 21 – 46, mean education = 13.57, education range = 8 – 16) who took part in Experiment 2(a) also participated in the present Experiment.
The inclusion criteria for the present Experiment were the same as those indicated in Experiment 2(a). Please refer to Table 4.1b for selected characteristics of tests and amnesic patient performance.

4.3.2.2 Materials and Methods

The general method of the delay interval aspect of the current Experiment was based on a powerful tool designed by Watkins et al. (1973): Watkins et al. (1973) examined delayed recall of visually presented words in normals following a 20s delay in which tones had to be *attended to* and following a delay in which the very same tones could be *ignored*. They found that while there was a marked reduction in delayed recall when tones had to be attended to, no forgetting occurred in the control condition, in which the tones could be ignored.

In a highly similar fashion the delay intervals of the current Experiment either consisted of the *attending to* or *ignoring of* the tone detection stimuli. Hence the only difference between the two Delay Conditions was the presence or absence of mental effort.

All participants were presented with two prose passages verbally which they were asked to try and remember for subsequent immediate recall. The prose passages were taken from Italian prose memory tests (Spinnler and Tognoni, 1987; Novelli et al., 1986) (see Appendix C) and differed from the ones utilized in Experiment 2(a). As in Experiment 2(a) prose presentation was followed by free immediate recall in both trials. The end of immediate recall marked the start of a ten minute delay interval, which was always followed by delayed recall.

Trial 1 of the present Experiment mirrored Trials 2 and 4 of Experiment 2(a) with the exception that the participants were told to simply rest and ignore the presented material (i.e. the tone detection material). The pc mouse was removed during this trial so that participants would not try to respond to the tones.
Trial 2 of the present Experiment mirrored Trials 2 and 4 of Experiment 2(a) completely. Thus participants were asked to attend to the sound track, listen out for the piano notes and indicate detection of the notes by clicking the left mouse button.

4.3.2.3 Counterbalancing

In line with the counterbalancing of Experiment 2(a), participants presented with prose 'A' in Trial 1 of Experiment 2(a) were presented with prose '1' in Trial 1 of Experiment 2(b) and prose '2' in trial 2 of Experiment 2(b). Those participants presented with prose 'B' in trial '1' of Experiment 2(a) were presented with prose '2' in trial '1' of Experiment 2(b) and prose '1' in trial 2 of Experiment 2(b).

4.3.3 Results

Figures 4.11 to 4.14 depict proportion retention (number of prose ideas recalled/total number of prose ideas within presented prose) at delayed and immediate recall of the 'ignore' and the 'attend' trials for the two groups separately.

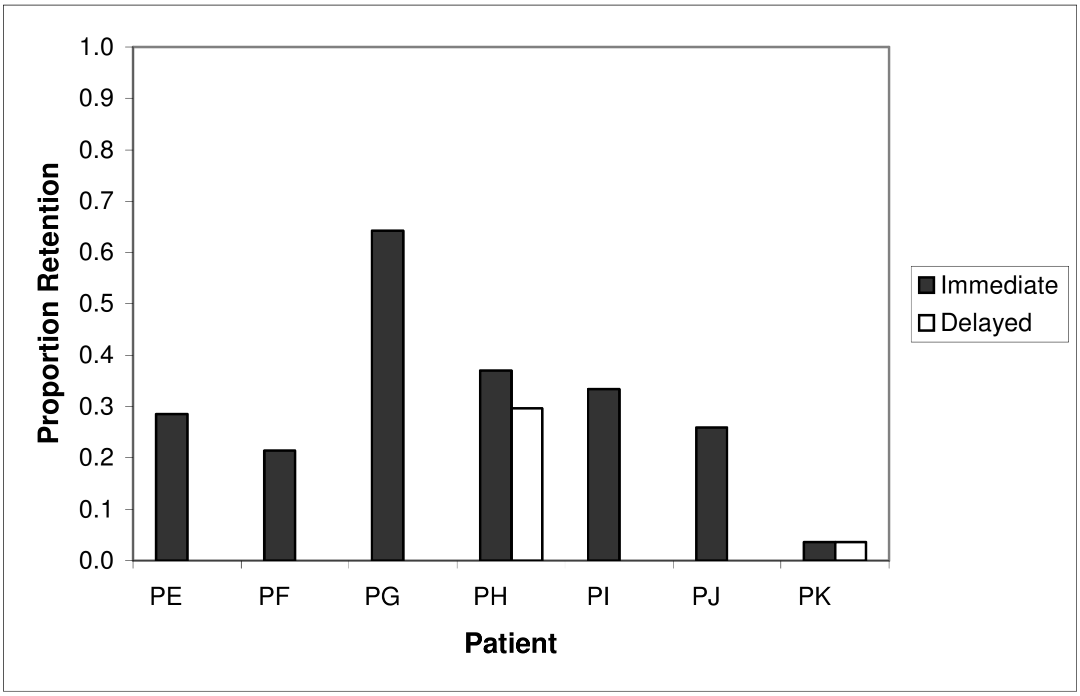


Figure 4.11. Patient proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the 'attend' condition.

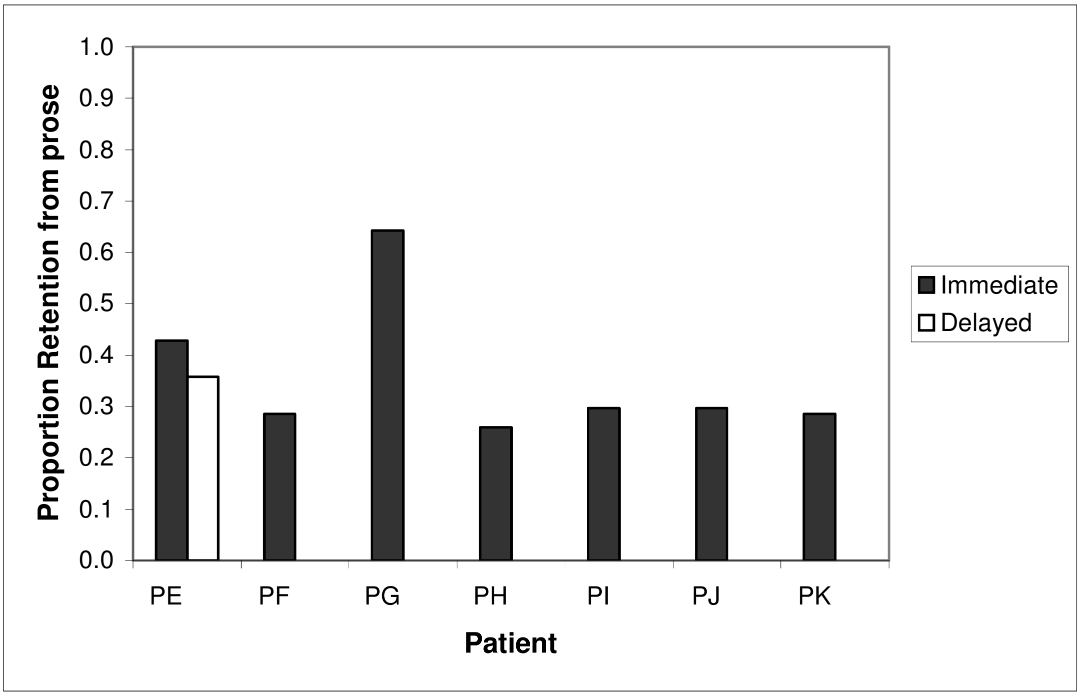


Figure 4.12. Patient proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the 'ignore' condition.

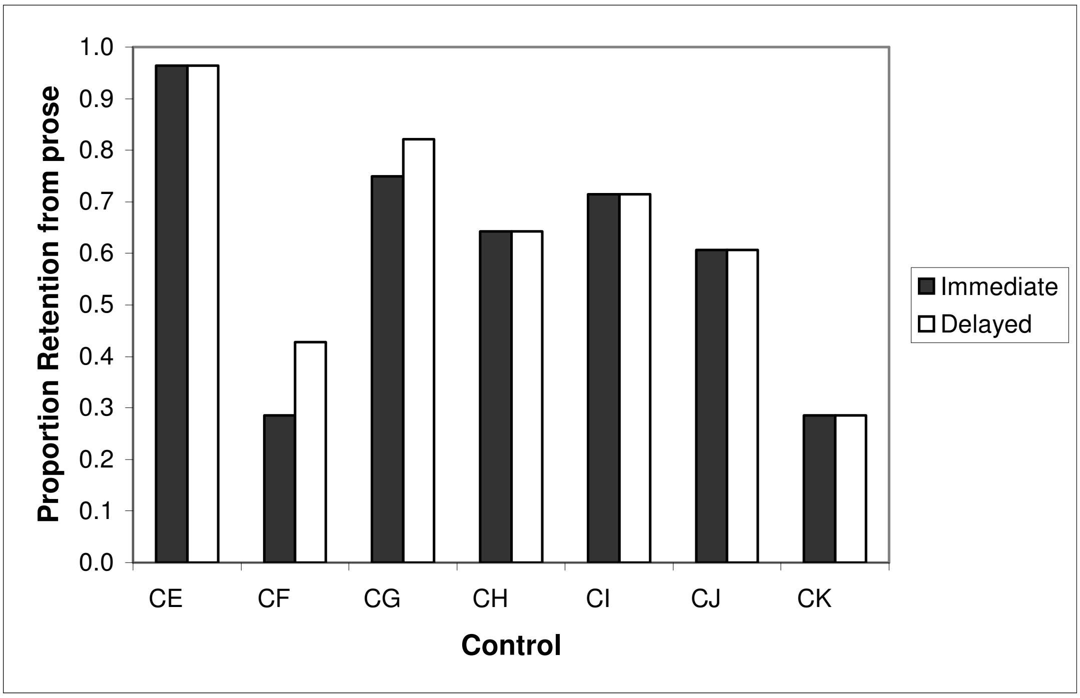


Figure 4.13. Control proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the 'attend' condition.

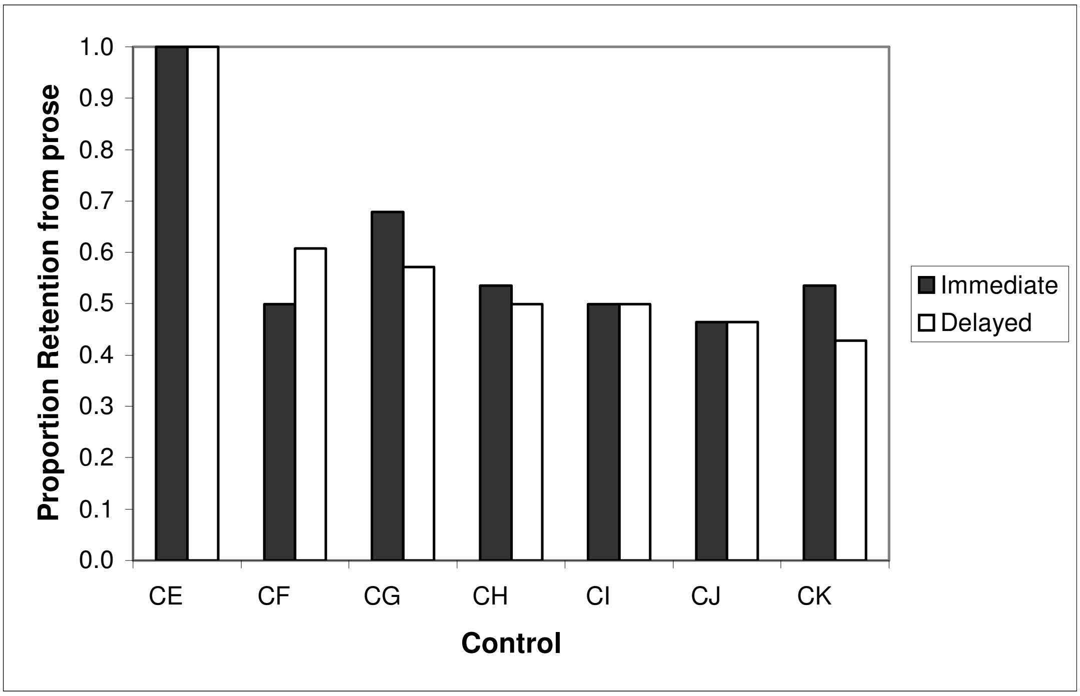


Figure 4.14. Control proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall and delayed recall in the 'ignore' condition.

A mixed factors ANOVA on proportion correct immediate recall with within subjects factor Delay Condition ('ignore' vs. 'attend') and between subjects factor Group (Patients vs. Controls) was initially run to assess the state of memory before a delay was imposed. The ANOVA revealed that proportion correct immediate recall did not differ significantly across the two conditions for either group. However, a main effect of Group was obtained, with the control group performing significantly better at immediate recall than the patient group, $F(1, 12) = 8.289$, $p < 0.05$. Group mean immediate proportion correct and SD was 0.331 (0.151) and 0.605 (0.0.2) for the patients and the controls respectively. No Delay Condition x Group interaction was found.

As in Experiment 2(a) and the previous studies on RI in amnesia (Della Sala et al., 2005; Cowan et al. 2004) retention at delayed recall was measured as the number of correct words recalled at delayed recall divided by the number of correct words recalled at immediate recall in the same condition (i.e. Delayed Recall/Immediate Recall; DR/IR).

A mixed factors ANOVA with within subjects factor Delay Condition (ignore vs. attend) and between subjects factor Group (Patients vs. Controls) was subsequently run on these retention scores. The only significant effect to be revealed in this ANOVA was a significant Group main effects, $F(1, 12) = 73.968$, $p < 0.001$, which was the product of a greatly higher retention score in the controls than the patients.

Group means and SEMs are depicted in Figure 4.15 below.

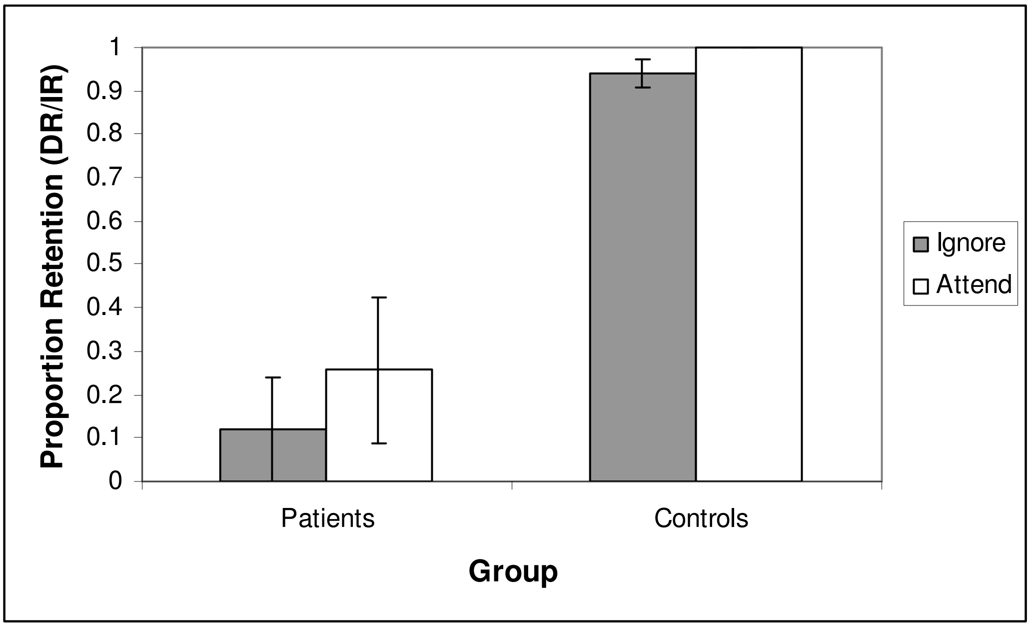


Figure 4.15. Mean Group proportion retention of story material (Delayed Recall/Immediate Recall) following the ‘attend’ and ‘ignore’ conditions.

4.3.4 Discussion

As a whole the results of the present study do not provide any evidence for a *mental effort* hypothesis of RI susceptibility in anterograde amnesiacs. Thus, overall the data tentatively suggests that all material, whether attended to or not must be removed for patients to benefit from Minimal RI, and hence that such patients may be susceptible to *any* RI. Indeed it appears that only PE showed the pattern that would be expected if the benefit of Minimal RI were due to the absence of mental effort in such patient group. Indeed, none of the other three patients who had benefited from Minimal RI in Experiment 2(a) (i.e. PG, PH and PI) showed any retention following the delay in which tones were to be ignored. In fact one patient, PH, actually showed somewhat large retention following the attend condition while scoring 0 in the ignore condition. It was also rather unexpected that Patient PK, who had not benefited from Minimal RI in Experiment 2 (a), should show any retention following the attend condition in Experiment 2(b).

Overall such tentative findings are relevant with respect to Müller and Pilzecker's (1900) definition of RI in terms of *mental effort* as well as our (Dewar et al., in press) term *'diversion RI'*. If such patients are indeed susceptible to all RI, as opposed to mental effort and hence *diversion* RI, the definition of the non-material specific RI examined and discussed in this thesis may need to be revised in the future. Thus, it may be the case that any information that is encoded following encoding of to-be-retained material has a disruptive effect on the latter, whether such information requires conscious mental effort or not. Indeed it is likely that the encoding and processing of any new information will require some degree of mental effort even if it is not embedded within an explicitly mentally effortful task.

However, prior to considering revision of the definition of RI, it is important to examine a number of potential factors and limitations that may have affected and complicated the results and their interpretation somewhat.

Firstly, with respect to the lack of retention following the ignore condition in patients PG, PH and PI (i.e. those patients who had benefited from Minimal RI in Experiment 2(a)) it is important to note that the instructions to rest and *ignore* the tones may not have necessarily been followed. Hence, it is possible that at least some of these patients may have nevertheless attended to the piano notes. Indeed, the explicit instructions to 'ignore' the notes may have led to an opposite effect akin to the classical thought suppression findings by Wegner et al. (1987). Wegner et al. (1987) elucidated that the instruction *not* to think of a white bear actually resulted in neurologically intact participants thinking of a white bear on numerous occasions during a five minute interval. Hence, the instructions to ignore the piano notes may have in actual fact resulted in the patients attending to the notes. While post experimental feedback on activities undertaken during the ignore condition revealed no attending to the tones in such patients, it is plausible that these severely amnesia patients did not remember what they had done during this interval. Two of the patients who did not benefit during Minimal RI in Experiment 2(a) or the ignore condition revealed during post experimental debriefing that they had found the ignore task difficult. In fact they rated this task as being more difficult than the detection of tones. Patient PF stated for example that it was 'impossible' to ignore the tones and that she hence attended to them. Moreover, it was noticed that patient PJ actually tapped the table with his index finger on frequent occasions during the ignore condition, which suggested that he was listening out for the notes and responding to them in a way that reflected the previous tone detection trials of Experiment 2(a). Indeed, following the 10 minute ignore interval patient PJ told the Experimenter the number of notes he had heard in the sound track. While no such behaviour or feedback was obtained from patients PG, PH and PI it is nevertheless possible that they, too, attended to the tones on at least some occasions.

Furthermore it is possible that the patients who had already partaken in the four trials of Experiment 2(a) as well as a further trial (to be reported in Chapter 5) were fatigued during Experiment 2(b). Any such fatigue may have augmented a difficulty in ignoring the notes or it may have simply lowered their performance irrespective of the instructions given.

Moreover, the conducting of Experiment 2(b) on the same day as Experiment 2(a) (in order to avoid multiple hospital visits for the patients) of course also limited the number of trials that could be run without over taxing the patients. Thus, only one trial could be run per condition which, coupled with the aforementioned potential limitations of this experiment may not have sufficed to provide sound and generalizable data regarding the question posed.

Such limitations of the present study highlight that future research of this type is necessary in order to provide conclusive evidence regarding the specific requirements (i.e. removal of mental effort or all RI) for a benefit to emerge in patients with anterograde amnesia. A potential study could replicate the present experiment as a stand-alone experiment, i.e. with no prior trials. The first Delay Condition, the ignore condition, would thus be the first condition encountered by the patients. This would mean that the patients would (a) not be fatigued and (b) not have any explicit or implicit memories of having to respond or attend to the notes. By presenting the ignore condition as the first condition during patient testing one could also avoid the need to instruct the patients to 'ignore' the tones. Thus, one could simply tell the patients that they would be asked to rest and that they would be given headphones playing back relaxing noise. In the second trial the patients would then be asked to attend to the notes as in the present experiment. Multiple trials of each condition would also be advantageous.

Replication of the present tentative findings of no retention following the ignore condition in anterograde amnesiacs who benefit from removal of all RI, would provide strong evidence that indeed removal of all RI may be necessary for such benefit of Minimal RI to emerge and thus that the patient's susceptibility encompasses not only mental effort, but all RI. However, without such further research the present findings can be treated as tentative only.

It is also important to note that revision of the *overall* definition of RI would also require findings of a lower proportion retention following the ignore condition than the Minimal RI Condition in neurologically intact individuals. Given the ceiling effect of the present control sample, no such inferences can be made via the current study. Thus, future research will also need to focus on such question in the neurologically intact population.

Even if *any* new material has a disruptive effect on memory processing in some anterograde amnesiacs (and neurologically intact individuals) it remains to be explained how two patients (PH and PK) were able to retain material following the attend condition even though they had not shown any such retention following tone detection in Experiment 2(a). Indeed, as reported in Experiment 2(a), PH in fact could not remember having been presented with a prose passage when asked to recount this after tone detection in Experiment 2(a).

It appears that PH’s retention following the attend condition in the present experiment could have been the product of previous presentations of that particular story: As the story was being read out to him, PH stated that he already knew this story and also that he knew a girl with the same name as the main protagonist (‘Anna Pesenti’).

Following the Experiment he explained that he remembered the story from multiple previous testing session and hence that remembering the story was easy for him. He did state however that he did not know how he could remember the story from previous testing. Thus, given this patient’s 0 retention in the tone detection trials in Experiment 2(a) it is highly probable that PH would not have shown any retention following tone detection in Experiment 2(b) if a different story had been used. Nevertheless the fact that he did remember this story from previous testing cannot be ignored. Indeed, given his severe amnesia such retention from a previous testing session was somewhat remarkable.

With respect to patient PK’s retention following the attend condition, it should be noted that while PK showed a retention score of 1 following tone detection, this retention was based on one single idea being recalled at immediate recall and delayed recall. Moreover she recalled ‘un uomo’ (‘a man’), which had indeed occurred in the prose presented to her prior to the attend delay interval. However, she had already recalled ‘un uomo’ at immediate recall in two prior trials (Experiment 2(a)), in which the stories’ lead protagonist was a man. It is thus possible that she simply remembered ‘un uomo’ from such previous Minimal RI trials. Thus while it cannot be excluded that patient PK was able to retain one idea from the tone detection story, it is important to take note of such alternative explanation for her perfect retention following tone detection, which obviously had a large effect on the group mean.

4.3.5 Conclusion

The results of the present Experiment provide very tentative evidence that all RI, as opposed to mental effort (only) has to be removed for a benefit of Minimal RI to emerge in at least some patients with anterograde amnesia.

Thus, it appears that the susceptibility to RI in some patients with anterograde amnesia may embody a susceptibility to *all* new encoded information as opposed to mental effort (only), meaning that the original definition of RI (Müller and Pizecker, 1900) may need to be revised in order to encompass ‘any new information’.

However, several limitations of the present experiment render such conclusions highly tentative at present. Future research on both anterograde amnesiacs as well as neurologically intact individuals is thus necessary in order to demonstrate whether or not such tentative findings and conclusions can be sustained.

Chapter 5: Cognitive Processes underlying the benefit of Minimal Retroactive Interference - Amnesic brain injury patients (1)

5.1 Introduction[5]

The aforementioned studies on diversion RI and forgetting suggest that both neurologically intact people as well as at least some anterograde amnesiacs perform better at delayed recall of to-be-retained material when the delay interval is unfilled (i.e. Minimal RI) than when it is filled with non-similar, yet mentally effortful and thus diversion RI-inducing material. Thus, both populations appear to show a *benefit of Minimal RI*.

However, the *cognitive processes* that underlie such *benefit of Minimal RI* remain to be established.

The possibilities that will be discussed and investigated subsequently are as follows:

(1) Minimizing RI may allow the information to persist in some sort of short-term memory. It could be the conventional time-limited concept of short-term memory (Baddeley and Hitch, 1974; Baddeley, 1986), or it could be the focus of attention (Cowan, 2001), or it could be memory for the most recent items, (2) Minimizing RI may allow the material to be consolidated better in long-term memory, (3) Minimizing RI may allow the material to be retrieved better from long-term memory because of an absence of RI material competing for retrieval with the to-be-retrieved stimuli.

[5] This chapter introduction has largely been taken from Dewar et al., (in press).
A published conference abstract on the chapter introduction also exists: Dewar, M.T., Della Sala, S. & Cowan, N. (2006). Forgetting due to retroactive interference: A fuse of Müller and Pilzecker's (1900) early insights into forgetting and recent research on anterograde amnesia. Abstract of paper presented at the 16th annual meeting of Theoretical & Experimental Neuropsychology (TENNET 16). Symposium IV – History of memory. *Brain and Cognition*, *60*, 333-334.

5.1.1 Uninterrupted short-term memory maintenance?

The benefit of Minimal RI could underlie uninterrupted short-term memory maintenance of the to-be-retained stimuli either within a time-or a capacity limited short-term mechanism. These two possibilities will be discussed separately.

5.1.1.1 'Uninterrupted' rehearsal within time limited Working Memory?

An obvious candidate for increased delayed recall following an unfilled interval is conscious rehearsal of the to-be-retained material within working memory (Logie and D'Esposito, 2007). Hence, neurologically intact participants and anterograde amnesia patients alike could in theory consciously rehearse the to-be-retained information during the unfilled delay (Scoville and Milner, 1957; Milner, 1968; Odgen, 1996). There is however a large pool of evidence against this working memory rehearsal alternative.

Neurologically intact population

With respect to the neurologically intact population it is important to go back to Müller and Pilzecker's (1900) pioneer research. In their conclusions on RI Müller and Pilzecker (1900) argue that the effects of RI could not have emerged as a consequence of the participants not being able to think of the stimuli. They draw evidence from the fact that participants rarely reported appearance of the stimuli in consciousness. Furthermore they stated that RI was also found when using the savings method and that appearance of stimuli in consciousness would not lead to any beneficial effect when using such a method. Indeed the participants in these experiments (Experiments 36 and 37) were asked to learn list 1, which was followed by a rest period of four minutes. The participant was subsequently presented with list 2, which was immediately followed by another list. This sequence was then repeated. Subsequently the participant rested for 10 minutes prior to relearning list 1 and list 2 (errorless). Less repetitions were required for list 1 than list 2. Müller and Pilzecker

(1900) state that such benefit cannot have emerged due to rehearsal as any rehearsal of list 1 would have been followed by further trials before relearning.

Further evidence against a rehearsal account comes from Skaggs (1925) who was also very aware of such alternative explanation as can be gleaned from his comment: *'It may be claimed that the advantage of the rest interval lay in the very fact, namely, that during the rest the subject repeated the learning whereas during the work he could not. The point is a very crucial one'* (p.13). However, Skaggs (1925) tested both naïve participants as well as a small group of participants who had been trained *'in the art of giving keen and thorough introspections and were able to adjust themselves to the conditions of the experiment'* (p.1). In order to tackle the rehearsal hypothesis Skaggs (1925) considered the data of the trained participants and analysed only the trials from those rest intervals that *'were free from any consciousness of the original learning, with the exception of a short after-image which was always present'* (p.13). The results were in line with his previous findings of a substantial benefit of Minimal RI therefore providing further evidence that the difference in recall between the filled and unfilled conditions cannot be attributed to conscious rehearsal of the material during the delay period.

It should be noted that the majority of neurologically intact controls in Experiment 2(a) (see Table 4.2) reported to have attempted to rehearse the presented story material at some points during the Minimal RI (as well as some of the RI) delay intervals. Although, given the ceiling effects in the control sample's proportion retention in both the Minimal RI and RI Conditions, and hence no elucidation of a benefit of Minimal RI, it cannot be inferred to what extent such rehearsal may have aided retention at delayed recall. However, comparison of the controls who did and did not rehearse the prose material during the delay intervals shows no differences in proportion retention. Such lack of difference in retention in turn suggests that it is unlikely that prose retention was substantially enhanced by rehearsal in the controls in Experiment 2(a).

Overall then, there appears to be little evidence for an explicit rehearsal account of the benefit of Minimal RI in the neurologically intact population.

Turning to the amnesic group (i.e. Cowan et al., 2004; Della Sala et al., 2005; Experiment 2(a)), there are three main sources of evidence that speak against the conscious rehearsal account: Firstly the initial delayed recall came as surprise, meaning that participants had little if no incentive to consciously rehearse the material for up to an hour, yet did not lead to poorer recall than later trials. Furthermore, the to-be-retained information in Della Sala et al.'s (2005) study, Cowan et al.'s (2004) second experiment as well as Experiment 2(a) was a prose passage consisting of a much larger quantity of information than can be rehearsed within the traditional time limited working memory. If rehearsal were the only cognitive process underlying the benefit, patients should have only recalled as much information as can be actively rehearsed in working memory. Finally, two patients in the study by Cowan et al. (2004) were observed to be sleeping (identified by loud snoring, a state in which conscious rehearsal would be carried out with some difficulty) during some hour-long retention intervals with minimal interference, yet benefited from minimal interference as much as on other trials, and as much as other patients did.

5.1.1.2 'Uninterrupted' Capacity limited short-term retention?

There is the possibility of a short-term memory mechanism that can hold only a small amount of information, which is displaced by subsequent stimulus inputs, or even by the retrieval of competing thoughts (Baddeley, 2001; Cowan, 2001).

Cowan (2001) suggested that this type of information storage occurred in the focus of attention, and Baddeley (2000, 2001) has not clearly addressed the attention requirements of the mechanism of this type he introduced, the 'episodic buffer'.

Neurologically intact population

As discussed above there is strong evidence that improvement in delayed recall following Minimal RI is not dependent upon constant attention towards the to-be-retained material in neurologically intact participants (c.f. Müller and Pilzecker, 1900; Skaggs, 1925). Hence, if such improvement in this population did underlie the workings of a capacity limited short-term store, such store would have to be in the form of a mechanism independent from attention during retention, which would conflict with the theoretical mechanism that Cowan (2001) suggested for limited-capacity storage.

Moreover, while the inclusion of RI does lead to a decrease in delayed recall in the neurologically intact population, performance does not drop to floor as is the case with the amnesiacs. As to-be-retained material would be displaced by RI if it were retained within a capacity limited short-term store, it is unlikely that such mechanism can account for the retention of the to-be-retained material in the RI Condition. While in turn it is theoretically possible that the improved retention following *Minimal* RI could underlie a capacity-limited short-term store (which would have to be independent from attention), it appears much more plausible that such Minimal RI retention would underlie the same mechanism as does retention following RI.

Anterograde amnesiacs

It appears that the amnesiacs who benefited from Minimal RI were able to do so without having to attend to the to-be-retained material (i.e. during 'surprise' and 'sleep'). As already discussed with respect to the neurologically intact population such finding is at odds with the capacity limited short-term retention mechanism proposed by Cowan (2001).

It is possible that information is maintained within a temporary retention buffer that requires attention for the entry of information, but not for its maintenance.

Therefore, once within the buffer, information would be maintained automatically without the need for attention until distracting material or tasks (i.e. RI) entered the buffer. The benefit would therefore occur due to a lack of displacing material entering such temporary retention buffer.

Evidence for the existence of such buffer would indeed be highly interesting as the period of temporary retention of information, up to an hour or more, is far beyond what has been proposed previously for temporary memory storage mechanisms.

5.1.2 Uninterrupted long-term memory consolidation?

Neurologically intact population

As discussed in Chapter 2, Müller and Pilzecker (1900) proposed that the unfilled period allowed uninterrupted consolidation to take place in neurologically intact people. Evidence for this account comes from their own and Skaggs' (1925) findings of better recall following late onset RI than immediate onset RI. In line with such evidence Wixted (2004) theorises that resources are limited and that new learning requires resources that are simultaneously required by the *consolidation* of the to-be-retained material. Further evidence for an uninterrupted consolidation hypothesis of the benefit of Minimal RI in neurologically intact individuals can be gleaned from the contemporary neuroscience literature (c.f. Dudai, 2004), which is reviewed in brief in Chapter 1.

In light of the above evidence and theories it seems highly probable that uninterrupted *consolidation* is a key candidate for explaining the benefit of Minimal RI in neurologically intact people.

Anterograde amnesia patients

As already hypothesized in more detail in Chapter 1, it is possible that Minimal RI may also lead to some uninterrupted *consolidation* in at least some patients with anterograde amnesia. It may for example be postulated that under conditions of RI, the (possibly impaired) consolidation system is overloaded, resulting in the prevention of consolidation of the materials to be remembered. In the absence of RI, though, this might not be a problem; the consolidation mechanism might then be able to successfully retain and process the material presented last, except perhaps in patients with sufficiently severe damage to such mechanism.

5.1.3 Uninterrupted retrieval?

Neurologically intact population

Some researchers argue that interference-induced forgetting occurs during retrieval of to-be-retained information (e.g. McGeoch and Nolen, 1933; Anderson and Bjork, 1994; Anderson, 2003). However it appears that similarity in to-be-retained and interpolated materials is a prerequisite for RI to occur at retrieval. Hence, it is assumed that similarity in material (Skaggs, 1933; McGeoch and Nolen, 1933) as well as similarity in retrieval cues, such as explicit retrieval cues (i.e. 'A' in A-B, A-C paradigms) and contextual cues (Mensink & Raajmakers, 1988; Anderson and Bjork, 1994) all render the to-be-retained and interpolated material highly similar, thus leading to competition for retrieval when the participant is asked to recall the to-be-retained material. Minimal RI should hence lead to a lack of other items competing for retrieval and therefore to improved recall of the to-be-retained material.

While 'uninterrupted' retrieval is likely to account for the 'benefit' of Minimal *similarity* RI (i.e. higher delayed recall following mental effort than similar material, c.f. McGeoch and McDonald 1931; Robinson,1920; Dey, 1969; Skaggs, 1925), it is unlikely to account for any further improvement caused by Minimal RI (i.e. the benefit of Minimal *diversion RI* found by Müller and Pizecker, 1900, Skaggs, 1925 and elucidated in Experiment 1) as neither Minimal RI nor mental effort contain material that is similar to the to-be-retained material.

It is nevertheless possible that diversion RI may interfere at retrieval due to becoming associated with the retrieval context of the to-be-retained material. However it is highly unlikely that such factor could account for all of the difference in delayed recall following Minimal RI and diversion RI. Tone detection, for example, contains no similar or even meaningful material. Hence the retrieval context could only cue a more general memory of the task itself. While such memory may compete for retrieval with the to-be-retained material to some extent, the Experimenter's request for the participant to recall the previous world list should provide stronger retrieval cues for the to-be-retained material than any memories of tone detection. Thus, it appears somewhat unlikely that the observed drop in delayed recall following tone detection can be solely accounted for by such contextual effects.

This prediction is supported by Watkins et al. (1973) who elucidated that delayed recall was much poorer when tones presented during the delay had to be attended to than when they could be ignored, demonstrating that after any effects of the actual interference stimuli and their associations with the retrieval context have been accounted for, mental effort still leads to a reduction in delayed recall (note that due to the ceiling effects obtained in both the ignore and attend to tones conditions in the controls in Experiment 2(b), no such argument can be made for the neurologically intact participants tested in the present research). Hence, while minimising similarity RI (including any items forming associations with the retrieval context of the to-be-retained material) and thus interference at retrieval undoubtedly aids memory in neurologically intact people, it cannot wholly explain the benefit of Minimal RI relative to diversion RI elucidated in the above reported diversion RI studies. Further research is required to examine the relative benefits gained by minimising similarity RI and diversion RI.

Anterograde amnesia patients

A similar argument can be raised for the anterograde amnesia group tested by Cowan et al. (2004), Della Sala et al. (2005) and in Experiment 2(a). Indeed, it appears highly unlikely that the benefit of minimal interference in such patients was solely due to a lack of similar material. If this were the case the patients should have benefited following the interpolated intervals as well, as these did not contain any material that was highly similar in content to the to-be-retained stimuli. Indeed, the RI delay interval in Experiment 2(a) (i.e. tone detection) did not even contain any new modality specific or even semantically meaningful material. However no such 'benefit' of Minimal material specific RI was observed which leaves little evidence for a retrieval account of the benefit seen in the patients. It is possible that some of the benefit could have resulted from a lack of additional material associated with the retrieval context. Nonetheless, it is very unlikely that such factor could explain all or a large part of the benefit of Minimal diversion RI as this would imply a large susceptibility to interference at retrieval by items cued by the same contextual retrieval cues as to-be-retained material. However such deficit would mean (a) that memory should be intact for materials with contextual retrieval cues not shared by other items and (b) that the presence of such a specific context-related retrieval deficit should also manifest itself in retrieval of retrograde memory. However the patients benefiting from Minimal RI in the studies by Cowan et al. (2004), Della Sala et al. (2005) as well as in Experiment 2(a) had global anterograde amnesia with spared remote retrograde memory (i.e. only a the most recent premorbid retrograde memory was impaired).

In light of the above discussion it appears somewhat unlikely that the referred-to amnesiacs showed a specific susceptibility to interference at retrieval and therefore that their 'benefit' could be traced back to 'uninterrupted' retrieval processes. However, additional work is under way to test such hypothesis more thoroughly.

5.1.4 Further experimental examination of the cognitive process(es) underlying the benefit of Minimal RI in amnesic brain injury patients

The above discussion of the various potential cognitive processes that may underlie the benefit of Minimal RI in some patients with anterograde amnesia, suggests that the most likely candidates for the benefit of Minimal RI are either uninterrupted maintenance within a *capacity limited buffer* that does *not* require attention for such maintenance and retains to-be-remembered information until such is *displaced by* further incoming material, or *uninterrupted consolidation*. It is thus of great interest to examine these two possibilities further. Nonetheless, it is important to underline that the other discussed STM accounts cannot be fully excluded at this stage.

Thus in order to examine and tease apart these various potential cognitive processes underlying the benefit of Minimal RI, a series of experiments was set up and run. These shall be reported in the present chapter (Amnesic brain injury patients) as well as in Chapter 6 (aMCI).

5.2 Experiment 3 – Case study 1: Apparent LTM consolidation in an anterograde amnesiac following Minimal RI

5.2.1 Introduction

In view of the aforementioned potential cognitive processes underlying the benefit of Minimal RI in anterograde amnesiacs it was hypothesized that if the improvement in retention following Minimal RI were the product of uninterrupted STM maintenance (time limited or capacity limited), the benefit of Minimal RI should be very short lived.

Thus one would predict that any material retained following Minimal RI would fall prey to the time-or-capacity limits of such STM *as soon* as RI occurred. On the other hand, it was predicted that if the improvement in retention following Minimal RI were the product of some uninterrupted LTM consolidation, at least some of the material retained *following* Minimal RI may continue to be retained even after emergence of subsequent post Minimal RI interference. Hence in line with Müller and Pilzecker's (1900) original hypothesis of Minimal RI in neurologically intact individuals as well as contemporary neuroscience theories of consolidation, it was postulated that in some anterograde amnesiacs the to-be-retained material may become sufficiently strengthened during Minimal RI for it to be less vulnerable to subsequent RI.

5.2.2 Aims of Experiment 3

The aims of Experiment 3 were thus to investigate in a single case study whether post Minimal RI retention would persist at least to some extent following the emergence of post Minimal RI interference or whether retention would drop to floor once such post Minimal RI interference occurred.

5.2.3 Case description

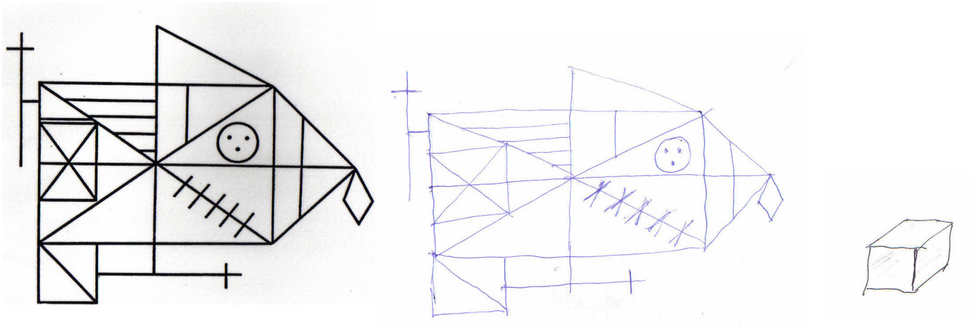
PB (who participated in Experiment 2(a)), a 72 year old male retired University educated senior schoolteacher (science) first presented with a sudden onset of dense anterograde amnesia in 2003 and was subsequently diagnosed with limbic encephalitis. His anterograde amnesia has persisted to this day and is very severe. Indeed, he appears to forget information within minutes or seconds. For example, he could not recall how or even that he had traveled to the hospital shortly after arriving on the ward for neuropsychological testing. As a second example, only minutes after saying good bye to a close family friend from abroad, PB had no recollection that this friend had been visiting him and his wife for the last several days.

PB also shows some recent premorbid retrograde amnesia, which extends back to approximately 10 years prior to the onset of his anterograde amnesia. For example, he looked for his daughter in the house she had been living in 10 years prior to onset of his illness. Moreover, while he is now retired, PB still talks about his job as a teacher as if he were still working.

5.2.4 Neuropsychological Profile

PB underwent a thorough neuropsychological assessment prior to experimental testing which provided objective evidence of a dense anterograde amnesia: He showed a below-cut off score in the Selective Verbal Learning Test including delayed recall (Buschke, 1975) a below-cut off score in the WMS-III paired associative learning test including delayed recall (Wechsler, 1997), and a below-cut off score in the Rey Osterrieth Figure delayed recall (Caffara et al. 2002). In fact BP could not remember having copied a figure previously and produced a picture of a box when asked to guess (see Figure 5.1). When shown his own previously copied version of the Figure subsequently in order to examine whether he would be able to recognize it, he had no recollection of the Figure or having copied it.

In contrast to his severe LTM deficit PB showed above-cut off scores in the WMS-III digit span (Wechsler, 1997) and the WMS-III spatial span. Moreover, PB did not manifest any language problems as evidenced by the Frenchay Aphasia Screening Test (FAST) (Enderby et al., 1987). Moreover his ability to carry out simple verbal commands in the FAST (e.g. 'Before pointing to the duck near the bridge, show me the middle hill') indicated no semantic STM loss. PB showed no apparent attentional problems as shown by Raven's Progressive Matrices (Raven, 1996). Furthermore PB scored above cut-off in the Rey Osterrieth Figure copy (Caffara et al., 2002) (see Figure 5.1). He showed no deficits in verbal reasoning as evinced by an above cut-off score on the WAIS-III similarities (Wechsler, 1997). The Modified Card Sorting Task (Nelson, 1976) was also administered in order to further assess PB's executive functioning but could not be undertaken properly due to the patient's severe amnesia. His trail making score for part B and B-A were 402s and 271s respectively, tentatively showing some potential executive difficulties. His scores can be found in Table 4.1a (PB).



Original Figure — PB's copy — PB's 30 min delayed recall (when asked to guess)

Figure 5.1 PB's Rey Osterrieth Figure Copy and Delayed Recall

5.2.5 Neuropathology

PB's MRI scan (see Figures 5.2a and 5.2b below) undertaken approximately 9 months following the current Experiment showed some focal abnormalities: There was mild diffuse cerebral volume loss and some volume loss of the medial temporal lobes and hippocampi bilaterally with subtle increased signal in the hippocampi on FLAIR sequences. There was also mild white matter microvascular disease.

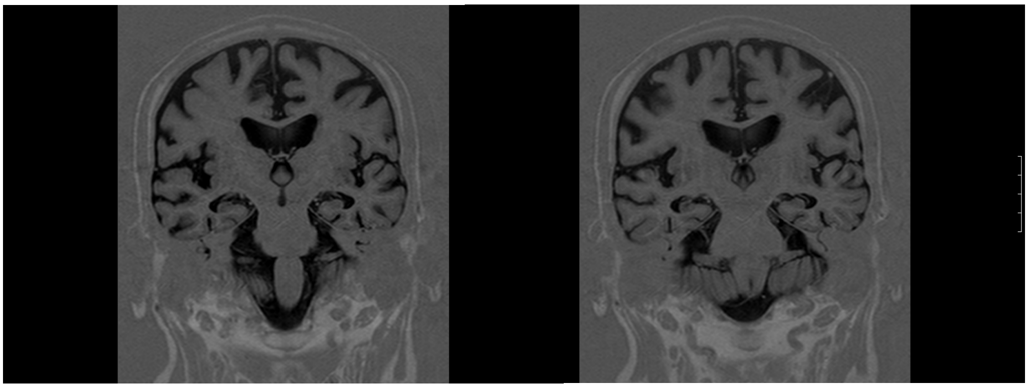


Figure 5.2a. MRI scan (coronal T1) of PB's brain.

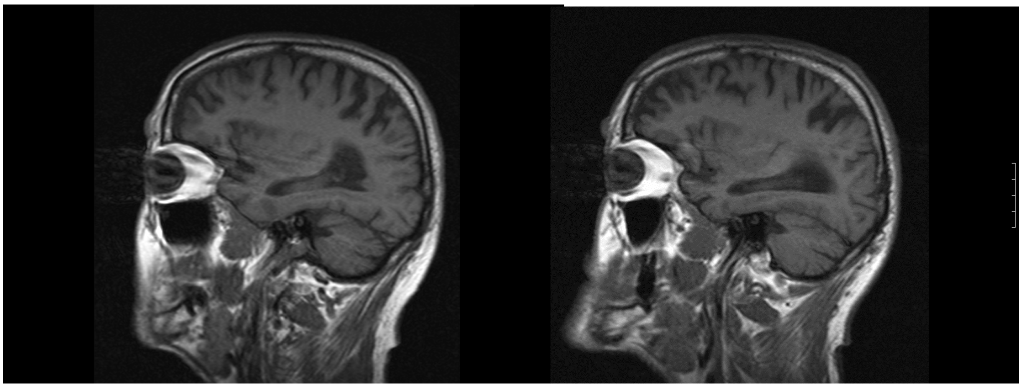


Figure 5.2b. MRI scan (saggital T1) of PB's brain.

5.2.6 Methods and results

Experiment 3 was an extension of Experiment 2(a), which is fully outlined in Chapter 4. The study was undertaken in a quiet room at the Department of Clinical Neurosciences, Western General Hospital, Edinburgh, Scotland. The last Minimal RI trial of Experiment 2(a) formed the first part of Experiment 3. Thus the patient was verbally presented with a story taken from the Rivermead Behavioural Memory Test (Story A) and asked to remember as many of the details as possible for subsequent immediate recall. It should be noted that this trial had already been undertaken once before (as trial 1 of Experiment 2(a)) but had to be repeated at the end of Experiment 2(a) due to Hospital equipment problems during the Minimal RI delay (Patient PB was receiving intravenous therapy at the time of testing). However, PB did not remember that this story had been read out to him during the previous trial.

The story presented to PB in this trial was the following:

Mr Brian Kelly a security Express Employee was shot dead on Monday during a bank raid in Brighton. The four raiders all wore masks and one carried a sawn-off shotgun. Police detectives were sifting through eye-witness accounts last night. A police spokesman said 'He was a very brave man. He went for the armed raider and put up a hell of a fight.'

Immediately following prose presentation PB was asked to recall as much as he could from the prose passage. The patient was then asked to rest alone in the darkened quiet room for a duration of ten minutes. As for previous Minimal RI Conditions the procedure was set to involve the Experimenter returning to the room and asking the patient to recall as much as he could from the previously read out story. However as the Experimenter opened the door to reenter the room PB laughed and showed seeming familiarity of the Experimenter. Such was in stark contrast to the RI-filled delay intervals, after which PB showed no apparent recognition of the Experimenter.

Rather than simply asking PB to try and recall the prose (as done in Experiment 2(a)), it was decided to explore whether or not PB had any idea as to why the Experimenter had entered the room.

As elucidated by the original transcript of this particular part of the experiment provided below, PB showed some remarkable insight into why the Experimenter had entered the room (E = Experimenter, PB = patient):

E: *So what do you think I'm going to ask you now?*
PB: *I' m not sure but I'm assuming that you are going to ask me to do a certain summary of what you allowed me to read about Mr Kelly and his work in the bank and all that sort of thing.*

PB was then asked to recall as many other details as he could from the prose.

<u>Delayed Recall 1 (including the correct details above)</u>

PB: *Well, this gentleman he must have obviously been employed in some security capacity I think but eh obviously he was able to eh…see off a few people who might have been considered as being criminals, about to raid the bank…and eh that's the summary of what I remember but whether it's even in the slightest way accurate I wouldn't know.*

Following such delayed recall of the story (proportion retention = 0.66 where proportion retention = Delayed recall/Immediate recall), the patient was given a short conversation filled break (RI) (approximately 2- 3 minutes) in order to distract him from the story. Without a warning the experimenter subsequently asked the patient whether or not he could remember anything from the previously read out story. Remarkably, PB was still able to recall some of the story material following the conversation. This is elucidated in the original transcript of this part of the testing session:

<u>Delayed Recall 2</u>

E: *What can you remember about the story?*
PB: *Just basically that in fact there was a bank raid taking place and that this person who in fact had something eh…was an employer, or no sorry was an employee with the bank and he saw off the bank raiders. Is that about…an employee?*
E: Yes
PB: *…and considered therefore a bit of a hero in that respect. And that's about the gist of it.*

In order to examine whether or not such extended retention would last following yet another conversation filled break, PB was once more engaged in conversation and then asked to once again try and recall anything he remembered from the prose. As previously, such delayed recall came as a surprise. The transcript is provided below:

<u>Delayed Recall 3:</u>

E: *…I won't bother you more but just try and remember the story again, just one last time.*
PB: *Well, basically the banking situation is…where Mr Kelly is something to do with the bank and he's either the teller or he's the bank manager, I would have put him the bank manager probably or I'm not even now sure what his capacity was, but he's*

an employee, right. And the story describes how a group of men are going to rob this bank and they come in and the activities of Mr Kelly are such that he frightens them off and they therefore don't…even though in fact he must have been quite a robust and courageous man that he in fact frightens them off and therefore they don't get what they thought they might get…and in that respect this is an article demonstrating the heroism and the bravery of, if you like the great behaviour of this man, Mr Kelly. So that' that, that's a summary of my mind of what the story was about…

The procedure was repeated once more (in the presence of PB's wife), again revealing some apparent extended retention of the story.

Delayed Recall 4:

E: *Now, how about you tell your wife what you remember?*
PB: *Yes!*
PB: *Well basically the article or the story is about a bank manager or a bank teller who has a great deal of bravery in that he takes on the people who were robbing the bank and frightens them to the extent that they don't get away with any of the money (whatever may or may be the money in the till)*
And this is really, the article is really describing how this individual stand up to the individuals and they don't benefit from the attack on the… either the teller..or…the position, whether it was the bank manager or the bank teller I am not quite sure, that's the summary of what I remember.

Following a brief conversation with PB and his wife the Experimenter once more asked PB to recall anything he could remember from the story.

Delayed Recall 5:

E: *Let's just try it one more time. What can you remember from the story?*
PB: *Well the story is about how a bank manager is in charge of a small bank and during the time that he's there, there are 3 individuals who come and break into and*

hold the bag up and it demonstrates how he has got to sort of show courage and sort of being able to prevent these people from getting away with the money in the bank. That's a brief synopsis of the situation…I can't go beyond that. As I get further and further away from reading it then in fact it's getting more obscured or even eclipsed, it's just something I am just aware, I can't even…Reilly was the man, was the man called Reilly. I am trying to think of the name of the bank manager

E: *Think. Just have a little think, if not I'll give you a little prompt.*

PB: *'O', there's an O in front of his name, no, no there isn't, no*

E: *It started wit K, the surname*

PB: *Kelly! So I almost got the Irish connotation here, yes.*

PB: *But I can't remember the other details*

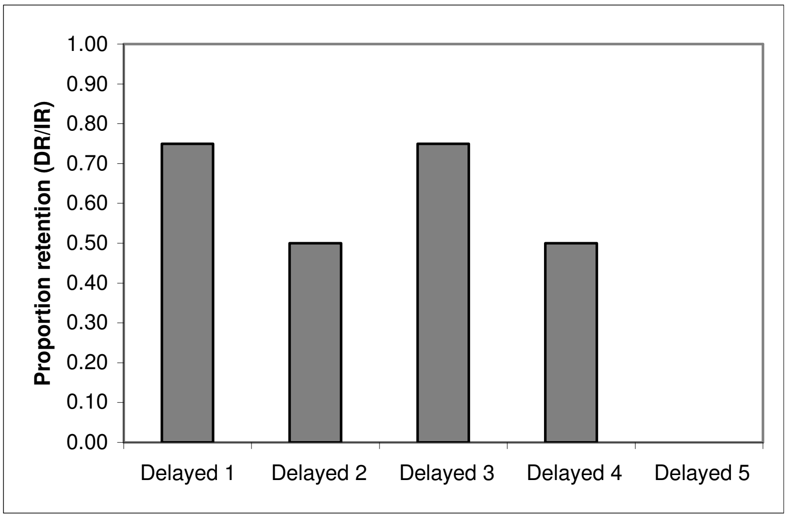


Figure 5.3. PB's proportion retention (Delayed recall/Immediate recall) for each of the five Delayed recall trials. Note that while PB could remember some gist of the prose at Delayed 5 his recall did not qualify as verbatim recall and was thus scored as 0.

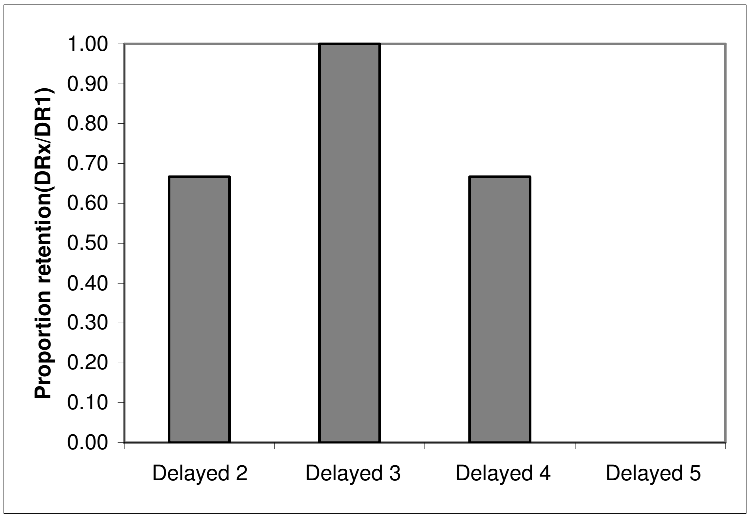


Figure 5.4. PB's performance at Delayed 2, Delayed 3, Delayed 4 and Delayed 5 (i.e. following some post Minimal RI interference) as a proportion retention from Delayed 1 (i.e. delayed recall following Minimal RI). As above PB's score for Delayed 5 was 0 due to no verbatim recall in this trial.

PB could not remember any prose details, nor having been presented with a prose or in fact the experimenter *following RI* in Experiment 2(a). It was thus of further interest to examine whether PB's more general memory of the prose presentation episode may have also been ameliorated by Minimal RI in the present Experiment, and more importantly whether any such memory was still present following the post Minimal RI interference. PB was thus asked several questions regarding the story presentation episode. The original transcript is provided below:

E: *Do you remember that I was sitting here reading a story?*

PB: *Oh yes, oh yes*

E: Do *you have quite a vivid memory of that?*

PB: *Yes, Oh, yes…no question about that at all…no, I mean the story had to come from you, I didn't create it, no.*

E: *Because earlier on when I read a story, you thought that you had read it.*

PB: *Did I?*

E: *You thought that, but with this one you definitely remember that I read it?*

PB: *Oh, no, no you read the story, there's no question about that. It came from a script of paper, which in fact was type paper or whatever it was.*

It should be noted that both PB's wife and PB himself were very surprised by his somewhat enhanced and extended retention. Indeed, following the Experiment his wife, the best judge of his memory performance stated that such performance in her husband was 'very encouraging'. And PB himself said '*very encouraging, and thank you very much that helps'*.

5.2.7 Discussion

The present pilot study revealed that PB, a severely amnesic patient who showed a benefit of Minimal RI in Experiment 2(a), was able to retain details of a prose presented to him prior to Minimal RI even after post Minimal RI interference. Such 'extended' retention is remarkable given the patient's very dense anterograde amnesia.

This finding is of great importance with respect to the question of which cognitive process underlies the benefit or Minimal RI. As reasoned above, no such extended retention should have been present if PB's benefit had solely been the result of uninterrupted STM maintenance. Hence, if PB had simply retained some of the prose material at Delayed Recall1 due to maintenance within a STM system, any such material should have fallen prey to the time/capacity limitations of such a system shortly after onset of the post delayed recall conversation.

Indeed, given that PB was engaged in conversation it would have been very difficult for him to explicitly maintain some of the prose material during such period. Moreover, it must be underlined that PB was not forewarned about such further delayed recall(s) meaning that he should have not been very motivated to try and explicitly maintain such material while engaged in a conversation.

The data thus strongly suggest that PB's benefit of Minimal RI, at least in the present Experiment, was the product of some LTM improvement.

Given his 0 retention following tone detection (in Experiment 2(a)), and hence following *non*-material specific RI, an uninterrupted *LTM retrieval* account of PB's benefit of Minimal RI appears highly unlikely. Thus, as argued in more detail in the introduction to this chapter, a patient benefiting from Minimal RI due to uninterrupted retrieval would be predicted to be highly susceptible to *similarity RI* rather than *diversion RI*. It would hence be predicted that such patient would not be affected to a large extent by a task such as tone detection. Moreover, one would predict such a patient to (a) show some spared anterograde memory in the absence of similarity RI in every day life and (b) to also show some impairment in the retrieval of retrograde memory in the presence of similarity RI and PI.
However, none of these apply to patient PB.

While such LTM retrieval hypothesis cannot be entirely excluded, it appears somewhat more likely that PB's benefit of Minimal RI underlay some LTM *consolidation*, i.e. the strengthening of to-be-retained material over time leading to a reduced susceptibility to subsequent distraction (Müller and Pilzecker, 1900; Dudai, 2002).

Such in turn would suggest that PB is *capable of forming new LTM* (at least to some extent), but that an apparent high *susceptibility to diversion RI* may prevent such process from occurring. Indeed, given the near-to-constant presence of diversion RI in everyday life as well as neuropsychological testing, it would not be surprising that a patient with some spared consolidation yet a high susceptibility to diversion RI should show such severe anterograde amnesia as does PB.

The present pilot case study hence provides tentative evidence for a *consolidation*-based hypothesis of Minimal RI, at least for the present patient.
It is important however to note that the apparent extended retention of the prose in PB over a period of approximately 30 minutes cannot be generalized to much longer periods. Indeed, when PB was seen again by the same examiner, in the same room (i.e. when encoding and retrieval contexts would have been optimal) following 10 months, he showed no apparent retention of the previously retained prose passage. In

fact he did not even remember the experimenter nor having ever been at the particular hospital before.

Similar findings were made by Cowan et al. (2004) who called their patients five months following original testing. None of the patients in their study were able to recall any of the presented material, having been presented with stories or indeed having been at the hospital, indicating that any potential consolidation during Minimal RI cannot have allowed for long lasting LTM. However, none of these patients were tested for extended retention shortly following the experiment as in the presented study. Thus, it is not known whether the patients who benefited in the Cowan et al. (2004) study benefited due to some uninterrupted consolidation, as appears to be the case for PB, or whether their benefit of Minimal RI may have underlain maintenance within a capacity limited STM buffer.

While patient PB's apparent consolidation following Minimal RI seems to be at odds with his lack of retention of the story material or the testing session itself following 10 months, such conflicting findings could in fact be explained by the hypothesized existence of a fast 'synaptic' consolidation, hypothesized to map onto Müller and Pilzecker's (1900) postulated type of consolidation (Wixted, 2004), and a slow 'systems' consolidation (c.f. Dudai., 2004, see Chapter 1 for a review of such neuroscience theory of consolidation).

Indeed, within such theoretical framework it could be postulated that PB shows an impairment of synaptic consolidation, which can, to some extent be ameliorated via Minimal RI, as well as an impairment in systems consolidation, which may not benefit from Minimal RI, at least not from the duration and type of Minimal RI that was utilized in the present experiment. In fact, such hypothesis could also explain PB's temporally graded retrograde amnesia, a type of amnesia postulated to underlie impaired consolidation. Such dissociation in impairment of the two consolidation types is not implausible. Indeed, the research on accelerated forgetting or Long Term Amnesia in epilepsy (c.f. Kapur et al., 1997; O'Connor et al., 1997; Zeman et al., 1998; Blake et al., 2000, Mayes, 2003, see also Chapter 1) revealing apparent intact retention following short delay intervals (30 min) yet not following longer delay intervals (i.e. days to weeks), provide strong evidence for the possibility of an impairment of systems consolidation and sparing of synaptic consolidation.

Further Minimal RI research, containing various temporal delays, is planned to investigate such potential dissociation in consolidation types in patient PB.

5.2.8 Conclusion

In conclusion, this single case pilot study revealed that PB, a densely amnesic patient who showed 0 retention following RI in Experiment 2(a), appears to be able to retain some prose material in the presence of RI, *if* such RI is preceded by a period of Minimal RI.

Such finding strongly suggest that the benefit of Minimal RI does not underlie uninterrupted STM maintenance but some uninterrupted LTM consolidation, at least in this particular patient. Such in turn suggests that PB may have some spared capacity for consolidation, but that a heightened susceptibility to RI hinders such process somewhat, meaning that consolidation can only take place under conditions of Minimal RI.

However, PB's lack of memory of the prose or the experiment following a period of 10 months suggests that the apparent LTM benefit of Minimal RI is unlikely to be long-lasting.

Overall the data very tentatively suggest that PB might have two memory impairments, firstly, an impairment of slow 'systems' consolidation that may not be aided by Minimal RI, and secondly, an impairment of fast 'synaptic' consolidation that could be lessened under conditions of Minimal RI.

Further research on a larger sample of anterograde amnesiacs is necessary in order to examine whether or not the here-postulated 'uninterrupted consolidation' hypothesis of Minimal RI can be sustained. Moreover, future research is also required in order to examine whether the elucidated short-lived LTM benefit of Minimal RI is replicated in further patients or whether some patients may show a longer lasting benefit or Minimal RI.

5.3 Experiment 4(a) Apparent LTM consolidation in anterograde amnesia following Minimal RI: A larger sample of focal brain injury anterograde amnesiacs (I)

5.3.1 Introduction

Experiment 3 provided some evidence that uninterrupted consolidation may underlie the benefit of Minimal RI in anterograde amnesia. However, given the variability in deficit and lesion site, and indeed in the magnitude of the benefit of Minimal RI in patients with anterograde amnesia, such apparent uninterrupted consolidation in one patient cannot be generalized to the population of anterograde amnesiacs who benefit from Minimal RI. Indeed, it cannot be excluded that the benefit of Minimal RI observed in the previous studies (i.e. Cowan et al., 2004; Della Sala et al., 2005 and in Experiment 2(a)) may underlie varying cognitive processes in different patients. Thus, it is plausible that Minimal RI may allow for some LTM consolidation in some patients, such as PB, but only for short-term improvements in others.

5.3.2 Aims of Experiment 4(a)

The aim of this experiment was thus to examine whether or not and to what extent the findings of extended retention on a second delayed recall trial following a short period of post Minimal RI interference in patient PB would be replicated in a larger sample of patients with anterograde amnesia.

5.3.3 Methods

5.3.3.1 Participants

The seven Italian anterograde amnesiacs (PE-PK; 4m/3f, mean age = 32.857, age range = 20 – 47; mean education = 11.43, education range = 8 – 16) and seven

Italian age and education matched controls (CE-CK; 4m/3f, mean age = 33.43, age range = 21 – 46, mean education = 13.57, education range = 8 – 16) who took part in Experiment 2(a) and 2(b) also participated in the present Experiment.

The inclusion criteria for the present Experiment were the same as those indicated in Experiment 2(a). Please refer to Table 4.1b for selected characteristics of tests and amnesic patient performance.

5.3.3.2 Materials

Italian versions of stories A and B from the Rivermead Behavioural Memory Test (Brazzelli et al., 1993) were used in this experiment.

5.3.3.3 Procedure

This experiment was undertaken in the same testing session as Experiment 2(a) and (b). Shortly following Trial 4 of Experiment 2(a) participants were informed that they would be presented with a further short story, which they should listen to carefully as they would be asked to recall as many of the story details immediately following story presentation (See Figure 5.5). Participants presented with Story A during trial 1 of Experiment 2(a) were again presented with this story. Participants presented with Story B during trial 1 of Experiment 2(b) were again presented with story B in the present experiment. The Experiment 2(a) trial 1 story was repeated in the present Experiment to replicate Experiment 3 as closely as possible (Trial 1 had to be repeated in the case study due to the hospital equipment problems described above).

Following story presentation participants were asked to recall as many details as they could from the story (see Figure 5.5). They were then left alone in the darkened room for 10 minutes as in trial 1 of Experiment 2(a) (see Figure 5.5). Following the 10 minute delay interval the experimenters reentered the room and asked the participant to try to recall as many of the details from the previously presented story as possible (see Figure 5.5). Following Delayed recall the patient was informed that a short break would be taking place (see Figure 5.5). Patients were provided with a hot drink and some biscuits and were engaged in conversations with the experimenters. Care was taken not to talk about the experiment (patients were asked questions about their home, families, their work and the incidents causing their memory problems). Some patients stood up and moved around the room a little bit. Following approximately 5 minutes the participants were asked to sit down again for the next set of tests. They were then asked to try and recall as many of the details of the story they had been presented with last (see Figure 5.5). Participants were not warned about such second delayed recall before the break.

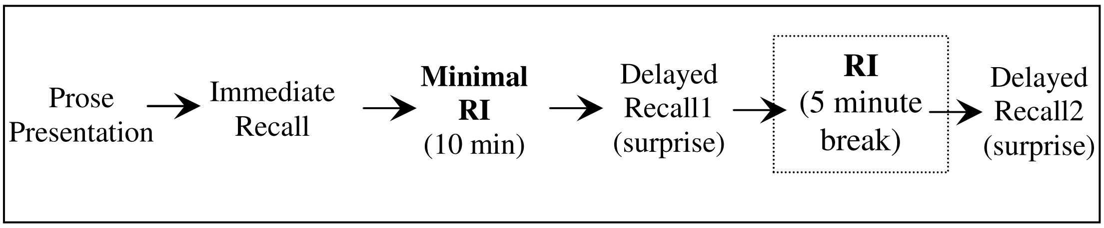


Figure 5.5. Procedure of Experiment 4(a).

5.3.4 Results

Inspection of the raw data revealed that only three of the seven patients (PF, PG and PI) showed the 'basic' benefit of Minimal RI following the 10 minute interval (see Figure 5.6 and 5.7). Out of these three patients two (PF and PG) also showed some retention of the prose material at the second delayed recall (i.e. following the post Minimal RI conversation – filled break) (see Figure 5.6). As depicted in Figure 5.6 one patient (Patient PK) showed some retention at the second delayed recall, yet not at the first delayed recall (i.e. she showed no 'basic' benefit of Minimal RI).

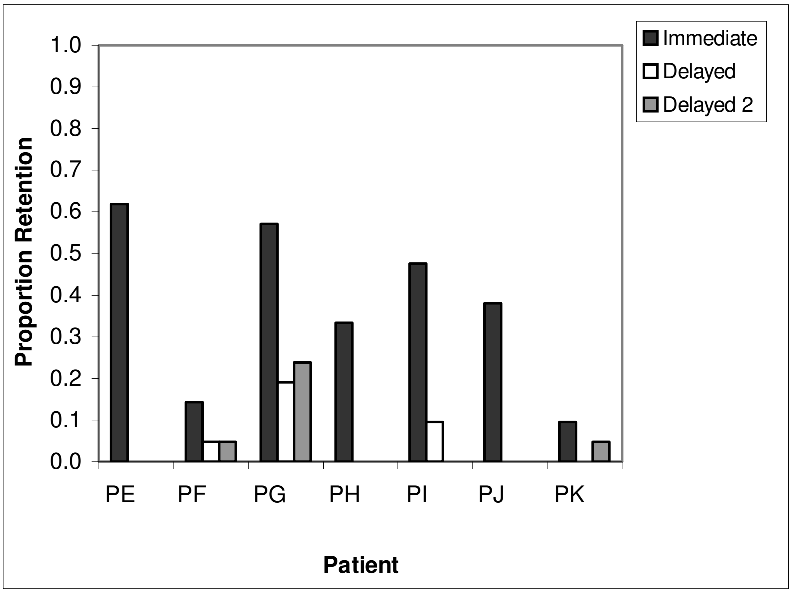


Figure 5.6. Patient proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall, delayed recall and second delayed recall.

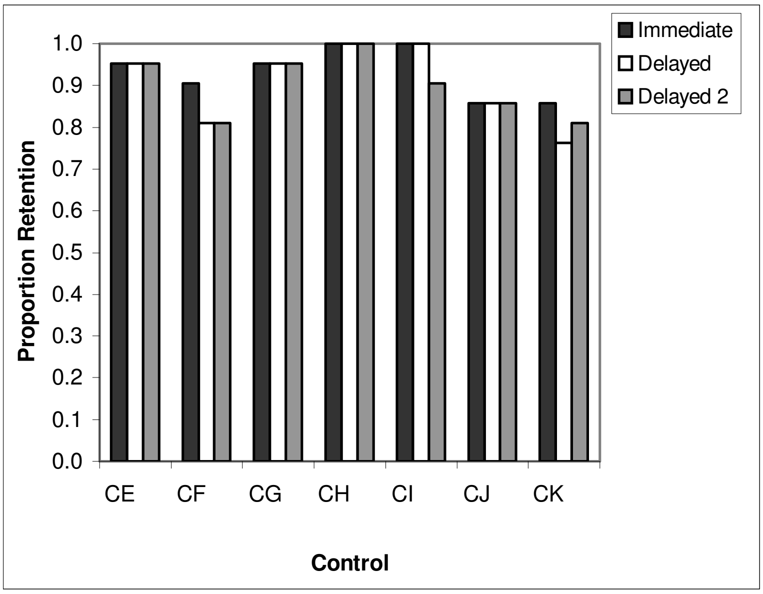


Figure 5.7. Control proportion retention of story material (number of prose ideas recalled/total number of prose ideas within presented prose) at immediate recall, delayed recall and second delayed recall.

Three retention scores were computed for each participant:

1) Basic proportion retention: DR/IR (as utilised in Experiment 2(a) and 2(b) and Della Sala et al., 2005; Cowan et al. 2004)
2) Proportion retention at second delayed recall from immediate recall: DR2/IR
3) Proportion retention at second delayed recall from first delayed recall: DR2/DR

Figures 5.8 and 5.9 depict individual participant data for each of these three scores.

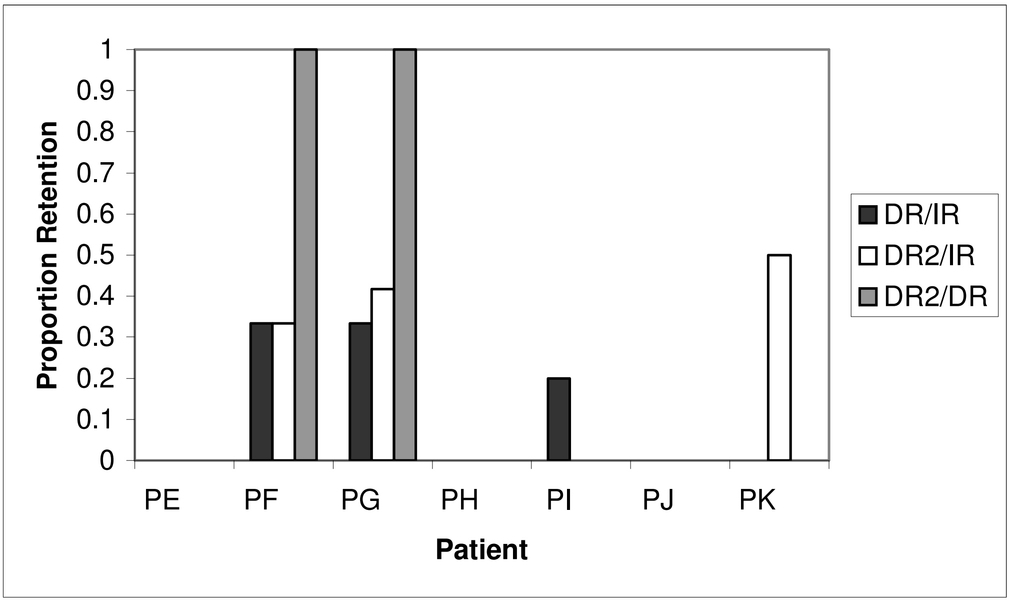


Figure 5.8. Patient proportion retention of story material, DR/IR, DR2/IR and DR2/DR.

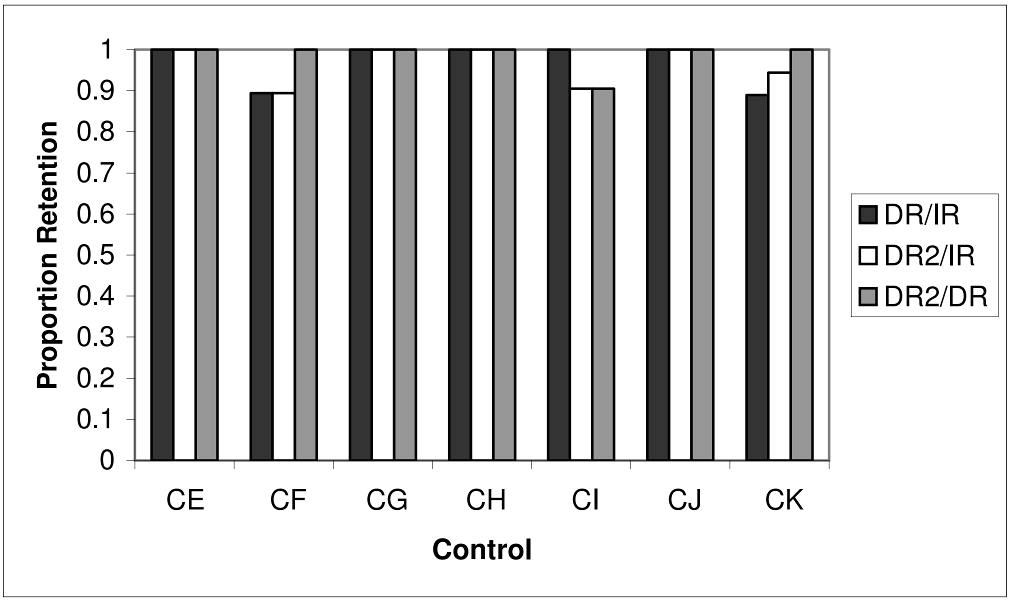


Figure 5.9 Control proportion retention of story material, DR/IR, DR2/IR and DR2/DR.

An initial one-way ANOVA with between subjects factor Group (Patients vs. Controls) was set up to examine basic proportion retention scores (i.e. DR/IR). The Levene's test of equality of error variances revealed that homogeneity of variance could not be assumed for the two groups ($p < 0.001$). A Welch corrected ANOVA, which is robust to the variance assumption, was thus also applied. The ANOVA revealed a significantly higher proportion retention for the control group than the patient group, $F(1, 13) = 174.818$, $p < 0.001$, a finding that was supported by the Welch corrected ANOVA, $F(1, 7.282) = 174.818$, $p < 0.001$. Group means and SEMs are depicted in Figure 5.10.

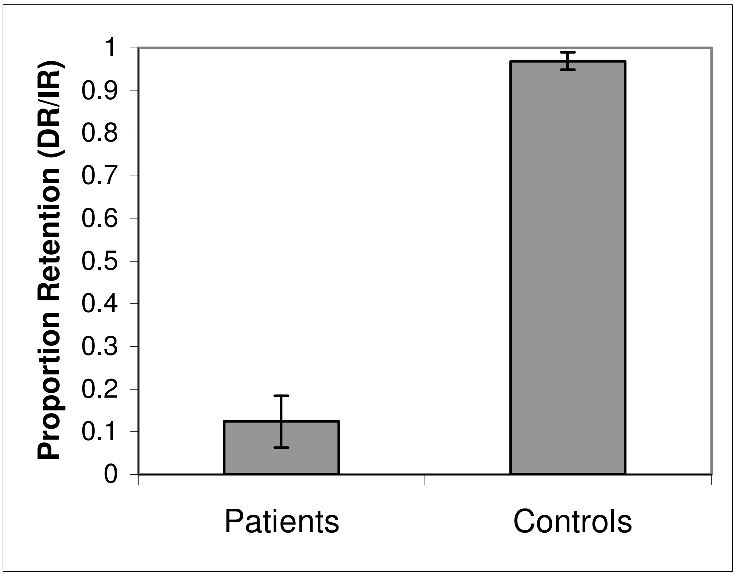


Figure 5.10. Mean Group proportion retention of story material (Delayed Recall/Immediate Recall) following Minimal RI.

A further one-way ANOVA with between subjects factor Group (Patients vs. Controls) was set up to examine proportion retention at second delayed recall from immediate recall (i.e. DR2/IR). The Levene's test of equality of error variances revealed that homogeneity of variance could not be assumed for the two groups ($p < 0.001$). A Welch corrected ANOVA was thus also applied. The ANOVA revealed a significantly higher proportion retention for the control group than the patient group, $F(1, 13) = 79.512$, $p < 0.001$, a finding that was supported by the Welch corrected ANOVA, $F(1, 6.533) = 79.512$, $p < 0.001$. Group means and SEMs are depicted in Figure 5.11.

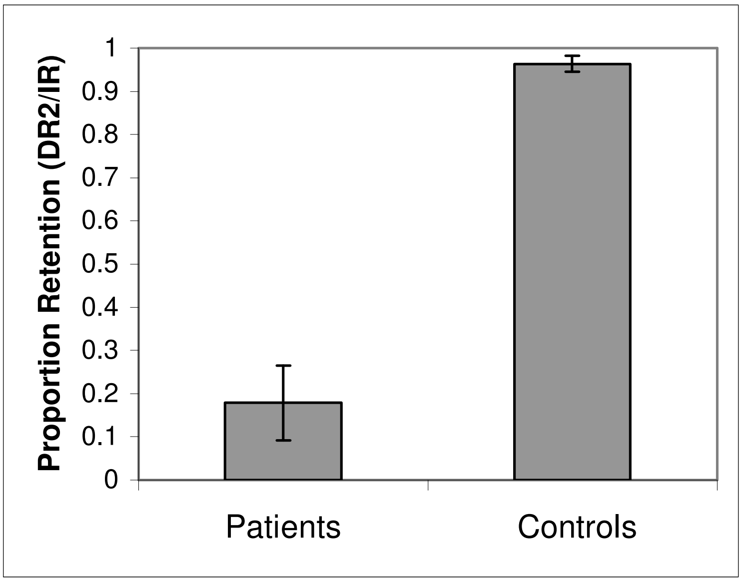


Figure 5.11. Mean Group proportion retention of story material (second Delayed Recall/Immediate Recall) following Minimal RI.

Given that only three patients showed some retention at first delayed recall, it was decided to re-run the above ANOVA (on DR2/IR) following exclusion of all patients who scored 0 at first delayed recall.

The Levene's test of equality of error variances revealed that homogeneity of variance could not be assumed for the two groups ($p < 0.01$). A Welch corrected ANOVA was thus also applied. The ANOVA revealed a significantly higher proportion retention for the control group than the patient group, $F(1, 9) = 76.969$, $p < 0.001$. The Welch corrected ANOVA, $F(1, 2.08) = 30.783$, $p < 0.05$ supported such result. Group means and SEMs are depicted in Figure 5.12.

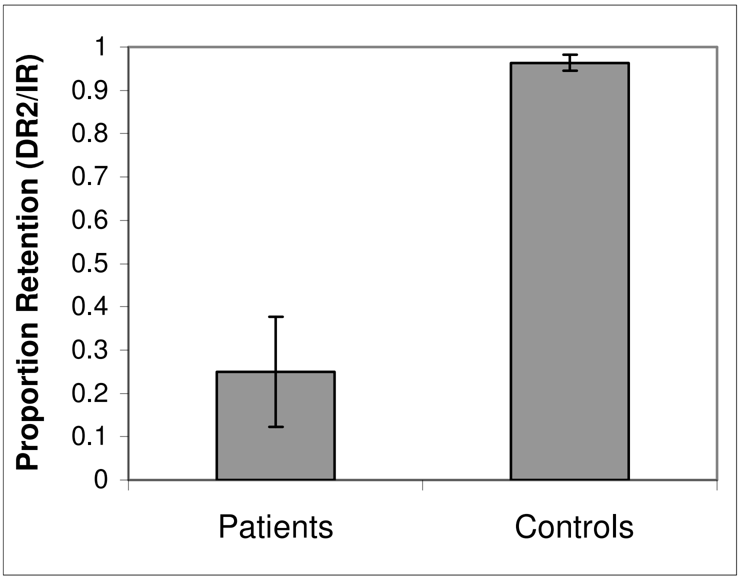


Figure 5.12. Mean Group proportion retention of story material (second Delayed Recall/Immediate Recall) following Minimal RI (after exclusion of four patients whose proportion retention following Minimal RI was 0)

A further one-way ANOVA with between subjects factor Group (Patients vs. Controls) was set up to examine proportion retention at second delayed recall from first delayed recall (i.e. DR2/DR). As in the previous ANOVA all patients performing 0 at first delayed recall were excluded for this ANOVA. The Levene's test of equality of error variances revealed that homogeneity of variance could not be assumed for the two groups ($p < 0.01$). A Welch corrected ANOVA was thus also applied. The ANOVA revealed no significant difference between the patients and controls for proportion retention at second delayed recall from first delayed recall, a finding that was supported by the Welch corrected ANOVA. Group means and SEMs are depicted in Figure 5.13.

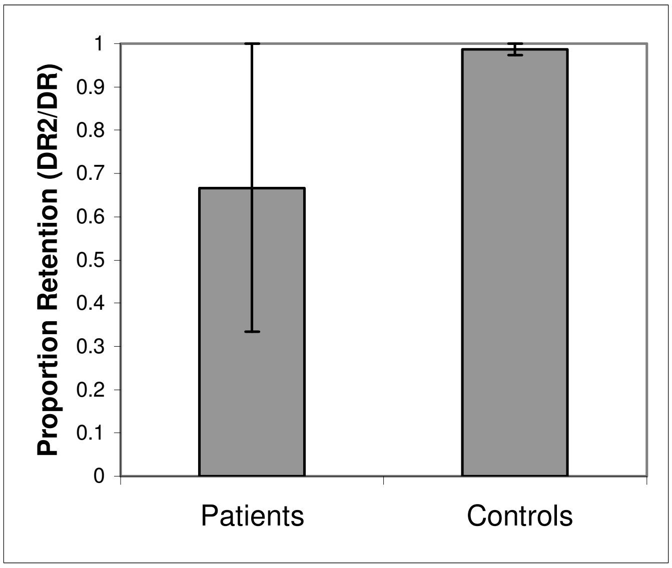


Figure 5.13. Mean Group proportion retention of story material (second Delayed Recall/Delayed Recall) following Minimal RI (after exclusion of three patients whose proportion retention following Minimal RI was 0)

5.3.5 Discussion

The aim of this experiment was to investigate whether or not and to what extent the findings of extended retention on a second delayed recall trial following a short period of post Minimal RI interference in patient PB would be replicated in a larger sample of patients with anterograde amnesia. The present results indicate that indeed such exact findings were replicated within this Experiment in two further patients with anterograde amnesia. More precisely, out of the *three* patients who showed an initial *'basic' benefit of Minimal RI* (i.e. on the first Delayed Recall trial*)* *two* patients (PF and PG) continued to show some prose retention following the post Minimal RI interference (i.e. on the second Delayed Recall trial). In fact as indicated in Figure 5.8, their retention at second delayed recall from first delayed recall (i.e. DR2/DR) did not differ from that of the age and education matched controls.

Such replication of some extended retention following post Minimal RI interference in more anterograde amnesiacs is of great interest as it provides further evidence for the *consolidation hypothesis* of the benefit of Minimal RI in some patients with anterograde amnesia that was postulated in Experiment 3.

Nonetheless, it remains to be explained why the findings of extended retention in patient PB could only be replicated in two patients and hence whether or not the benefit of Minimal RI may underlie differing cognitive processes in different patient groups.

Given patient PJ's lack of a basic benefit of Minimal RI in Experiment 2(a) as well as the current Experiment the lack of extended retention following Minimal RI does not come as a surprise and shall not be considered further within this chapter (though see Chapter 8 for a discussion of potential neural correlates of the benefit of Minimal RI).

The finding of no basic benefit of Minimal RI in patients PE and PH, who had shown large benefits of Minimal RI in Experiment 2(a), *is* however unexpected and impedes any interpretation of the cognitive processes underlying the benefit of Minimal RI demonstrated in such patients in the previous experiment. Such in turn has a knock on effect on the general results of the present findings. Hence, it is plausible that the findings of extended retention could have been replicated in at least two more patients if such extended retention had been tested in Experiment 2(a) during which patients PE and PH did show a basic benefit.

Why no such basic benefit was observed in these two patients in the current Experiment is unclear.

One possibility is that the two patients were fatigued during this Experiment, which as stated above, took place during the same testing session as and following Experiment 2(a). A second possibility, perhaps related to the first, could be that these patients were distracted by stimuli outside the experimenter's control, or perhaps by their own potentially distracting thoughts. Indeed, it is not known, as yet, to what extent a patient's own thoughts or even just a glance at the door or the wall may be sufficient to cause interference with memory processing. The tentative findings of Experiment 2(b) (i.e. the detrimental effects of the ignore tones delay period) certainly demonstrate how little distraction it may require for memory processing to be disrupted in some patients with anterograde amnesia.

A further somewhat unexpected finding in the present experiment was that of a basic benefit of Minimal RI as well as extended retention in patient PF who had shown no basic benefit in the aforementioned Experiment 2(a). Thus Patient PF showed quite the opposite pattern of performance from PE and PH. It is unclear why PF was able to benefit from Minimal RI during this Experiment but not so during Experiment 2(a). She was somewhat quiet and shy during Experiment 2(a) to begin with though appeared to relax a little more during the latter trials of the testing session. It is thus possible that a reduction in anxiety and increase in confidence may help to explain at least some of the deviation in her performance in Experiment 2(a) and that in the present Experiment. Thus PF may have performed better during the present Experiment due to increased confidence. However such hypothesis is highly tentative only and lacks any empirical evidence.

PK's apparent extended retention was a further slightly unexpected finding. Indeed, like PF, PK did not show any evidence of a benefit of Minimal RI in Experiment 2(a). Moreover, like PF PK also appeared somewhat shy and anxious during the initial trials of Experiment 2(a), yet seemed to gain in confidence during the latter trials. In contrast to PF however, PK did not appear to benefit from Minimal RI during the present Experiment either. Thus, if her extended retention in the present Experiment had been the product of a gain in confidence during the latter part of the testing session, some retention would have also been predicted at the first Delayed Recall. It is thus unclear as to why and how PK was able to recall some story material at Delayed Recall 2.

Of particular interest to the aims of this present experiment are the results of patients PG and PI. Both patients showed a basic benefit of Minimal RI during Experiment 2(a) *as well as* in the present Experiment. Hence, they were matched with respect to the basic benefit of Minimal RI. However, while PI showed *no* retention of prose material at the second Delayed Recall, PG showed retention at the second delayed recall trial. In fact, as shown in Figure 5.6 there was no decrease in PG's retention from Delayed Recall 1 to Delayed Recall 2. Indeed, PG actually recalled more on the second Delayed Recall trial than the first Delayed Recall trial. Such contrasting findings in extended retention in PG and PI raises the possibility that different cognitive processes may have underlain the benefit of Minimal RI in these two patients: some uninterrupted consolidation in PG and possibly some uninterrupted STM maintenance in PI. It may thus be postulated whether such findings of two qualitatively different types of benefits may possibly further generalize to the wider anterograde amnesia population.

However, a word of caution is required with particular respect to PI's lack of extended retention: This Experiment had to be repeated for PI who walked out of the testing room during Minimal RI after hearing his mother call good bye to the experimenters who were waiting outside the room. He was somewhat agitated and asked for his mother. The Experiment was repeated after a brief coffee break with the patient. However he continued to be restless and agitated throughout the Experiment. It may thus be plausible that such restlessness could have played a role in the lack of extended retention in this patient. However, if such has been the case one would have expected PI to also show a lack of a basic benefit of Minimal RI. While such was not the case, PI's proportion retention of 0.2 in the current Experiment was certainly smaller than that of the two Minimal RI trials of Experiment 2(a) (0.8 and 0.514), thus possibly indicating that his restlessness may have had an effect on the basic benefit of Minimal RI. Assuming for a moment that PI *is* capable of consolidating some material at least to some extent under conditions of Minimal RI, it could be postulated whether PI's restlessness may have (a) led to less material being consolidated (leading to a smaller basic benefit of Minimal RI) and (b) weaker consolidation, thus rendering the material more susceptible to the post Minimal RI interference.

In addition to the aforementioned problem regarding PI's data, there are two potential limitations to the present Experiment which could affect interpretation of the current findings.

Firstly, given the apparent variability in emergence of a basic benefit of Minimal RI, it would have been advantageous if more trials had been run per participant in the present experiment. Future research should thus include a series of identical trials to allow for any within subjects variability in the basic benefit of Minimal RI.

Moreover, such research should also be conducted as a stand alone Experiment with no trials preceding it to minimize fatigue.

A second potential limitation of the present experiment is the lack of a second Delayed Recall trial following tone detection. While the majority of patients did not show any retention following tone detection in Experiment 2(a), thus making a second delayed recall somewhat redundant, such trial could have nonetheless been useful for various reasons:

Firstly, patients PE and PG did show some retention following tone detection in Experiment 2(a). Thus, it would have been interesting to examine whether or not they would have been able to retain such material after a post tone detection conversation-filled break. Findings of such extended retention of material presented prior to tone detection would have certainly rendered PG's extended retention following Minimal RI less noteworthy.

Secondly, PK's apparent retention at the second yet not at the first delayed recall in the present experiment tentatively suggests that a lack of delayed recall immediately following the delay interval does not necessarily mean that no LTM was formed of the material presented prior to the delay. Thus there is the possibility that PK was simply unable to retrieve such information immediately following the delay. Given such very tentative speculation, it could be argued that story details presented prior to tone detection may have also been consolidated in PK as well as perhaps some of the other patients taking part in Experiment 2(a), but that such story details were not retrievable immediately following the tone detection period. Given the severe anterograde amnesia of the patients tested in Experiment 2(a) as well as the current Experiment, it would seem highly unlikely that such patients' deficit were a specific impairment in the retrieval of material immediately following a filled delay interval but not after a longer time interval. Indeed if such were the case, one would expect these patients to show much less severe anterograde memory problems in their day to day life. However all patients included in this study showed a dense anterograde amnesia. Nonetheless, it would have been beneficial to have had empirical evidence against such hypothesis as opposed to having to rest on an assumption.

5.3.6 Conclusion

In conclusion then, the present Experiment provided some further evidence for the postulated *consolidation* hypothesis of the benefit of Minimal RI.
However, the findings and resulting interpretations of the present Experiment were somewhat eclipsed by inconsistencies between the present Minimal RI data and those of Experiment 2(a), as well as by the limited data obtained for each patient. Thus, more research containing multiple trials (including RI trials) is required in order to (a) strengthen the evidence for a consolidation hypothesis of Minimal RI in anterograde amnesia and (b) examine whether *all* anterograde amnesiacs benefiting from Minimal RI do so due to uninterrupted consolidation or whether the benefit of Minimal RI may underlie different processes (i.e. LTM and STM) in different patients.

5.4 Experiment 4(b) Apparent LTM consolidation in anterograde amnesia following Minimal RI: A larger sample of focal brain injury anterograde amnesiacs (II)

5.4.1 Introduction

Experiment 4(a) provided some further evidence for the *consolidation hypothesis* of the benefit of Minimal RI that was postulated in Experiment 3. Nonetheless, the inconsistencies between some patients' basic benefit data in Experiment 2(a) and Experiment 4(a) limited the extent to which such hypothesis could be examined and hence supported.

Moreover, it was highlighted in the discussion of Experiment 4(a) that inclusion of a further delayed recall of material presented prior to tone detection may have been beneficial in order to examine whether any patients would have been able to recall such material at a second delayed recall trial. Indeed, a lack of extended retention of material presented prior to tone detection in the presence of extended retention from story material presented prior to Minimal RI would strengthen the consolidation hypothesis of the benefit of Minimal RI somewhat.

Furthermore, while Experiment 4(a) indicated that at least two patients were able to benefit from Minimal RI due to some uninterrupted consolidation, it could not be deduced from Experiment 4(a)'s data whether or not the patients' benefit of Minimal RI would be long lasting, i.e. whether the patients had formed a durable LTM.

As discussed in Experiment 3, no such durable LTM of the prose material or even the testing session was observed in patient PB. It was thus very tentatively postulated that the relatively short-lived LTM benefit of Minimal RI in PB may have underlain uninterrupted *synaptic consolidation* (c.f. Dudai, 2004) in this single case. Given such finding and tentative hypothesis from the single case study, elucidation of either a long-lived or indeed a short-lived benefit of Minimal RI in further anterograde amnesiacs would be of great interest.

5.4.2 Aims of Experiment 4(b)

The aims of the present Experiment were hence to:

(1) Further examine extended retention of prose material presented prior to Minimal RI in the sample of patients taking part in the testing session containing Experiment 2(a) (tone detection vs. Minimal RI, Chapter 4), 2(b) (ignore tones vs. attend to tones, Chapter 4) and 4(a) (Delayed recall following post Minimal RI interference, Chapter 5).

(2) Examine whether or not any of these patients show extended retention of prose material presented prior to tone detection.

(3) Examine whether any of these patients show any long-lasting benefits of Minimal RI.

5.4.3 Method

5.4.3.1 Participants

The seven Italian anterograde amnesiacs (PE-PK; 4m/3f, mean age = 32.857, age range = 20 – 47; mean education = 11.43, education range = 8 – 16) and seven Italian age and education matched controls (CE-CK; 4m/3f, mean age = 33.43, age range = 21 – 46, mean education = 13.57, education range = 8 – 16) who took part in Experiment 2(a), 2(b) and 4(a) also participated in the present Experiment (Note that only the patient group was assessed following one year and that only data for 5 controls is available for the Post Experimental delayed recall)

The inclusion criteria for the present Experiment were the same as those indicated in Experiment 2(a). Please refer to Table 4.1b for selected characteristics of tests and amnesic patient performance.

5.4.3.2 Post Experimental delayed recall

5.4.3.2.1 Materials and Procedure

The Post Experimental part of Experiment 4(b) formed the last part of the testing session containing Experiments 2(a), 2(b) and 4(a) and 4(b) (see Figure 5.14).

1.)	Experiment 2(a)	Tone detection vs. Minimal RI (Chapter 4)	Testing Session (approximately 2.5 hours)
2.)	Experiment 4(a)	Delayed recall following post Minimal RI interference (Chapter 5)	
3.)	Break (25 min)		
4.)	Experiment 2(b)	Ignore tones vs. attend to tones (Chapter 4)	
5.)	Experiment 4(b)	Post Experimental delayed recall	
6.)	Experiment 4(b)	One year delayed recall	One year following testing session

Figure 5.14. The Testing Session consisting of Experiment 2(a), 2(b), 4(a) and 4(b). The Experiments are listed in the order they took place in. The Post Experimental part of Experiment 4(b) formed the last part of the Testing Session.

Following Experiment 2(b), each participant was informed that they would be asked a few questions about the various experiments they had taken part in.
In order to examine their general memory of the testing session as well as to distract them from the last prose passage they were firstly asked (in Italian):

'Can you tell me a bit about the assessment we just did? What did you have to do?'

This was followed by:

'You were presented with short stories. Can you remember what they were about?'

It was reasoned that if the Minimal RI delays of Experiments 2(a) and/or 4(a) had allowed for some uninterrupted consolidation of presented prose material, some of such material should still be retained at the time the present Post Experimental delayed recall took place (i.e. following Experiments 2(a), 2(b) and 4(a)), i.e. aim one.

Similarly, it was predicted that any potential extended retention of prose material from the tone detection trials of Experiments 2(a) and 2(b) may be revealed at Post Experimental delayed recall as well, i.e. aim two.

If a participant could not remember anything they were provided with a cue relating to one of the stories presented prior to a Minimal RI delay and one of the stories presented prior to a tone detection delay.

5.4.3.3 <u>One year delayed recall</u>

5.4.3.3.1 Materials and Procedure

The one year delayed recall part of Experiment 4(b) took place approximately one year following the Testing Session (see Figure 5.14).

Each patient was called approximately one year following the main Experiment and asked the following questions (in Italian):

1.) *Can you remember that you came to the hospital last year and that you had to learn some stories?*
2.) *You came to the hospital and you had to learn some stories. Can you remember anything about the assessment? The room, the people, what you had to do?*

3.) *I read out some stories to you to remember. Can you remember anything from the stories?*

4.) *One story was about a bank robbery. Can you remember anything about that?*

5.) *One story was about an oil tanker. Can you remember anything about that?*

6.) *One story was about a fire. Can you remember anything about that?*

7.) *One story was about a strike. Can you remember anything about that?*

8.) *One story was about a poor lady. Can you remember anything about that?*

9.) *One story was about a river. Can you remember anything about that?*

5.4.4 Results

5.4.4.1 Post Experimental delayed recall

Initial inspection of the raw extended retention data (see Figure 5.15 below) elucidated that three out of the eight patients taking part in this Experiment (PE, PF and PH) were able to freely recall some of the prose material they had been presented with during Experiments 2(a), Experiment 2(b) and Experiment 4(a). Moreover, one additional patient was able to recall some material after receiving a cue for two of the prose passages. Figure 5.16 shows that all controls were able to freely recall a large amount of previously presented prose material.

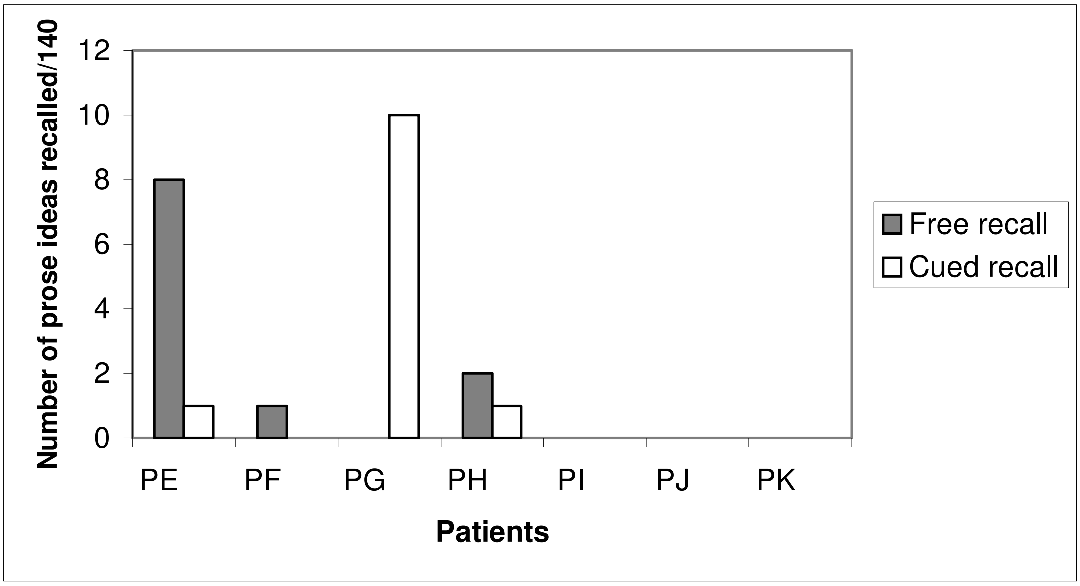


Figure 5.15. Post Experimental prose Recall: Number of prose ideas recalled by each patient (PE-PK) from any of the prose passages presented to them during Experiments 2(a), 2(b) and 4(a). Total number of prose ideas = 140.The gray bars depict free recall, the white bars depict cued recall.

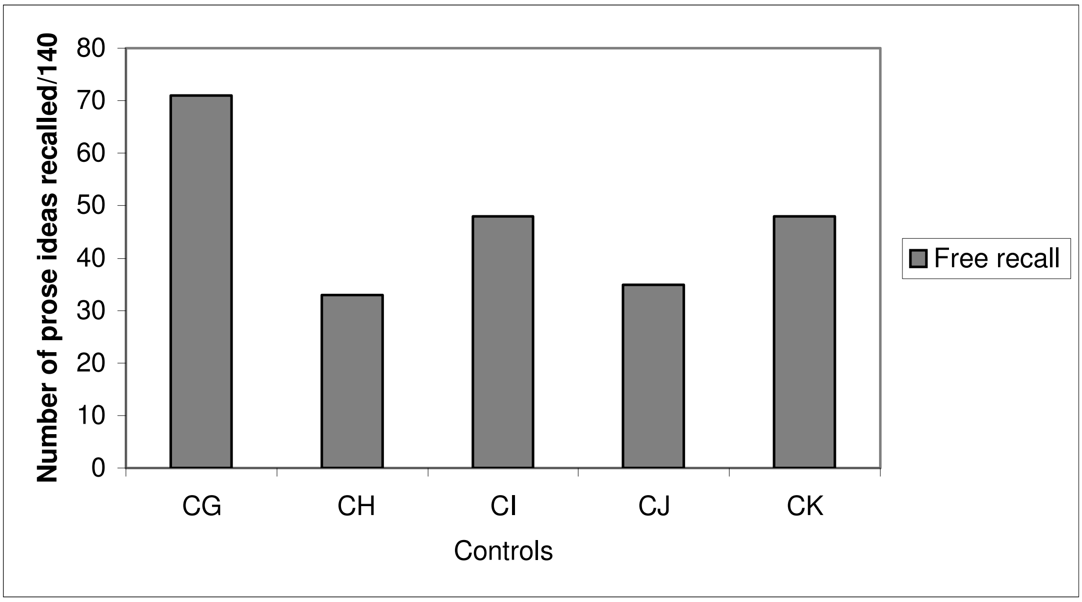


Figure 5.16. Post Experimental prose Recall: Number of prose ideas recalled by each control (CE-CK) from any of the prose passages presented to them during Experiments 2(a), 2(b) and 4(a). Total number of prose ideas = 140.

The Post Experimental data was further examined in order to assess (a) the particular trial within the Testing Session from which each freely recalled story idea had been retained from, and (b) the proportion retention at Post Experimental Recall from delayed recall of the individual trials of Experiments 2(a), 2(b) and 4(a), i.e. (Number of prose ideas recalled during the present Post Experimental delayed recall from trial x/number of prose ideas recalled at delayed recall of trial x),
where x =
Experiment 2(a): *MinRI incidental, MinRI intentional, Tone detection incidental, Tone detection intentional* (see Chapter 4)
Experiment 2(b): *ignore tones, attend tones* (Chapter 4)
Experiment 4(a): *MinRI delayed recall, MinRI second delayed recall* (Chapter 5)

As depicted in Table 5.1 PE and PF retained story material from Minimal RI (and the ignore tones in the case of PE) but not from tone detection. PH on the other hand retained story material from both Minimal RI and the attend trial of Experiment 2(b).
With respect to the proportion retention at Post Experimental Recall from delayed recall of the previous Experiments, the table illustrates further that PE retained 40% of the material recalled following the intentional Minimal RI delay and 50% of the material recalled following the ignore tones delay of Experiment 2(b). PF retained 100% of the material recalled following Minimal RI as well as following the conversation filled delay interval in Experiment 4(a). PH retained 17% of material previously recalled following the intentional Minimal RI delay of Experiment 2(a) and 37.5% of the material he had recalled following the attend tone detection trial of Experiment 2(b)

	Experiment 2(a)				Experiment 2(b)		Experiment 4(a)	
	MinRI		Tone detection		Tone detection		MinRI	
	Inc	Int	Inc	Int	Ignore	Attend	D1	D2
PE	**0**	**0.4**	**0**	/	**0.5**	/	/	/
PF	/	/	/	/	/	/	**1**	**1**
PG	**0**	**0**	**0**	/	/	/	**0**	**0**
PH	**0**	**0.17**	/	/	/	**0.375**	/	/
PI	**0**	**0**	/	/	/	/	**0**	/
PJ	/	/	/	/	/	/	/	/
PK	/	/	/	/	/	**0**	/	**0**

Table 5.1. Table 5.1 shows the trials within the Testing Session from which patients showed extended retention during the Post Experimental delayed recall (marked >0), and trials from which no extended retention was observed (marked 0). Trials for which retention during Post Experimental Recall >0 contain the exact proportion retention at Post Experimental delayed recall from delayed recall of the trial. (e.g., at Post Experimental Recall, PE showed 0.4 proportion retention from material previously recalled at delayed recall of the MinRI Inc trial of Experiment 2(a)).
/ = depicts trials for which delayed recall during the trials in the previous Experiments was 0.
Inc = Incidental, Int = Intentional, D1 = delayed recall in Experiment 4(a), D2 = delayed recall following post Minimal RI interference.

A set of one-way ANOVAs with between subjects factor Group (Patients vs. Group) was set up to compare the proportion retention of story material from each of the trials of Experiment 2(a), 2(b) and 4(a) of the patient and control group. Patients who scored 0 at delayed recall of any of the 8 recall trials were excluded pair-wise (i.e. their data was only excluded for those recall sessions in which their delayed recall score was 0). It should be highlighted that there were no patients who showed extended retention from a delayed recall session for which he/she had scored 0. Note that no ANOVA could be run for Experiment 2(a)'s tone detection intentional trial as none of the patients scored > 0 at delayed recall of this trial.

A Levene's test of homogeneity of variances indicated that the assumptions for this ANOVA could not be assumed for the Group comparisons of Experiment 2(a)'s MinRI inc trial and Experiment 4(a)'s MinRI D1 or D2 trials. Welch corrected ANOVAs were thus also applied for these comparisons. No Levene's test of homogeneity of variances could be run for the ignore trial of Experiment 2(b) as only one patient could be included in the ANOVA, thus leaving 0 variance in the patient group.

The main ANOVAs revealed significantly higher proportion retention of material in the control than the patient group from Experiment 2(a)'s MinRI inc trial, $F(1, 8) = 12.646$, $p < 0.01$ and MinRI int trial, $F(1, 8) = 21.714$, $p < 0.01$. No further significant group differences were found. The Welch corrected ANOVAs confirmed the findings of no significant group differences for Experiment 4(a)'s trials. Note however that no Welch-corrected ANOVA could be run for Experiment 2(a)'s MinRI inc trial due to 0 variance in the patient group. Group means and SEMs for proportion retention from each of the 8 recall trials are depicted in Figure 5.17.

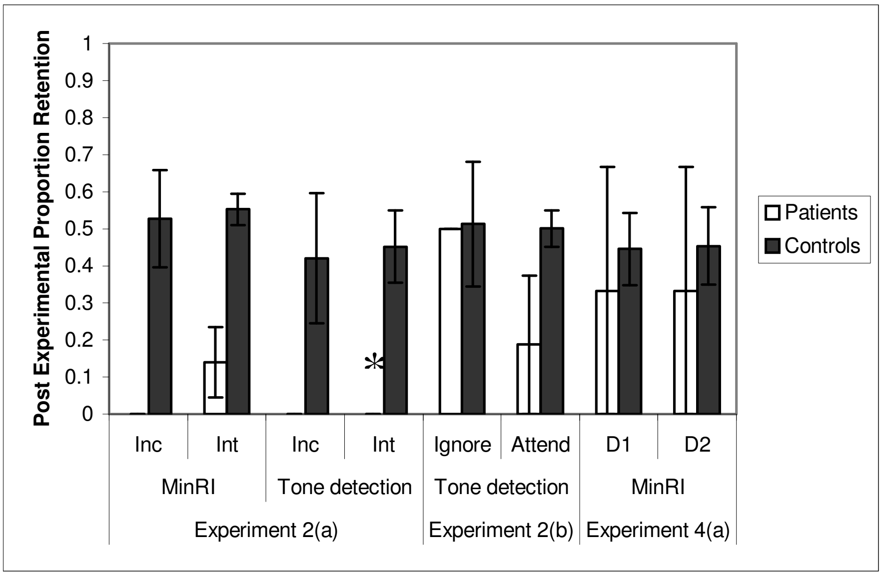


Figure 5.17. Group mean proportion retention at Post Experimental delayed recall from delayed recall of the individual trials of the Testing Session containing Experiments 2(a), 2(b) and 4(a). Error bars = SEM. Means and SEMs based based on 5 controls and on the patients who showed > 0 on delayed recall in the individual trials (i.e. trials marked '/' in Table 5.1.) * None of the patients showed > 0 delayed recall in Experiment 2(a)'s intentional tone detection trial.

5.4.4.1.1 Cues

Number of correct story ideas recalled following the cues is indicated in Figure 5.15 above. As depicted, such cueing aided two of the patients, PE and PG. While, as stated above, PE had been able to recall some material previously without any cues, PG went from 0 story ideas at free recall to 10 story ideas (from two stories) at cued recall. PE recalled 1 story idea from the incidental Minimal RI story of Experiment 2(a) and/or the Minimal RI story of Experiment 4(a) while PG recalled 5 story ideas from the incidental Minimal RI story of Experiment 2(a) and/or the Minimal RI story of Experiment 4(a) as well as 5 story ideas from the intentional tone detection trials of Experiment 2(a) (i.e. from the two stories for which a cue was given). His corresponding proportion retention scores were 1 proportion retention from the incidental Minimal RI trial of Experiment 2(a) and/or the second Delayed Recall trial of Experiment 4(a). Given that PG showed 0 proportion retention in the intentional tone detection trial of Experiment 2(a) no actual proportion retention score could be computed for this trial.

5.4.4.2 Delayed recall following one year

Three patients (PE, PF and PK) responded 'yes' to Question 1 (*'Can you remember that you came to the hospital last year and that you had to learn some stories'*). One patient (PH) responded that he remembered 'an English doctor' when asked Question 2 ('*You came to the hospital and you had to learn some stories. Can you remember anything about the assessment? The room, the people, what you had to do?')*.

Furthermore, two patients (PE and PH) responded 'yes' to question 8 ('*One story was about a poor lady. Can you remember anything about that?'*). This prose was presented to PE prior to the ignore delay of Experiment 2(b) and to PH prior to the attend delay of Experiment 2(b). PE responded 'had two children' (correct story ideas = 'had 4 children') while PH responded 'Anna Pesenti' (= 2 correct story ideas). PE's proportion retention following one year from delayed recall of this particular prose in the Post Experimental Delayed Recall was 0.2. PH's proportion score following one year from delayed recall of this particular prose was 0.67.

Neither PE, PF, PH or PK remembered anything else about the experiment (i.e. all other questions were answered 'No'). Moreover, neither patients PG, PI or PJ could remember anything about the experiment (i.e. all questions, including questions 1 and 8 were answered 'No').

	PE	PF	PG	PH	PI	PJ	PK
Extended benefit at Post Experimental delayed recall?	**Y**	**Y**	N	**Y**	N	N*	N
Remembers something about the testing session a year later?	**Y**	**Y**	N	**Y**	N	N	Y

Table 5.2. Table 5.2 indicates which of the seven patients showed an extended benefit of Minimal RI at Post Experimental delayed recall (Y = extended benefit, N = no extended benefit) and which patients remembered something about the testing session a year after the Testing Session (Y = remembers something about Testing Session a year before, based on a 'Yes' response to either question 1 or 2; N = does not remember anything about the testing session a year before, i.e. a 'No' response to both questions 1 and 2). * = no 'basic' benefit during Experiments 2(a) or 3(b).

5.4.5 Discussion

5.4.5.1 <u>Post Experimental Delayed Recall</u>

The present Experiment elucidated that three out of the six patients who had shown a basic benefit of Minimal RI in Experiment 2(a) and/or Experiment 4(a) still showed some retention from such trials following completion of the Experiments (i.e. following post Minimal RI interference), thus providing further evidence for a *consolidation hypothesis* of the benefit of Minimal RI.

With particular respect to Experiment 4(a), the present data showed that one out of the three patients (PF) who had shown some extended retention on the second

Delayed Recall trial of Experiment 4(a) still showed retention (100%) of such material on a third Delayed Recall trial, which took place following further experimental trials (Experiment 2(b)) a finding that strengthens the evidence that some uninterrupted consolidation is highly likely to underlie the benefit of Minimal RI in this particular patient. Interestingly however, neither PG or PK, who had also shown some extended retention on the second Delayed Recall trial of Experiment 4(a) showed any retention on this third Delayed Recall trial. Nonetheless, when provided with a cue of the story presented in Experiment 4(a), PG showed 100% retention from the second Delayed Recall trial of Experiment 4(a), tentatively indicating that the material may have indeed been consolidated during Minimal RI but possibly rendered less retrievable following the Experiment. However, it is important to highlight, that when cued in the present Experiment, PG also showed retention of material presented to him prior to the intentional tone detection trial of Experiment 2(a). Crucially, PG had shown 0 proportion retention of such prose passage at delayed recall in Experiment 2(a). Thus, it would appear unlikely that the cueing specifically aided retrieval of material consolidated during *Minimal RI*. Indeed, PG's retention of material presented prior to tone detection when a cue was provided strongly suggests that such material, too, must have been consolidated for it to be available for retrieval following the experiment. In fact, as highlighted in Experiment 2(a) PG showed some retention following the incidental tone detection delay even when free recall was required. While PG nevertheless showed a benefit of Minimal RI, the present findings suggest that some caution is required when interpreting PG's benefit of Minimal RI in Experiment 2(a) and his extended retention in the second Delayed Recall trial of Experiment 4(a) in terms of uninterrupted consolidation. Indeed, it appears plausible that in PG the benefit of Minimal RI may at least to some extent underlie improved retrieval. Future research will be necessary in order to examine such hypothesis further.

The only other patient to show some retention of material presented prior to tone detection was PH who was able to *freely* recall some material from the story presented to him prior to the attend trial of Experiment 2(b). However, in contrast to Patient PG, PH had already shown explicit retention of this very material at delayed recall of the attend trial. Moreover, as discussed in Experiment 2(b) PH's apparent retention of such material following the attend condition may have been greatly affected by his recollection of the main protagonist from pervious neuropsychological assessment.

Importantly, neither PH nor any other patients (besides PG) showed any retention in the present Experiment of prose material presented prior to tone detection in Experiment 2(a) and/or 2(b). Such finding is of particular relevance with respect to the three patients (PE, PF and PH) who showed retention in the present Experiment of prose material presented to them prior to Minimal RI. Indeed as argued in the Introduction, elucidation of such extended retention of material presented prior to Minimal RI, yet *not* of material presented prior to tone detection greatly strengthens the evidence for an uninterrupted consolidation as opposed to an uninterrupted retrieval hypothesis of the benefit of Minimal RI.

Interestingly, two of the patients who showed extended retention in the present Experiment from prose material presented to them prior to Minimal RI were patients PE and PH, the two patients who had previously failed to show a basic benefit of Minimal RI and subsequent retention at the second delayed recall trial in Experiment 4(a). The lack of such a basic benefit of Minimal RI in Experiment 4(a) meant that the cognitive processes underlying their previous benefit of Minimal RI could not be examined. The present finding is thus of great interest as it suggests that the benefit of Minimal RI elucidated in these two patients in Experiment 2(a) is likely to underlie some uninterrupted consolidation, thus strengthening the evidence for a consolidation hypothesis of the benefit of Minimal RI.

PE's extended retention in the present Experiment of material presented to her prior to the ignore tone detection delay interval is of further interest as it suggests that in contrast to the other patients, PE appears to have been able to consolidate some material during such delay interval. However given the potential limitations of Experiment 2(b) (see discussion of Experiment 2(b)) it is not clear at present whether or not such may be due to a less severe susceptibility to diversion RI in PE than the other patients.

A further interesting finding in the present Experiment is that of no extended retention in PI. Indeed, despite showing a basic benefit of Minimal RI in Experiment

2(a) and 4(a) he was unable to recall any prose material, even when provided with a cue. Given that PI also failed to show any extended retention in experiment 4(a) it may thus be postulated whether PI's benefit of Minimal RI may indeed underlie STM maintenance as opposed to consolidation. If such were the case, the present study may provide evidence, not only for the existence of two types of anterograde amnesiacs: those who do and do not benefit from Minimal RI (see also Cowan et. al, 2004) but also for a further qualitative difference regarding the benefit of Minimal RI, namely a group of patients who benefit from Minimal RI due to STM maintenance and those who benefit due to uninterrupted consolidation.

Nonetheless, as argued in the discussion of Experiment 4(a), PI's restlessness and agitation may have affected his performance in Experiment 4(a) and 4(b) somewhat, thus rendering any hypothesis of qualitatively different benefits of Minimal RI highly tentative only at this point in time. Thus, future research on this patient as well as further patients will be necessary in order to establish whether or not patients who benefit from Minimal RI do so uniformly due to uninterrupted consolidation or whether some patients may benefit due to uninterrupted STM maintenance.

5.4.5.2 <u>Delayed recall following one year</u>

The data of the delayed recall following one year elucidated that none of the patients were able to freely recall any of the prose material they had been presented with a year before. However, two patients, PE and PH, were able to recall some information when provided with a cue. Nonetheless, while PH showed 0.67 proportion retention (from recall in the Post Experimental Delayed Recall) of the story he had been presented with prior to the attend trial of Experiment 2(b), it is possible that this recollection was not specific to the testing session reported here. Indeed, as stated in Experiments 2(b) and the Post Experimental Delayed Recall of the current Experiment, PH revealed that he knew this story from previous assessments. Moreover, following one year PH did not show any extended retention of the prose passage he had been presented with prior to the intentional Minimal RI delay even though he had shown some extended retention of this story in the present

Post Experimental Delayed Recall, i.e. shortly after the Experiment. Thus, it seems that while some initial consolidation of this particular story appears to have taken place during Minimal RI, it did not develop into a durable LTM, a finding that closely maps onto those reported in patient PB in Experiment 3.

PE's retention (0.2) following one year on the other hand suggests that perhaps in this patient a durable LTM was formed, at least of a very small part of the prose presented to her prior to the ignore delay of Experiment 2(b). Thus, the absence of mental effort during the ignore delay may have led to a long-lived memory improvement in PE. If such were indeed the case, the present finding would not only differentiate this patient from all other patients who showed no basic benefit of the sole removal of mental effort (though see limitations of Experiment 2(b) in Chapter 4), but also more specifically from PH as well as PB, none of whom were able to recall any details of prose presented to them prior to Minimal RI following a longer delay interval. Given that PE performed at cut off in the Rivermead Behavioural Memory Test, it may be postulated that this particular patient may have more spared memory capacity than the other patients and hence that she may be able to show longer lasting benefits of Minimal RI. Indeed, given the apparent presence of synaptic and systems consolidation, it could be very tentatively argued that in PE both types of consolidation might be impaired, yet not completely, and that both processes may be augmented via Minimal diversion RI.

Nonetheless, if PE were indeed able to form durable Long Term Memories of specific information such as prose under conditions of Minimal mental effort, one would have expected her to also show at least some degree of retention of the prose presented to her prior to the intentional Minimal RI delay of Experiment 2(a) (i.e. the prose from which she showed some retention in the present Main Experiment). However such was not the case. It may of course be argued that, given that both PE and PH were able to show some cued recall of the same story, irrespective of Delay Condition, that this story may, for some reason, be easier to remember, even for an amnesiac. Future research using long delay intervals as in the present study is thus necessary in order to establish if any patients do show any extended retention of prose material presented to them prior to Minimal RI. Importantly, such future research should also include control data for delayed recall following a long delay for controls in order to establish how much neurologically intact individuals can retain over such long delay intervals.

For the time being it then appears that there is little evidence for a long-lived benefit of Minimal RI for retention of prose, at least in the present patients and patient PB.

However, the finding that all three patients who had shown some extended retention at Post Experimental delayed recall (PE, PF and PH) showed some apparent recollection of the testing session following one year, while the other patients did not (apart from patient PK), is somewhat interesting. Indeed, such finding very tentatively suggests that perhaps these three patients were able to form a long lasting memory of the session, and thus that they have some spared systems consolidation, but that such memory is much less detailed and hence does not contain specific information pertaining to the prose passages presented. If such were the case, these patients would certainly differ from patient PB who showed no recollection whatsoever of the testing session.

However, it cannot be told from PE and PF's 'yes' response to question 1 whether they do in fact clearly remember the here reported testing session. PH's recollection of an 'English doctor' on the other hand strongly suggests that he could indeed remember something about this particular testing session as an English doctor is not the norm during neuropsychological testing in an Italian hospital.

Nonetheless it is important to underline that even though PH and perhaps PE and PF were able to remember the here reported testing session, there is no empirical evidence that the formation of such LTM memory was the product of uninterrupted consolidation during *Minimal RI* in these patients. Thus perhaps these patients would have also shown such LTM in the absence of any Minimal RI delays.

This problem could be tackled in future research by conducting Minimal RI trials during one session and RI trials during a different session (on different days). The sessions would have to differ in some aspects such as the Experimenter and/or the testing lab while all other aspects apart from Delay Condition would have to be identical. If any lasting memories of the session were the sole product of Minimal RI, and thus, uninterrupted consolidation during Minimal RI, patients should only remember specific aspects of the Minimal RI session.

5.4.6 Conclusion

The findings of the Post Experimental delayed recall provide further evidence for an uninterrupted consolidation hypothesis of the benefit of Minimal RI in at least some patients with anterograde amnesia. Indeed, the further testing of the patients who had previously failed to show a basic benefit of Minimal RI in Experiment 4(a) allowed for elucidation of some likely consolidation in such patients during Minimal RI.

Moreover, the assessment of potential extended recall from prose passages presented prior to *tone detection* and subsequent lack of such finding in the majority of patients indicated that the extended retention observed following Minimal RI was likely to be the product of uninterrupted consolidation during *Minimal RI*, as opposed to some beneficial effect of a later delayed recall trial per se.

Nonetheless, the results also highlighted the possibility that the benefit of Minimal RI may not underlie uninterrupted consolidation in all patients and thus that future research will be necessary in order to examine such possibility further.

The findings of the one year delayed recall trial provided very little evidence that patients showing apparent initial consolidation of material presented to them prior to Minimal RI shortly after the testing session were able to form durable LTM of such material. While some patients did appear to show some recollection of the testing session itself, and while future research on such longer delay intervals is necessary, the present findings may provide further very tentative evidence for the in Experiment 3 postulated hypothesis of a *synaptic consolidation* benefit of Minimal RI in at least some patients with anterograde amnesia.

Chapter 6: Cognitive Processes underlying the benefit of Minimal Retroactive Interference (2) aMCI

6.1 Introduction

The RI experiments on patients with anterograde amnesia due to focal brain injury reported in the previous Chapter demonstrate that at least some patients who performed at floor following RI, were able to retain some of the prose material presented to them prior to *Minimal RI* even *after* some post Minimal RI interference had occurred. Such findings strongly suggest that the benefit of Minimal RI in such patients cannot be explained via explicit STM maintenance, as any such explicit STM maintenance should have been greatly hindered by the post Minimal RI interference. Thus, it appears highly likely that such 'extended' retention following Minimal RI underlay some consolidation of the prose material during Minimal RI. Indeed, such findings map onto the consolidation theory originally proposed by Müller and Pilzecker (1900) and more latterly by neuroscientists (e.g. Dudai, 2004, see Chapter 1 for a review). As discussed in Chapter 1 such consolidation theory posits that in the intact memory system of the majority of, if not all species, information is gradually strengthened over time, thus rendering it less and less susceptible to disruption by further stimuli such as new information. Figure 6.1 for example illustrates % memory consolidation (measured as treatment-resistant LTM) over time in the goldfish (taken from Dudai, 2004, who based the graph on data by Agranoff et al. 1966, on shuttle box learning in the goldfish). As demonstrated in the graph Long Term Memories are strengthened and thus rendered resistant to disruption as a function of time.

Given such theory it would appear likely that patients showing extended retention of prose material presented to them prior to Minimal RI still have some capacity for LTM consolidation, but that they are only able to consolidate new information when encoding of information is immediately followed by a period of Minimal RI, i.e. when the period during which memories are most fragile is devoid of any disruption.

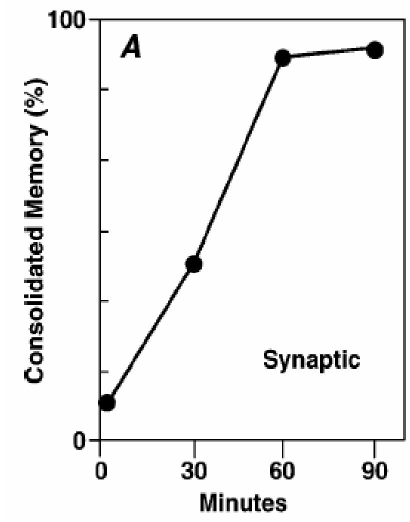


Figure 6.1. % memory consolidation (measured as treatment-resistant LTM) over time in the goldfish (taken from Dudai, 2004, who based the graph on data by Agranoff et al. 1966, on shuttle box learning in the goldfish).

Nonetheless, while the experiments reported in Chapter 5 provided strong evidence for a consolidation hypothesis of the benefit of Minimal RI, they were based on a small number of patients some of whom did not show any extended retention following Minimal RI or even a basic benefit of Minimal RI. While it is unknown as yet why some patients showed extended retention or indeed a basic benefit while others did not do so, it is plausible that the somewhat diverse range of etiologies and lesion sites may have played some role. For such reason it was decided to further investigate the consolidation hypothesis of the benefit of Minimal RI on patients with aMCI, a defined subcategory of amnesia, who present with anterograde amnesia in the absence of any other neuropsychological deficits and overt dementia, and who are known to benefit greatly from Minimal RI (Della Sala et al., 2005). aMCI carries an increased risk for progressing to Alzheimer's disease with a conversion rate of around 14% a year (Ritchie and Touchon, 2000). Research on this patient group is thus not only of theoretical but also clinical importance.

In order to provide stronger evidence for a *consolidation* hypothesis of the benefit of Minimal RI, and thus for a hypothesis that posits that RI susceptibility is

reduced as a function of time, it was further decided to refine the experimental design of the previous Experiments reported in Chapter 5 in the present study:
Rather than comparing proportion retention following an RI interval consisting of one type of RI (i.e. tone detection in Chapter 5) with proportion retention after an interval of Minimal RI *followed* by an interval of *another* type of RI (conversation in Chapter 5), it was decided in the present Experiment to compare proportion retention following a delay interval, in which the *same* type of RI either occurs at the *start* of the delay interval or at the *end* of the delay interval, which was of equal duration.
Moreover, it was decided to also include a condition, in which, RI occurred in the middle of the delay interval, the underlying reasoning being that, if indeed RI susceptibility is reduced as a function of time, proportion retention in such condition should lie in between that of the condition, in which RI occurs at the start and at the end of the delay interval. Thus, the critical manipulation in the present study was the *temporal onset* of RI within the delay interval.

The underlying prediction of the experiment as a whole was that if the memory improvement previously observed in patients with aMCI were the product of explicit STM maintenance, the *temporal onset* of RI should not have an effect; forgetting should occur as soon as RI appears, *irrespective* of its temporal onset. On the other hand, it was predicted that if the previously established memory improvement following Minimal RI were associated with LTM consolidation, aMCI patients should show a *temporal gradient of RI* (Wixted, 2004), thus, an *increasing* proportion retention as RI onset within the delay interval is *delayed* (as demonstrated in the goldfish data in Figure 6.1.)

6.2. Experiment 5(a): Apparent improved consolidation in aMCI following Minimal Retroactive Interference (I)

6.2.1 Aims of Experiment 5(a)

The aim of the present study was thus to examine whether or not *onset time* of RI within a delay interval would affect proportion retention in a sample of patients with aMCI and if so, whether a *temporal gradient of RI* would be elucidated.

6.2.2 Method

6.2.2.1 Participants

14 patients with aMCI (8 f/6m, mean age = 73.29 years, SD = 5.15, mean education = 7.21, SD = 3.47) and 14 age and education matched healthy controls (12f/2m), mean age = 71.29, SD = 6.32, mean education = 10.00, SD = 4.71) participated in the study. Their demographic data as well as neuropsychological assessment results are provided in Tables 6.1, 6.2a and 6.2b. In accordance with the criteria for aMCI by Petersen et al. (1999) all patients entering the study had a memory complaint that was corroborated by an informant. Moreover they presented with objective memory impairment as indicated by a low Spanish and English Verbal Learning Test (SEVLT) (Gonzalez et al. 2001) total immediate word learning score and low SEVLT delayed word list recall as well as a low score in the Rey-Osterrieth Figure delayed recall (Caffarra, 2002). Patient scores for the SEVLT total immediate learning were > 2SD below the control mean in 9/14 patients, and as shown in Tables 1 and 2, all patients showed a lower score in this measure than the lowest performing control. More specifically, the oldest control with low education scored better at this measure (C9, score = 43) than the youngest patient with matched education (P14, score = 27) and the patient with the highest education (P12, score = 35). Patient scores for the SEVLT delayed word list recall were > 2SD below the control mean in 14 patients. All patients also had a Clinical Dementia Rating Scale

(CDR; Hughes, Berg, Danzinger, Coben, & Martin, 1982) score equal to 0.5, indicating an overwhelming deficit in memory as compared to other cognitive domains and activities. However none were demented. All 14 patients showed intact activities of daily living as well as normal general cognitive functioning as evinced by a normal Mini-Mental State Examination score (Folstein et al., 1975) and mostly normal performance in a battery of neuropsychological tests (see Tables 6.1, 6.2a and 6.2b) except on Trail Making and Semantic Fluency. Moreover none of the patients (nor controls) showed signs of abnormalities in the neurological examination nor any signs of focal lesions (examined with MRI).

Any patients showing signs of dementia were excluded and are not reported here. Moreover any patients or controls performing at ceiling or floor in the experiment were excluded from the study and are not included here.

The Experiment took place in a darkened quiet laboratory at the Department of Cognitive Neuroscience within the Cuban Neuroscience Centre, Havana, Cuba. Informed consent was taken by Yuriem Fernandez Garcia (Neuropsychologist) who also provided the instructions and noted the participants' recall and picture naming under the supervision of Michaela Dewar who ran the trials on the computer.

	Patients		Controls		
	Mean	SD	Mean	SD	
Age	73.29	(5.15)	71.29	(6.32)	
Education (years)	7.21	(3.47)	10.00	(4.71)	
Estimated IQ (WAIS)	109.50	(10.95)	118.21	(8.17)	*
MMSE	26.64	(1.82)	28.29	(1.33)	*
CDR	0.50	(0.00)	0.00	(0.00)	
Word List Learning Total Immediate (SEVLT)	30.36	(4.57)	46.00	(5.55)	***
Word List Learning Total Immediate(SEVLT) corrected	35.30	(5.62)	49.78	(5.85)	***
Delayed Word List Recall (SEVLT)	6.64	(1.39)	10.86	(1.23)	***
Delayed Word List Recall (SEVLT) (corrected)	7.46	(1.47)	11.74	(1.82)	***
Word List Retention (%) (SEVLT)	63.17	(17.57)	87.19	(12.43)	***
Immediate Prose Recall (MODA)	6.47	(1.15)	7.70	(0.38)	***
Delayed Prose Recall (MODA)	5.49	(2.08)	7.50	(0.49)	**
Digit Span	5.00	(0.88)	5.86	(0.86)	*
Spatial Span	4.29	(0.91)	4.79	(0.58)	
Figure Copy (Rey)	32.25	(3.42)	34.36	(1.86)	
Figure Delayed Recall (Rey)	11.79	(3.28)	17.50	(2.82)	***
Trail Making B-A	210.64	(77.63)	77.71	(55.14)	***
Phonological Fluency	8.07	(2.06)	9.71	(2.20)	
Semantic Fluency	12.71	(2.13)	15.64	(2.68)	**
Token Test	32.79	(1.65)	33.79	(1.01)	
Attentional Matrices	47.21	(4.48)	51.71	(4.53)	*

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 6.1. Patient and Control group means and SDs for each of the demographic and neuropsychological measures. Significant Group differences are indicated with an asterisk (*).

Estimated IQ, (Silverstein, 1982); Mini Mental State Examination (MMSE)(Folstein et al., 1975); Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982); Spanish and English Verbal Learning Test (SEVLT) (Gonzalez et al. 2001); Prose recall, Milan Overall Dementia Assessment (MODA) (Brazzelli et al.,1994); Digit span (WASI-R) (Wechsler, 1981), Corsi span (Novelli et al., 1986); Rey Figure copy and recall (Caffarra et al., 2002); Trail Making (Giovagnoli et al., 1996); Phonoligical fluency (Carlesimo et al., 1996); Semantic fluency (Spinnler and Tognoni, 1987); Token Test (De Renzi and Fagliono, 1978); Attentional Matrices (Spinnler and Tognoni, 1987).

Measure	Control M (SD)		P1	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P14	P15	P16
			Patient Number													
Age	71.29	(6.32)	77	79	68	70	73	75	81	72	71	78	73	62	78	69
Education (years)	10	(4.71)	9	3	6	6	4	4	8	10	6	8	17	5	7	8
Gender	12f/2m		f	m	f	f	f	m	f	m	m	f	m	m	f	f
Wais-R Estimated IQ	118.21	(8.17)	120	111	124	95	92	111	124	98	114	104	124	109	108	99
MMSE	28.29	(1.33)	29	27	29	24	26	25	24	29	25	29	26	26	27	27
CDR	0	0	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Word List Learning Total Immediate (SEVLT)	46	(5.55)	33	25	36	27	25	25	27	34	32	36	35	27	27	36
Word List Learning Total Immediate (SEVLT).corrected	49.78	(5.85)	41.06	32.17	41.75	33.71	34.51	29.57	37.66	33.06	33.29	45.21	29.81	24.62	36.89	40.88
Delayed Word List Recall (SEVLT)	10.86	(1.23)	8	4	8	5	5	5	5	8	7	7	8	6	6	7
Delayed Word List Recall (SEVLT) (corrected)	11.74	(1.82)	10.01	5.57	9.27	6.53	7.23	5.89	7.69	7.61	7.07	9.29	6.70	5.03	8.44	8.11
Immediate Prose Recall (MODA)	7.7	(0.38)	7.6	6.4	6	4.4	5.8	6.8	4.3	5.5	7.6	7.7	6.7	6.7	7.7	7.4
Delayed Prose Recall (MODA)	7.5	(0.49)	7.6	0	6	3.3	5.5	6.5	3	5.5	7.6	6.6	6.7	6.7	6.4	5.4
Digit Span	5.86	(0.86)	5	4	5	5	5	6	6	4	6	4	4	6	4	6
Spatial Span	4.79	(0.58)	5	3	5	4	4	4	6	3	4	3	5	5	4	5
Figure Copy (Rey)	34.36	(1.86)	34	30.5	36	36	33	29	35	31	24	34	31	29	33	36
Figure Delayed Recall (Rey)	17.5	(2.82)	16	6	14	12	9.5	11	11.5	14	11.5	14.5	14.5	12	4.5	14
Trail Making B-A	77.71	(55.14)	153	268	165	377	178	225	143	283	243	140	177	126	148	323
Phonological Fluency	9.71	(2.2)	10	9	6	7	6	7	12	8	5	9	11	9	8	6
Semantic Fluency	15.64	(2.68)	11	12	13	10	13	12	16	13	14	12	12	18	11	11
Token Test	33.79	(1.01)	33.5	32.5	34.5	34	32	33.5	33	34.5	31	32	34.5	32	33.5	28.5
Attentional Matrices	51.71	(4.53)	45	46	50	46	47	47	60	44	45	40	48	50	48	45

Table 6.2a Selected characteristics of tests and amnesic patient performance

Measure	Control Number													
	C1	C2	C3	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16
Age	67	67	76	69	70	74	80	67	65	83	70	78	72	60
Education (years)	6	6	17	7	6	7	6	18	15	9	17	6	11	9
Gender	F	f	m	f	f	f	m	f	f	f	f	f	f	f
Wais-R Estimated IQ	102	114	130	108	117	117	120	123	123	108	117	130	124	122
MMSE	26	28	30	28	27	30	28	30	30	29	28	27	28	27
CDR	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Word List Learning Total Immediate (SEVLT)	45	43	51	40	56	45	43	53	45	42	40	39	54	48
Word List Learning Total Immediate (SEVLT).corrected	50.26	48.26	47.26	45.55	62.71	52.96	48.62	50.15	43.22	52.95	39.27	49.57	58.29	47.86
Delayed Word List Recall (SEVLT)	12	10	12	9	13	10	10	11	10	11	9	12	12	11
Delayed Word List Recall (SEVLT) (corrected)	13.137	11.137	11.099	10.253	14.533	11.913	11.255	10.361	9.541	13.805	8.905	14.589	13.057	10.769
Immediate Prose Recall (MODA)	7.9	7.8	8	7.7	7.8	6.8	6.9	8	7.8	7.7	7.7	7.7	8	8
Delayed Prose Recall (MODA)	7.6	7.5	8	7.7	7.8	6.8	6.9	7.5	7.7	6.3	7.7	7.7	8	7.8
Digit Span	6	6	7	5	6	5	6	6	8	6	5	5	6	5
Spatial Span	4	5	5	6	5	5	5	5	4	5	5	5	4	4
Figure Copy (Rey)	31	34	36	33	33	35	36	36	35	33	36	36	36	31
Figure Delayed Recall (Rey)	15.5	17	17	16.5	14	19	15.5	18	21	16	24	21	15.5	15
Trail Making B-A	134	83	55	34	82	63	39	46	35	226	21	80	53	137
Phonological Fluency	9	8	8	10	7	7	11	11	12	7	12	9	14	11
Semantic Fluency	13	13	16	13	18	17	11	17	19	17	17	20	13	15
Token Test	32.5	33.5	35	33.5	34	34	34.5	35	34	31.5	34.5	34.5	34	32.5
Attentional Matrices	47	50	53	46	58	47	50	60	54	51	45	55	53	55

Table 6.2b Selected characteristics of tests and control performance

6.2.2.2 Materials and Procedure

All participants were presented with four word lists verbally which they were asked to try and remember for subsequent immediate recall. Each word list contained 15 words, which were compiled from a list of standardized words (Manzano et al., 1997) (see Appendix D). The digitally recorded word lists were presented to the participants via headphones at a rate of one word every two seconds using the software MATLAB (The Maths Works.Inc). Word list presentation was followed by free immediate recall in all four conditions. The end of immediate recall marked the beginning of a nine minute delay interval, which was unfilled in one condition and partially filled in the other three conditions. In the unfilled Delay Condition the participant was left alone in the darkened quiet room (No RI) for the entire nine minutes. In the partially filled conditions the participant engaged in a picture naming task (RI) for three minutes while the remainder of the nine minute delay interval was spent alone in the darkened quiet room as for the No RI Condition. The RI stimuli consisted of four picture/name lists. Every list contained 45 individual pictures, each of which was paired with a superimposed word. The 180 pictures as well as the words were compiled from the Snodgrass and Vanderwart (1980) image bank using Cuban norms for this image bank (Manzano et al., 1997).

30 of the picture/word stimuli in each list were congruent in that the picture and its superimposed word matched (see Figure 6.2). The remaining 15 picture stimuli in each list were incongruent, meaning that the word and its superimposed word did not match (i.e. Picture–word 'Stroop' stimuli) (see Figure 6.2).

Congruent Picture/name stimulus Incongruent Picture/name stimulus

(Cat – Cat) (Lip – Nose)

Figure 6.2. Examples of picture-word stimuli

Incongruent and congruent picture-name stimuli were presented one by one in random order via MATLAB and remained on the screen for 4000ms each. Participants were instructed to name each picture aloud as quickly as possible without reading the superimposed word.

This picture naming task was designed and used in the present Experiment as it was a form of diversion RI and also acted as a verbal rehearsal blocker.

All names were recorded by the experimenter. Picture naming reaction time was recorded by a second experimenter by pressing the space bar when the participant began naming each picture. False RTs caused by sounds unrelated to the naming such as coughing or utterances prior to naming were thus not recorded as is the case with a voice key. When a participant corrected him/herself the second experimenter pressed the space bar a second time. In such a case the last RT was utilized for later computation of total RT.

A practice trial containing 15 picture-name pairs, both congruent and incongruent, took place before the main experiment began to ensure that all participants were familiar and confident with the task and thus to minimize further instructions during the main experiment. When a participant required more practice the 15 picture-name pairs were presented again.

The critical manipulation in the three delay intervals containing the three minute picture-naming task was the onset time of this task: In the *First RI Condition* the picture naming task was initiated promptly following immediate recall and thus took place in the *first three minutes*. The remaining six minutes of the delay interval were spent alone in the darkened quiet room. In the *Mid RI Condition* the picture naming task was initiated three minutes post immediate recall thus taking place in the *middle three minutes*. The first and last three minutes of this delay interval were spent alone in the darkened quiet room. In the *Last RI Condition* picture naming occurred six minutes post immediate recall, i.e. in the *last three minutes*, while the participant spent the first six minutes of the delay interval alone in the darkened quiet room. Delayed word list recall followed each of the four delay intervals. The four conditions are illustrated in Figure 6.3.

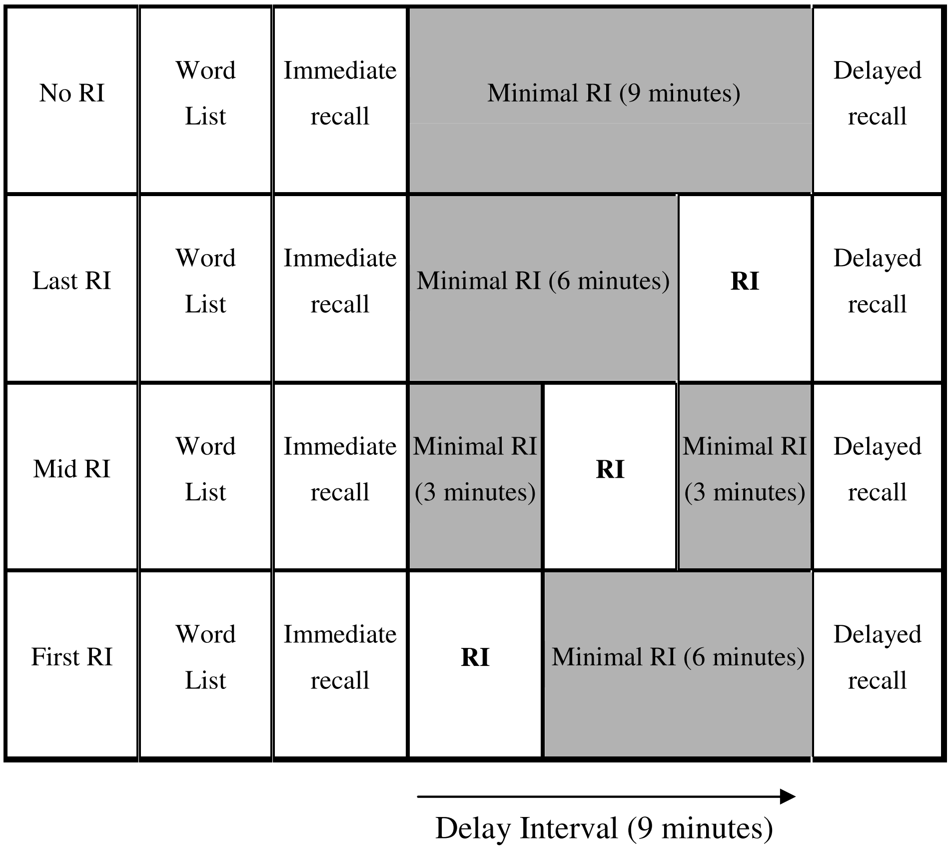


Figure 6.3. The four conditions in the study.

While participants were clearly informed that they would be presented with a list of words, which they would have to remember immediately following word list presentation, they were never informed about later delayed recall.

In order to avoid possible order effects of condition, half of the participants in each group undertook the 4 conditions in the order *No RI – Last RI – Mid RI – First RI* while the remainder participated in the order *First RI – Mid RI – Last RI – No RI*. The three picture-name lists were attached to a condition each, meaning that they were also presented in the two orders. Word list order was kept constant for all participants (1-2-3-4). Full counterbalancing of conditions and word lists was not utilized as this could have convoluted possible differences due to individual differences (i.e. in severity of amnesia and hippocampal volume).

Following the Experiment, feedback was obtained from each participant in the form of a questionnaire read out by the experimenter. Participants were also asked to try to recall again any words from the four presented lists at this point (see Experiment 5(b)).

6.2.2.2.1 Word list scoring

Only words recalled verbatim were scored as correct, i.e. variations or synonyms were not accepted.

6.2.2.2.2 Picture naming

Performance in the picture naming task was assessed via total list RT (i.e. the sum of all RTs for each of the 45 pictures in each list). For picture name pairs for which there was no response due to no or late naming of that picture the maximum RT of 4000ms was utilized. Total number correct picture naming (i.e. a score out of 45) was also computed. Synonyms and semantically similar names were accepted in the picture naming task.

6.2.2.2.3 Picture naming lists – Piloting of the Picture lists

A pilot study involving 12 healthy volunteers (4f/8m, mean age = 25 years, SD = 7.21, mean education = 14.08, SD = 2.57) was run to assess whether or not the three picture lists used in the study were comparable in cognitive demand as assessed via Total RT and Score. Instructions and procedure for this study was identical to the Picture naming instructions and procedure utilized in the main study. The lists were presented in the same two orders as in the main study. Six participants were presented with the lists in order one (Practise trial, List 1 – List 2 – List 3) while the other six participants were presented with the picture lists in order two (Practise trial, List 3, List, 2, List 1). This study showed that neither the Total RT nor the Score differed significantly for the three picture lists. Participants were further asked to provide feedback concerning any differences in subjective difficulty for the three lists. Eight participants revealed that they did not find any of the lists harder or easier than the others. Two participants stated that picture list 1 was more difficult than the others while one participants found picture list 3 harder than the others.

6.2.3 Results

A mixed factors ANOVA on proportion correct immediate recall (number of words recalled at immediate recall/total number of words within presented word list) with within subjects factor RI Condition (no RI vs. Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls) was initially run to assess the state of memory before a delay was imposed. The assumptions for such ANOVA were not violated as elucidated by an insignificant Mauchly' test of sphericity. The ANOVA revealed that proportion correct immediate recall did not differ significantly across the 4 conditions for either group. However, a main effect of Group was obtained, with the control group performing significantly better at immediate recall than the patient group, $F(1, 26) = 14.112$, $p < 0.01$. Group Mean Immediate recall proportion correct and SD was 0.378 (0.058) and 0.294 (0.059) for the controls and patients respectively. No RI Condition x Group interaction was found. The Group main effect was further examined via a one-way ANOVA with between subjects factor Group (Patients vs. Controls). This ANOVA showed that the Control group performed significantly better at immediate recall than the Patients in each of the 4 RI Condition trials, (No RI, $F (1, 27) = 6.971$, $p < 0.05$; Last RI, $F (1,27) = 12.887$, $p < 0.01$; Mid RI, $F(1, 27) = 4.773$, $p < 0.05$; First RI, $F(1, 27) = 6.596$, $p < 0.05$).

As in the previous patients studies on RI in amnesia (Della Sala et al., 2005; Cowan et al. 2004) retention at delayed recall was measured as the number of correct words recalled at delayed recall divided by the number of correct words recalled at immediate recall in the same condition (i.e. Delayed Recall/Immediate Recall).

A mixed factor ANOVA with within subjects factor RI Condition (First RI vs. Mid RI vs. Late RI vs. No RI) and between subjects factor Group (Patients vs. Controls) was set up. Prior to analysis the assumptions for such mixed factor ANOVA were checked via the Mauchly's test of sphericity, which was insignificant thus revealing that the assumptions for the planned ANOVA were not violated.

The subsequent ANOVA revealed a highly significant RI Condition main effect, $F(3, 78) = 23.140$, $p < 0.001$, and a highly significant Group main effect, $F(1, 26) = 34.419$, $p < 0.001$ and, most importantly, a significant RI Condition x Group interaction, $F(3, 78) = 4.876$, $p < 0.01$. In order to examine any specific effect of the *temporal position* of RI on proportion retention the above ANOVA was repeated without the No RI data. This ANOVA revealed a significant RI Condition main effect, $F(2, 52) = 12.002$, $p < 0.001$, and a highly significant Group main effect, $F(1, 26) = 48.397$, $p < 0.001$, as well as a significant RI Condition x Group interaction, $F(2, 52) = 3.446$, $p < 0.05$.

The means corresponding to these two ANOVAs are depicted in Figure 6.4. Individual participant retention data are depicted in Tables 6.7 and 6.8. As the figure shows, earlier RI resulted in a larger difference between groups.

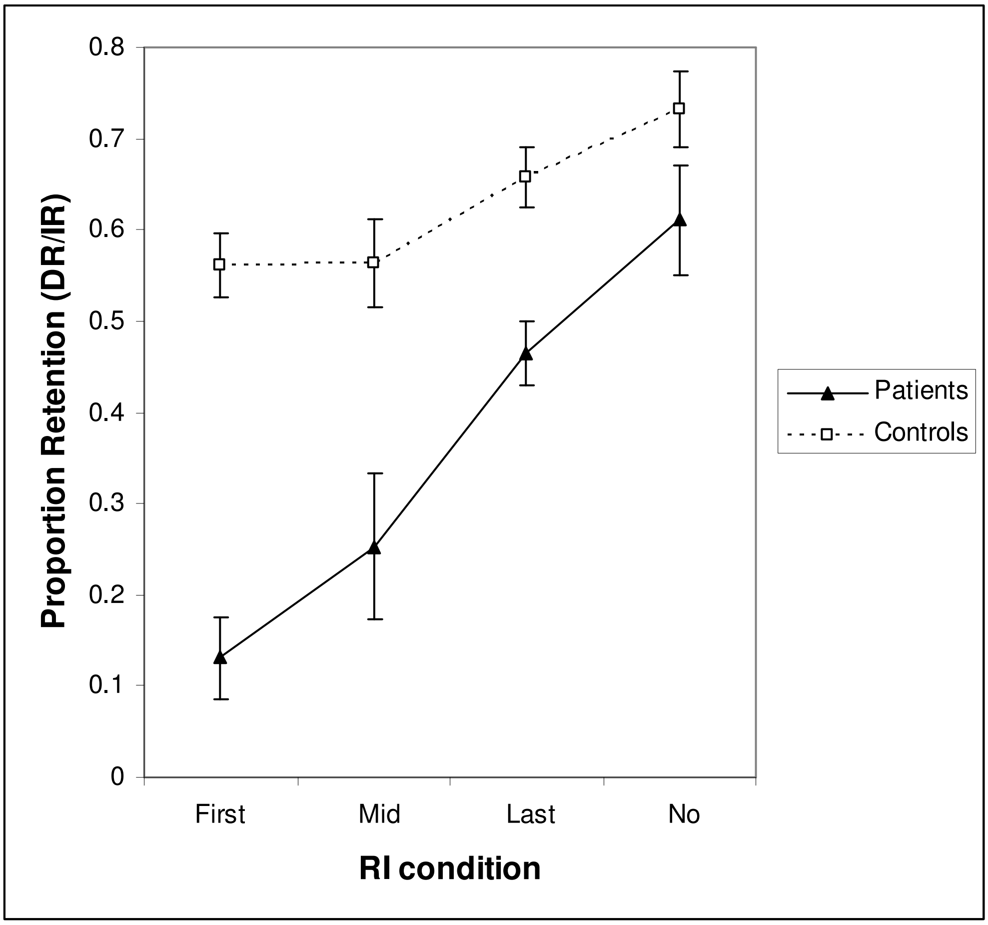


Figure 6.4: Mean Proportion Retention (DR/IR) as a function of Group and RI Condition. Error bars = SEM.

In order to examine the Group Main effects obtained in both above ANOVAs in more detail a simple main effects analysis was set up with between subjects factor Group (Controls vs. Patients). The Levene's test of equality of error variances revealed that homogeneity of variance could be assumed for the two groups for the No RI, the Last RI and the First RI Conditions but not for the Mid RI Condition ($p < 0.05$). It is suggested that the ANOVA is insensitive to slight to moderate violations to the homogeneity of variance assumptions when sample sizes are equal (c.f. Box, 1952). It was nevertheless decided to run both a one way ANOVA and a Welch correction ANOVA (Welch, 1951), which is robust to the variance assumption, on the retention group data for the Mid RI Condition.

It was found that the basis of the Group main effect was a significantly lower proportion retention in the patient group than the control group in all conditions containing RI (Last RI, $F (1, 27) = 15.676$, $p < 0.01$; Mid RI, $F (1, 27) = 11.128$, $p < 0.01$; First RI, $F (1, 27) = 58.792$, $p < 0.001$). There was no significant group difference in the No RI Condition. The Welch corrected ANOVA (applied due to the heterogeneity of variance in the Mid RI Condition) confirmed that the patient group had significantly lower retention than the control group in the Mid RI Condition, $F (1, 21.32) = 11.128$, $p < 0.01$.

In order to investigate the Condition main effects emerging in both ANOVAs in more detail, each combination of condition pairs was separately analysed in a mixed factors ANOVA with within subjects factor Condition (No RI vs. Last RI; No RI vs. Mid RI; No RI vs. First RI; Last RI vs. Mid RI; Last RI vs. First RI; Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls). These ANOVAs revealed that the significant main effect of condition in the ANOVA including the No RI Condition was caused by significantly higher retention following the No RI Condition than any of the other RI Conditions (No RI vs. Last RI, $F (1, 26) = 5.877$, $p < 0.05$; No RI vs. Mid RI, $F (1, 26) = 39.086$, $p < 0.001$; No vs. First RI, $F (1, 26) = 81.113$, $p < 0.001$), significantly higher retention following the Last RI than the Middle RI Condition, $F (1, 26) = 8.777$, $p < 0.01$, and significantly higher retention following the Last RI than the First RI Condition, $F (1, 26) = 36.632$, $p < 0.001$. No significant difference in retention was revealed between the First RI and Mid RI Condition.

A further set of ANOVAs further elucidated that the Condition x Group interaction obtained in the main ANOVA was the result of Condition x Group interactions for the No RI and Mid RI Condition comparison, $F (1, 26) = 5.002$, $p < 0.05$, the No RI and First RI Condition comparison, $F (1, 26) = 18.2$, $p < 0.001$ and the Last RI and First RI Condition comparison, $F (1, 26) = 11.142$, $p < 0.01$. The Condition x Group interaction for the Last RI and First RI Condition was also the basis of the Condition x Group interaction elucidated in the main ANOVA when the No RI Condition was excluded.

In order to examine the particular basis of these three Condition x Group Interactions three within subjects ANOVAs with within subjects Factor RI Condition (No RI vs. Mid RI, No RI vs. First RI and Last RI vs. First RI) were run separately for each of the two groups.

Mauchly's test of sphericity was not significant meaning that the assumptions for the planed ANOVAs were not violated. The ANOVA showed that Retention in the No RI Condition was significantly higher than in the Mid RI Condition in both groups($F(1, 13) = 29.442$, $p < 0.001$ for the patients and $F(1, 13) = 10.384$, $p < 0.01$ for the controls). Furthermore retention was also significantly higher following the No RI than the First RI Condition in both groups ($F(1, 13) = 51.871$, $p < 0.001$ for the patients and $F(1, 13) = 32.202$, $p < 0.001$ for the controls). Moreover, Retention following the Last RI was significantly higher than that following the First RI Condition in both groups ($F(1, 13) = 29.276$, $p < 0.001$, for the patients and $F(1, 13) = 7.458$, $p < 0.05$ for the controls)).

As both groups showed significant improvement from Mid RI to No RI, from First RI to No RI and from First RI to Last RI one way ANOVAs with between factor Group (patients vs. controls) were run to compare the groups on *magnitude* of improvement in each of the three condition pairs (i.e. retention No RI minus retention Mid RI, retention No RI minus retention First RI, and retention Last RI minus retention First RI). Levene's test was significant for the No RI to First RI improvement ($p < 0.001$). A Welch corrected ANOVA was thus also run for the Group comparison of this improvement. The ANOVAs elucidated significantly larger improvement in retention for the patients than the controls from Mid RI to No RI, from First RI to No RI and from First RI to Last RI ($F(1, 27) = 5.002$, $p < 0.05$, $F(1, 27) = 18.2$, $p < 0.001$ and $F(1, 27) = 10.921$, $p < 0.01$ respectively; The Welch corrected ANOVA for the First RI to Last RI improvement resulted in the same outcome, $F(1, 17.482) = 18.2$, $p < 0.001$). Group mean improvement in retention for these three condition pairs as well as the other four pairs are provided with corresponding SEMs in Table 6.4 below. The table also provides the percentage of patients and controls showing the improvements for the RI Conditions indicated above.

Conditions	Patients			Controls			
	Mean	SEM	% of sample showing effect	Mean	SEM	% of sample showing effect	
First RI ► No RI	**0.48**	**0.07**	92.8	**0.17**	**0.03**	92.86	*
First RI ► Last RI	**0.33**	**0.06**	92.8	**0.10**	**0.04**	71.43	*
First RI ► Mid RI	0.12	0.08		0.00	0.05		
Mid RI ► No RI	**0.36**	**0.07**	85.71	**0.17**	**0.05**	85.71	*
Mid RI ► Last RI	**0.21**	**0.10**	71.43	**0.09**	**0.04**	71.43	
Last RI ► No RI	0.15	0.08		0.08	0.04		

Table 6.4. Group mean improvement in proportion retention for each of the six RI Condition pairs (Improvement = Proportion retention for the condition to the right - Proportion condition for the condition to the left). Significant improvement is indicated in bold. The asterisk (*) indicates RI Condition pairs for which improvement was significantly larger in the patients than the controls. Also provided is the percentage of the patient and the control sample showing the given improvements.

6.2.3.1 <u>RI task performance</u>

Even though the aforementioned pilot study on the three picture lists demonstrated that the three lists were well matched with respect to cognitive demand (as measured via RT and total picture naming score and subjective feedback), picture naming RT and naming score data was examined for the three RI Conditions in order to check whether or not picture naming performance differed across the three RI Conditions.

RT

A mixed factors ANOVA with within subjects factor RI Condition (Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls) with Greenhouse- Geisser correction due to a significant Mauchly’s test of spericity

($p < 0.001$) showed no significant difference in RT between the three RI Conditions and no significant RI Condition x Group interaction. However, a main effect of Group was obtained, $F(1, 26) = 29.225$, $p < 0.001$, the basis of which being higher RT for the patients than the controls. Figure 6.5 shows Group Mean RT data.

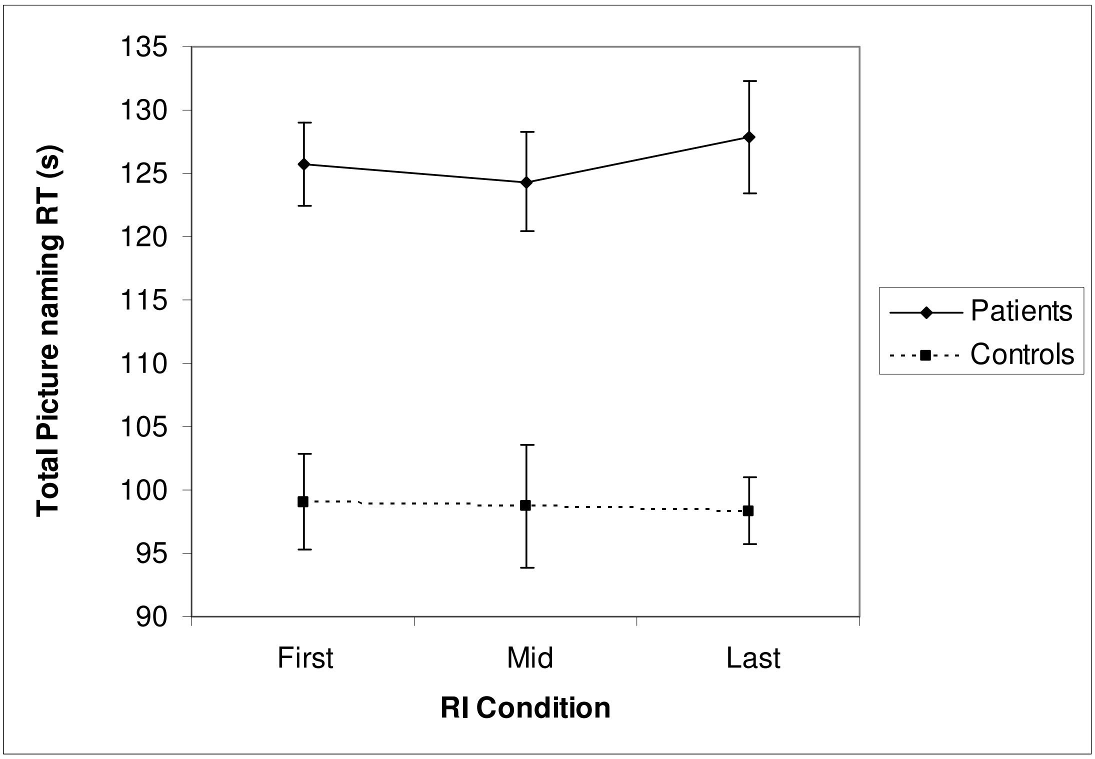


Figure 6.5. Group Mean Total Picture naming RT as a function of RI Condition. Error bars = SEM.

Naming scores

Naming score for each condition could be between 0 and 45, i.e. one point for each of the 45 pictures named correctly.

A mixed factors ANOVA with within subjects factor RI Condition (Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls) was set up. Mauchly's test of spericity was insignificant, indicating that the assumptions for this ANOVA were not violated. The ANOVA showed a significant difference in Picture naming score across the three RI Conditions, $F(2, 52) = 10.951$, $p < 0.001$. A significant main effect of Group in picture naming was also obtained, $F(1, 26) = 5.816$, $p < 0.05$. No RI Condition x Group interaction was shown. The Group Means are depicted in Figure 6.6.

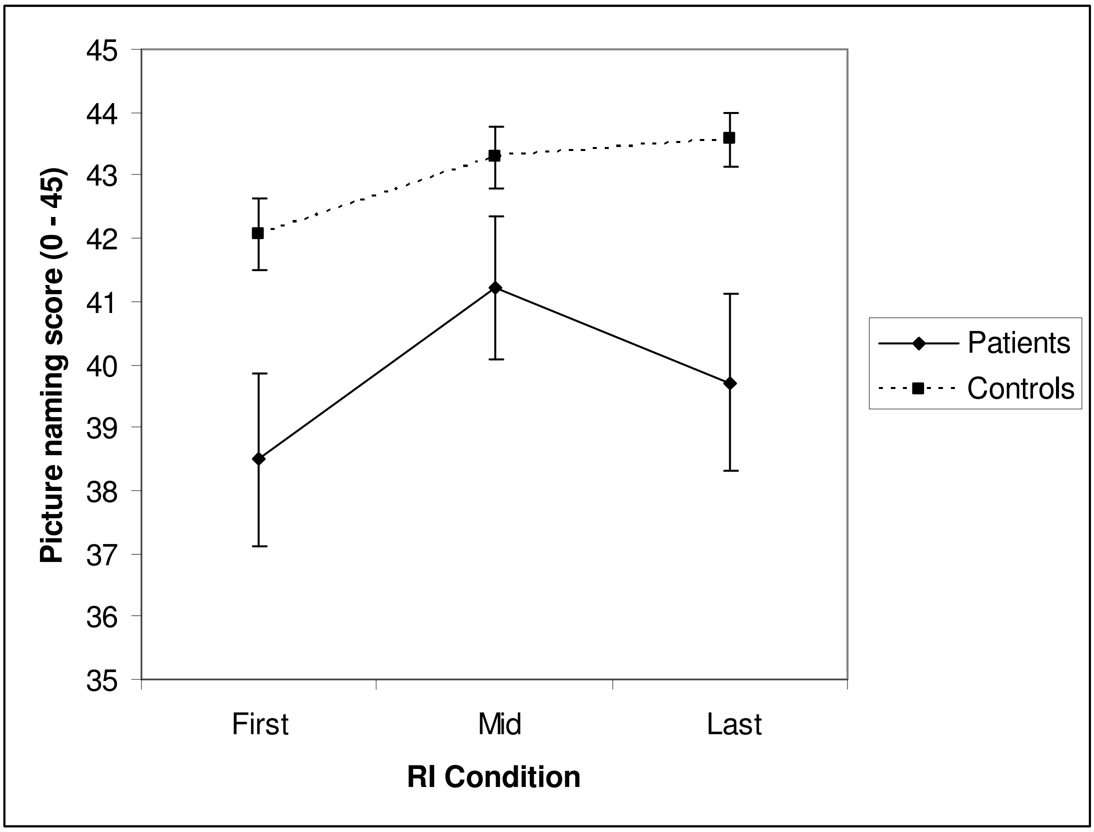


Figure 6.6. Group Mean Total Picture naming score as a function of RI Condition. Error bars = SEM.

A simple main effects analysis revealed that picture naming was significantly poorer in the First RI than Last RI Condition, $F(1, 26) = 9.587$, $p < 0.01$, and in the First RI than Mid RI Condition, $F(1, 26) = 17.002$, $p < 0.001$. No significant difference in picture naming emerged between the Last RI and Mid RI Conditions.

In order to examine this apparent significant difference in naming scores between the RI Conditions, and in especially the poorer naming performance in the First RI Condition, individual naming scores were inspected. These are depicted in Figures 6.7 and 6.8 below. The graphs show that while the picture naming pattern shown in

Figure 6.6 are obtained for some members in each group, this is not the case for all group members, some of whom show opposite patterns.

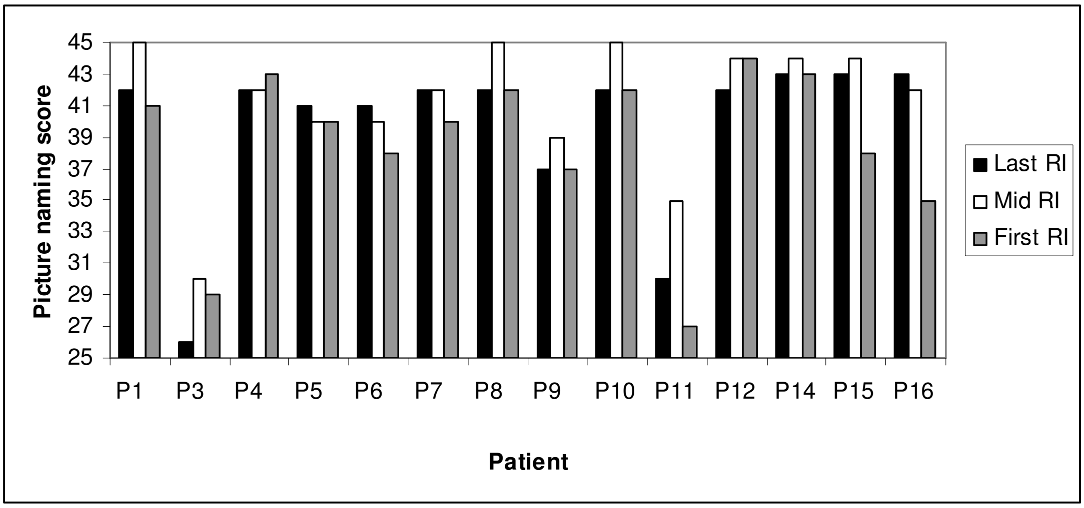


Figure 6.7. Patient Total picture naming score as a function of RI Condition

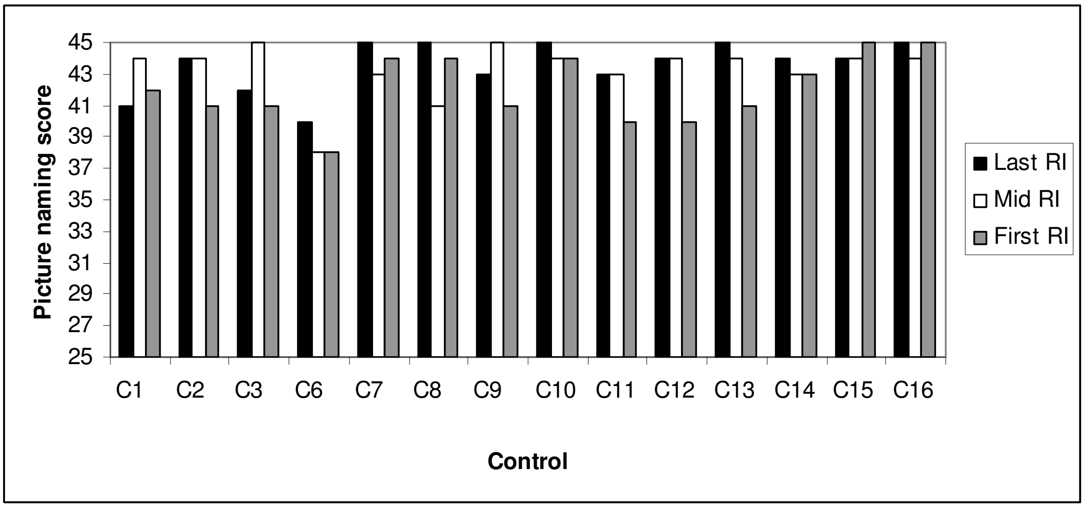


Figure 6.8. Control Total picture naming score as a function of RI Condition

In order to assess whether there was any indication of an association between picture naming score and proportion retention, bivariate correlations were run for each group between Picture Naming score and proportion retention for each of the three RI Conditions. No significant correlations were obtained. Figures 6.9 – 6.11 depict these data.

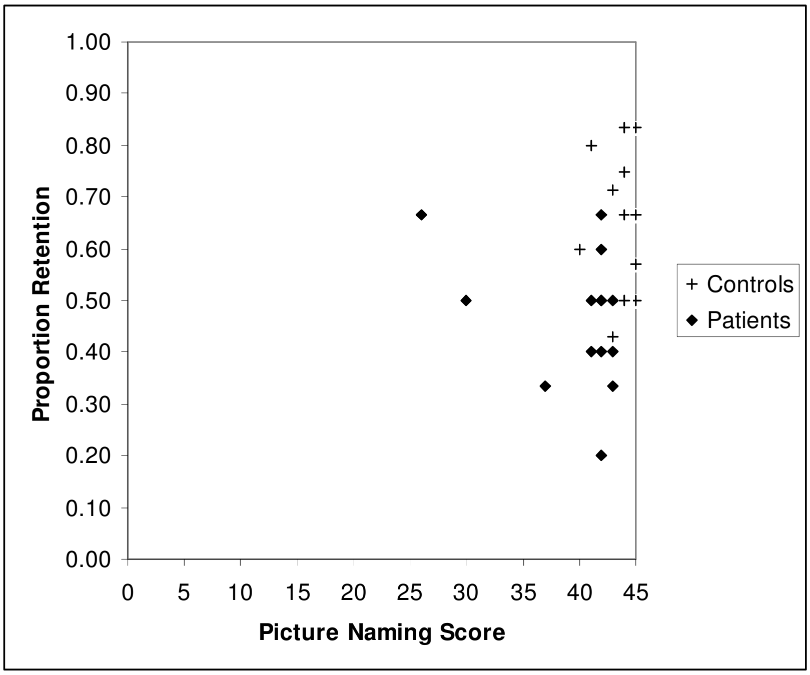


Figure 6.9. Patient and Control Proportion Retention plotted against Total Picture naming score (0-45) for the Last RI Condition.

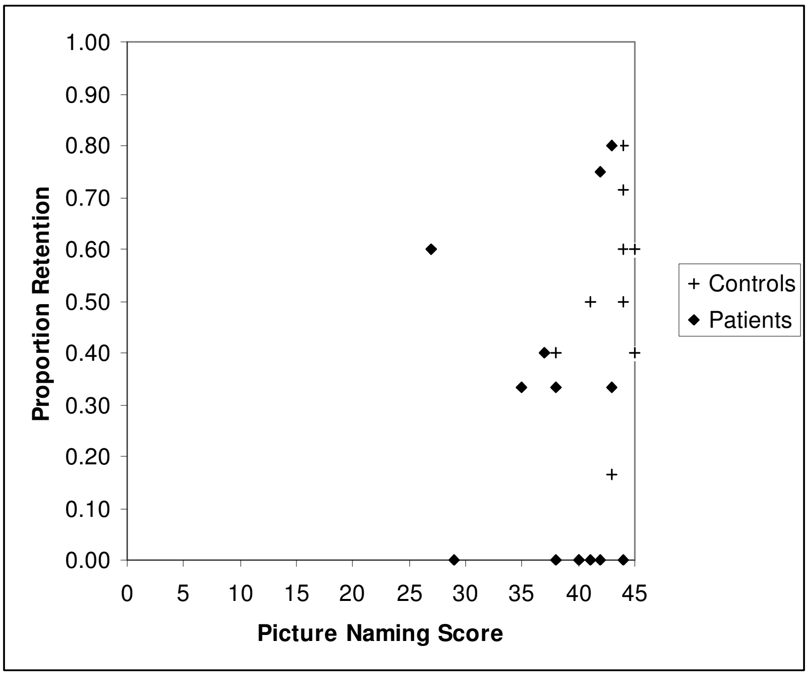


Figure 6.10. Patient and Control Proportion Retention plotted against Total Picture naming score (0-45) for the Mid RI Condition.

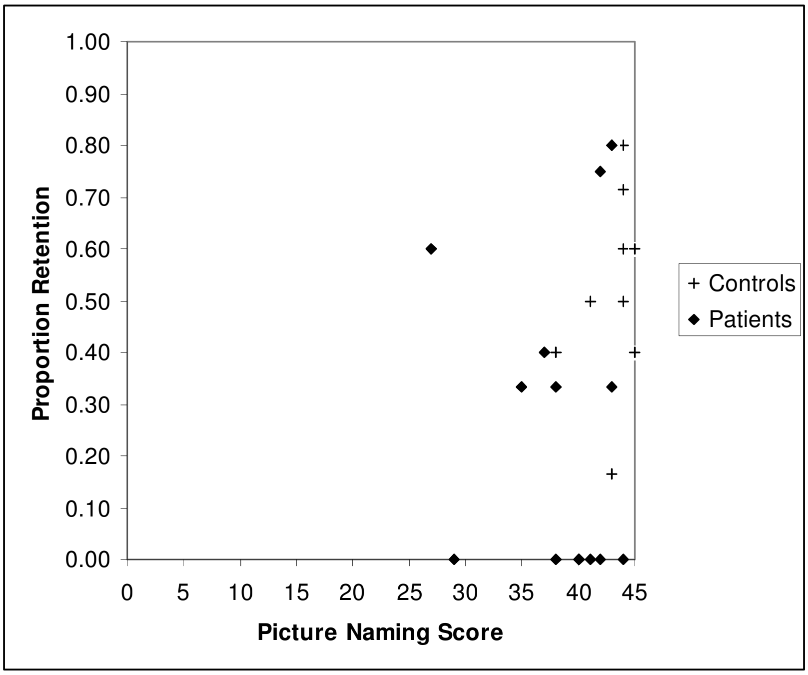


Figure 6.11. Patient and Control Proportion Retention plotted against Total Picture naming score (0-45) for the First RI Condition.

Figures 6.9 – 6.11 further show that while on the whole proportion decreases from Last RI to Mid RI to Last RI (i.e. Figure 6.9 to 6.10 to 6.11) no such trend is apparent for picture naming score. Nonetheless in order to establish statistically whether there was any association between individual participants' patterns of performance in picture naming and proportion retention across the three RI Conditions, it was decided to compute the picture naming score slope and the proportion retention slope over the three RI Conditions for each individual participant, i.e. ((Picture naming at Last RI – Picture naming at First RI)/2) and ((Proportion Retention at Last RI– Proportion Retention at First RI)/2) .

Pearson correlations were subsequently run for Picture naming score slope and Retention slope with both groups included as well as for each group separately. None of these correlations was significant. Figures 6.12 show these data.

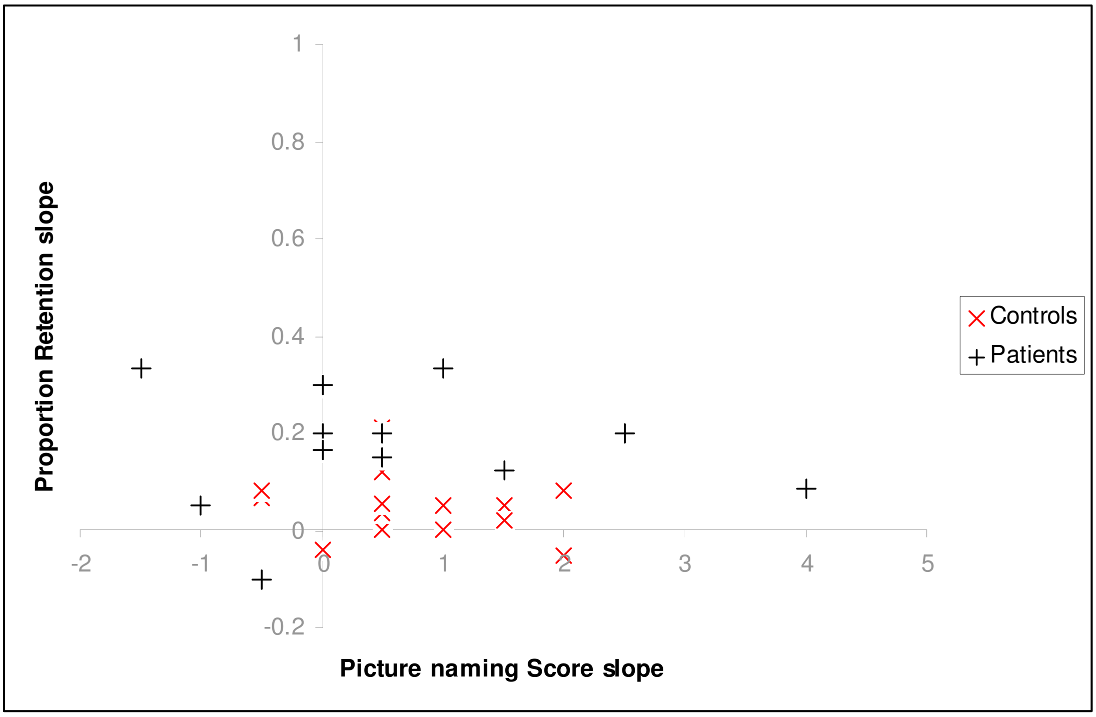


Figure 6.12. Patient and control Proportion Retention slope plotted against Picture naming slope.

While no apparent links between Retention and picture naming slopes were found and no RI Condition x Group interactions were found for Picture naming score, it was nevertheless decided to examine whether the aforementioned Group x RI Condition interaction for retention (i.e. the significantly larger slope in Retention for the Patients than the controls, see Figure 6.4) may have been associated with any non-significant group differences in the Picture naming slopes for the three RI Conditions.

First of all a one way ANOVA was performed on Retention slope, the between subjects factor being Group (Patients vs. Controls) to ascertain that the previously observed Group difference in Retention slope was also present when utilising this measure.

The ANOVA revealed a significant Group difference in the Retention slope, $F(1, 27) = 11.142$, $p < 0.01$, the basis of which being a larger slope in the Patient than Control group. Thus the Retention slope difference revealed by the Group x RI Condition Interaction was replicated using this measure.

A further one way ANOVA with between subjects factor Group (Patients vs. Controls) was conducted on Picture naming score slope No significant group differences were shown.

In order to examine whether any non-significant Group differences in Picture naming score slope and Picture naming RT slope may have nonetheless contributed to the large Group difference in Retention slope, an ANCOVA on Retention slope with between subjects Factor Group (Patients vs. Controls) and Picture naming score slope as covariate was run. The ANCOVA revealed that even when any Group non-significant differences in picture naming slopes were accounted for, the patients still had significantly larger Retention slopes than the controls, $F(1, 27) = 9.112$, $p < 0.01$.

Number of Picture-Word 'Stroop' effects

Inspection of the raw naming data for the incongruent stimuli revealed a number of picture-word stroop errors, i.e. instances in which the incongruent word as opposed to the actual picture name was voiced during picture naming.

In the patient group a total of 29 stroop errors were found across the three trials. In the elderly control group the total number of 7 stroop errors was observed across the three trials. It should be noted that 16 out of the 29 stroop errors made by the patient group were made by one patient (P3).

In order to examine whether or not there was a significant difference in the number of picture-name errors between the three trials a mixed factors ANOVA was set up with within subjects Factor RI Conditions (First RI vs. Mid RI vs. Last RI) and between subjects Factor Group (Patients vs. Controls). The assumptions for such ANOVA were not violated as indicated by a nonsignificant Mauchley's test of sphericity.

No significant main effect was found for RI Condition or Group. Moreover, no RI Condition x Group interaction was shown.

	First RI	Mid RI	Last RI
MCI	10 (4)	8 (5)	11 (7)
Controls	3	2	2

Table 6.5: Total number of picture-name stroop errors made by the two groups in the three RI Conditions. The figure in brackets indicates how many of the patient errors were made by patient P3 alone.

Subjective Picture naming feedback

Participant feedback was also checked for any possible links between subjective RI task difficulty ratings and proportion retention within each group. 11 of the 14 controls stated that they found the picture naming task 'very easy'. The remaining 3 said that they found the task 'easy'. 9 of the 14 patients stated that the task was 'very easy', 1 that it was 'easy', 3 that it was average and 1 that it was very difficult. However there was no apparent link between such subjective ratings and the participants' performance in the memory task.

6.2.3.2 Working memory rehearsal

The participant feedback further revealed that some participants tried to consciously rehearse the to-be-retained material while naming the pictures (i.e. during the RI task). It was thus decided to check whether the aforementioned significant RI Condition effect, the significant Group effect and significant RI Condition x Group interaction would hold following exclusion of such participants.
Some participants stated that even though they had tried to rehearse the words while naming the pictures they were unable to do so, and thus only rehearsed for a short while or only in one or two trials. Others explicitly stated in which condition they rehearsed or tried to rehearse. However, in order to ascertain that only those who did not try to rehearse during the naming tasks would be included in the ANOVA it was decided to exclude any participant who admitted to rehearsing or trying to rehearse. Feedback on rehearsal was unavailable for one patient. It was thus decided to

exclude this patient, too. Following exclusion 11 patients and 10 controls remained in the sample.

A mixed factor ANOVA as above with within subjects factor RI Condition (First RI vs. Mid RI vs. Late RI vs. No RI) and between subjects factor Group (Patients vs. Controls) was set up. Prior to analysis the assumptions for such mixed factor ANOVA were checked via the Mauchly's test of sphericity, which insignificant thus revealing that the assumptions for the planned ANOVA were not violated.

The subsequent ANOVA revealed a highly significant RI Condition main effect, $F(3, 57) = 13.614$, $p < 0.001$, and a highly significant Group main effect, $F(1, 19) = 25.809$, $p < 0.001$, as well as a marginally significant RI Condition x Group interaction, $F(3, 57) = 2.536$, $p = 0.066$. Group mean data and SEM is depicted in Figure 6.13. Individual participant retention data is provided in Tables 6.6 and 6.7.

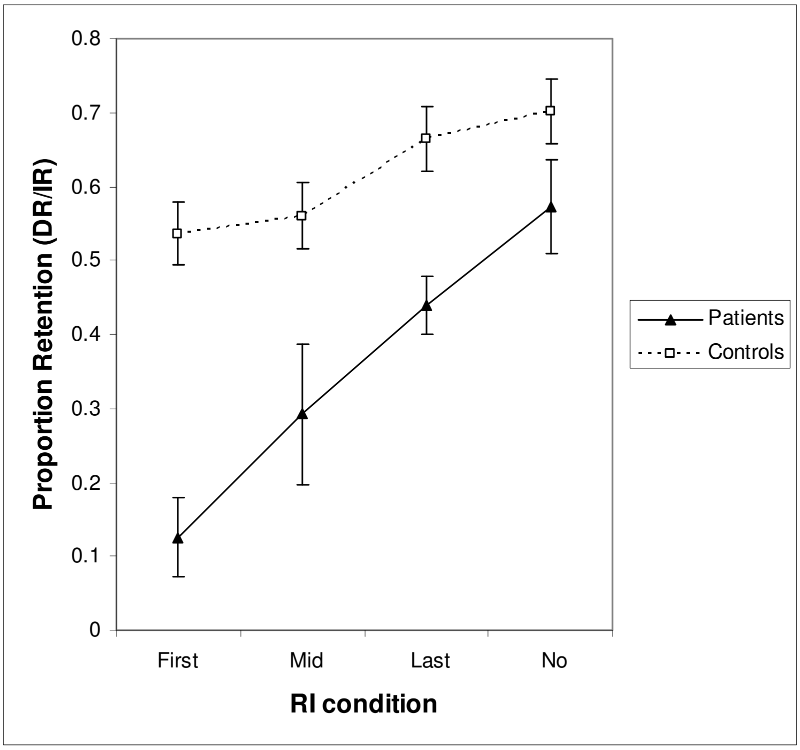


Figure 6.13: Mean Proportion Retention (DR/IR) as a function of Group and RI Condition when participants who tried to rehearse during the RI tasks are removed from the sample. N = 11 patients and 10 controls. Error bars = SEM.

The Group Main effects obtained in the above 'non-rehearser' ANOVAs were examined in more detail via a simple mains effects analysis with between subjects factor Group (Controls vs. Patients). The Levene's test of equality of error variances revealed that homogeneity of variance could be assumed for the two groups for the No RI, the Last RI and the First RI Conditions but not for the Mid RI Condition ($p < 0.05$). It was thus decided to run both a one way ANOVA and a Welch corrected ANOVA (Welch, 1951), which is robust to the variance assumption, on the retention group data for the Mid RI Condition.

The ANOVA showed that the basis of the Group main effect was significantly lower proportion retention in the patient group than the control group in all conditions containing RI (Last RI, $F(1, 20) = 14.448$, $p < 0.01$; Mid RI, $F(1, 20) = 6.027$, $p < 0.05$; First RI, $F(1, 20) = 35.070$, $p < 0.001$). There was no significant group difference in proportion retention for the No RI Condition. The Welch corrected ANOVA (applied due to the heterogeneity of variance in the Mid RI Condition) confirmed that the patient group had significantly lower retention than the control group in the Mid RI Condition, $F(1, 14.192) = 6.444$, $p < 0.05$.

In order to investigate the Condition main effects in the two ANOVAs in more detail, each combination of condition pairs was separately analysed in a mixed factors ANOVA with within subjects factor Condition (No RI vs. Last RI; No RI vs. Mid RI; No RI vs. First RI; Last RI vs. Mid RI; Last RI vs. First RI; Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls). ANOVAs indicated that the basis of the significant main effect of condition in the ANOVA including the No RI Condition was significantly higher retention following the No RI Condition than the Mid RI Condition, $F(1, 19) = 20.199$, $p < 0.001$, following the No RI than the First RI Condition, $F(1, 19) = 46.926$, $p < 0.001$), as well as significantly higher retention following the Last RI than the First RI Condition, $F(1, 19) = 26.395$, $p < 0.001$. Retention following the Last RI Condition was also marginally higher than that following the Mid RI Condition, $F(1, 19) = 4.256$, $p = 0.053$. No significant difference in retention was revealed between the First RI and Mid RI Condition or between the No RI and Last RI Conditions.

A further set of ANOVAs further elucidated that the marginally significant Condition x Group interaction was the result of a significant Condition x Group interaction for the No RI and First RI Condition comparison, $F(1, 19) = 9.871$, $p < 0.01$ and for the Last RI and First RI Condition comparison, $F(1, 19) = 4.953$, $p < 0.05$.

In order to examine the particular basis of these two Condition x Group Interactions two within subjects ANOVAs with within subjects Factor RI Condition (No RI vs. First RI and Last RI vs. First RI) were run separately for each of the two groups.

Mauchly's test of sphericity was not significant for either group meaning that the assumptions for the planed ANOVAs were not violated. The ANOVA showed that Retention in the No RI Condition was significantly higher following the No RI than the First RI Condition in both groups ($F(1, 10) = 30.631$, $p < 0.001$ for the patients and $F(1, 9) = 31.298$, $p < 0.001$ for the controls). Moreover, Retention following the Last RI was also significantly higher than that following the First RI Condition in both groups ($F(1, 10) = 19.116$, $p < 0.01$, for the patients and $F(1, 9) = 8.673$, $p < 0.05$ for the controls)).

As both groups showed significant improvement from First RI to No RI and from First RI to Last RI one way ANOVAs with between factor Group (patients vs. controls) were run to compare the groups on *magnitude* of improvement in each of the three condition pairs (i.e. retention No RI minus retention First RI and retention Last RI minus retention First RI). Due to a significant Levene's test for the improvement from First RI to Last RI, an ANOVA implementing Welch's correction was also run for the group comparison on this improvement. The ANOVAs elucidated that patients showed significantly larger improvement in retention than the controls from First RI to No RI, $F= (1, 20) = 9.871$, $p < 0.01$ ($F(1, 12.623) < 0.01$ following Welch's correction) and from First RI to Last RI, $F(1, 20) = 4.485$, $p < 0.05$ respectively). Group mean improvement in retention for the two condition pairs as well as the other four pairs are provided with corresponding SEMs in Table 6.6 below. The table also provides the percentage of patients and controls showing the improvements for the RI Conditions indicated above.

It was also decided to re-run the above main analyses on picture naming performance with this selected sample of non stroop rehearsers. This was done in order to assess whether or not the main Picture naming findings regarding performance in the three RI Conditions would alter following exclusion of the participants who tried to rehearse whilst naming the pictures. No changes in the main findings were made following exclusion of the stroop rehearsers.

Conditions	Patients			Controls			
	Mean	SEM	% of sample showing effect	Mean	SEM	% of sample showing effect	
First RI ► No RI	**0.45**	**0.08**	91	**0.17**	**0.03**	90	*
First RI ► Last RI	**0.31**	**0.07**	91	**0.13**	**0.04**	80	*
First RI ► Mid RI	0.17	0.09		0.02	0.06		
Mid RI ► No RI	**0.28**	**0.06**	82	0.14	0.07		
Mid RI ► Last RI	0.15	0.11		**0.11**	**0.04**	80	
Last RI ► No RI	0.13	0.09		0.04	0.05		

Table 6.6. Group mean improvement in proportion retention for each of the six RI Condition pairs (Improvement = Proportion retention for the condition to the right - Proportion condition for the condition to the left). Significant improvement is indicated in bold. * indicates RI Condition pairs for which improvement was significantly larger in the patients than the controls. Also provided is the % of the patient and the control sample showing the given improvements.

	Patient													
	P1	P3	P4*	P5*	P6	P7*	P8*	P9*	P10*	P11*	P12*	P14*	P15*	P16*
First RI	0.20	0.00	0.40	0.00	0.25	0.00	0.00	0.00	0.00	0.25	0.40	0.00	0.00	0.33
Mid RI	0.00	0.00	0.80	0.00	0.33	0.00	0.00	0.40	0.75	0.60	0.00	0.33	0.00	0.33
Last RI	0.50	0.67	0.20	0.40	0.50	0.67	0.40	0.33	0.60	0.50	0.50	0.33	0.40	0.50
No RI	0.75	0.50	1.00	0.40	1.00	0.40	0.40	0.67	0.67	0.60	0.33	0.83	0.60	0.40

Table 6.7. Individual patient proportion retention in the First RI, Mid RI, Last RI and No RI Conditions.

The Asterisk (*) indicates patients who did not rehearse during any of the picture naming trials (others excluded for the second main ANOVA)

	Control													
	C1*	C2	C3*	C6*	C7	C8*	C9*	C10*	C11	C12*	C13*	C14*	C15*	C16
First RI	0.67	0.57	0.43	0.60	0.50	0.50	0.33	0.56	0.67	0.60	0.67	0.33	0.67	0.75
Mid RI	0.60	0.60	0.60	0.40	0.17	0.50	0.40	0.50	0.80	0.50	0.80	0.80	0.50	0.71
Last RI	0.80	0.67	0.67	0.60	0.50	0.57	0.43	0.67	0.71	0.50	0.83	0.75	0.83	0.67
No RI	0.67	0.86	0.57	0.67	0.57	0.71	0.60	0.75	1.00	0.75	0.80	0.50	1.00	0.80

Table 6.8. Individual patient proportion retention in the First RI, Mid RI, Last RI and No RI Conditions.

The Asterisk (*) indicates controls who did not rehearse during any of the picture naming trials (others excluded for the second main ANOVA)

6.2.3.3 Picture intrusions at word List recall

Raw participant picture intrusion data was computed to derive 3 picture intrusion scores for each participant:

(a) Intrusions from same trial: Number of picture intrusions at delayed recall of the Last RI, Mid RI and First RI trials by pictures presented in the same trial (i.e. Last RI, Mid RI and First RI respectively). Thus while a Last RI picture falsely recalled at Last RI would be classified as 1 intrusion, a Last RI picture false recalled at First RI would not be counted as an intrusions.

(b) Intrusions from any trials at Delayed Recall: Total number of picture intrusions from any of the trials at delayed recall of the Last RI, Mid RI and First RI trials.

(c) Intrusions from any trials at Immediate Recall: Total number of picture intrusions from any of the trials at immediate recall of the Last RI, Mid RI and First RI trials.

Firstly measure (a) data was considered.

Inspection of the data (see Figures 6.14 and 6.15) showed that occurrence of picture intrusions from the same trial was very low, with a Total of 7 intrusions in the control Group and a Total of 12 intrusions in the Patient Group. 7 out of the 12 intrusions in the Patient group were made by the same patient (P10) as depicted in Figure 6.15 below.

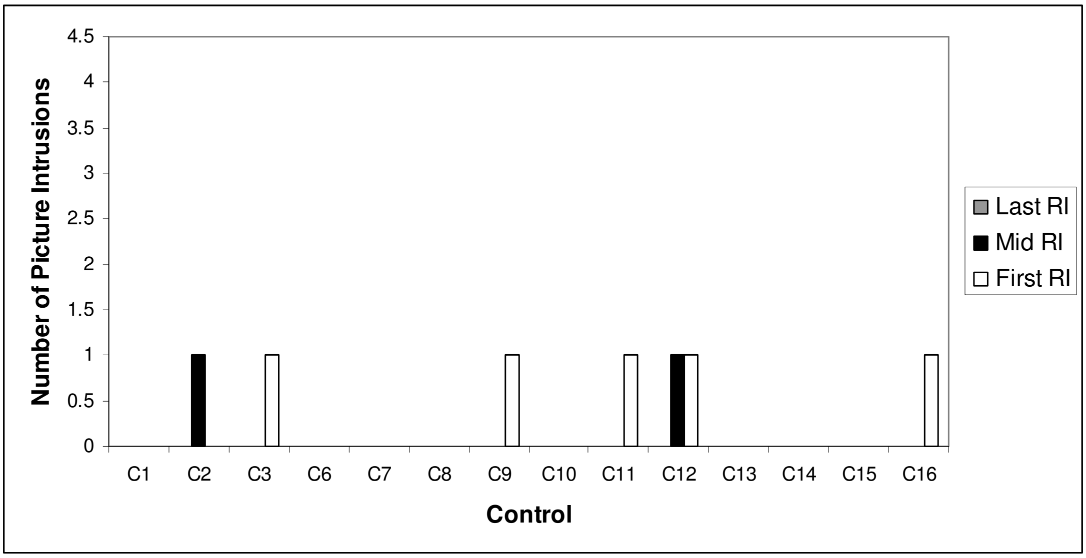


Figure 6.14. Number of picture intrusions in the control group as a function of RI Condition.

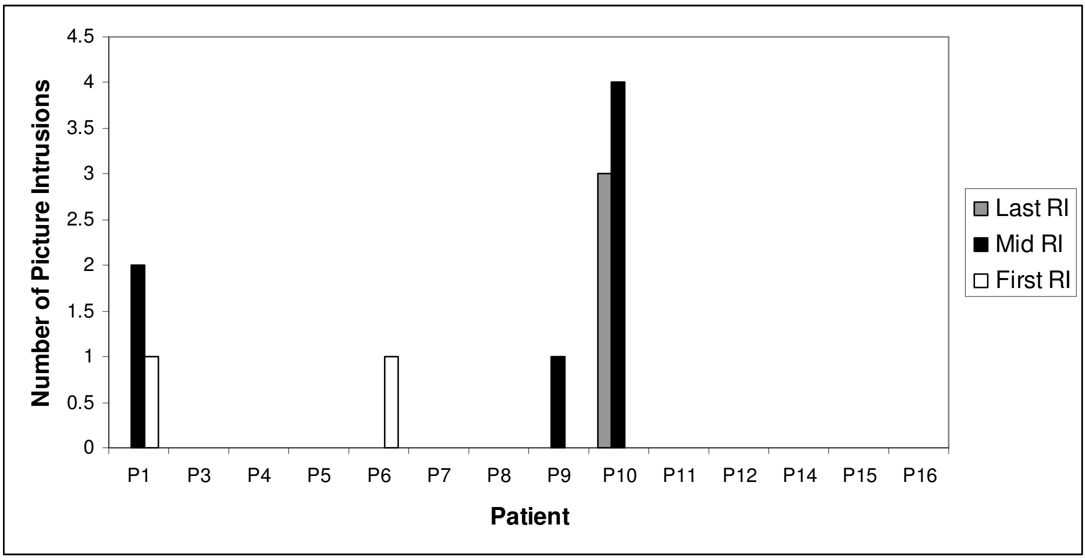


Figure 6.15. Number of picture intrusions in the patient group as a function of RI Condition.

A mixed factors ANOVA on measure (a) (Intrusions from same trial) with within subjects factor RI Condition (Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls) was carried out with Greenhouse-Geisser correction due to a significant Mauchly's test of spericity ($p < 0.01$).

The ANOVA revealed no significant differences in number of intrusions between the two groups or between the three RI Conditions. No Group x RI Condition interaction was obtained either. Group Picture intrusion means (measure a) as a function of RI Condition are depicted below in Figure 6.16.

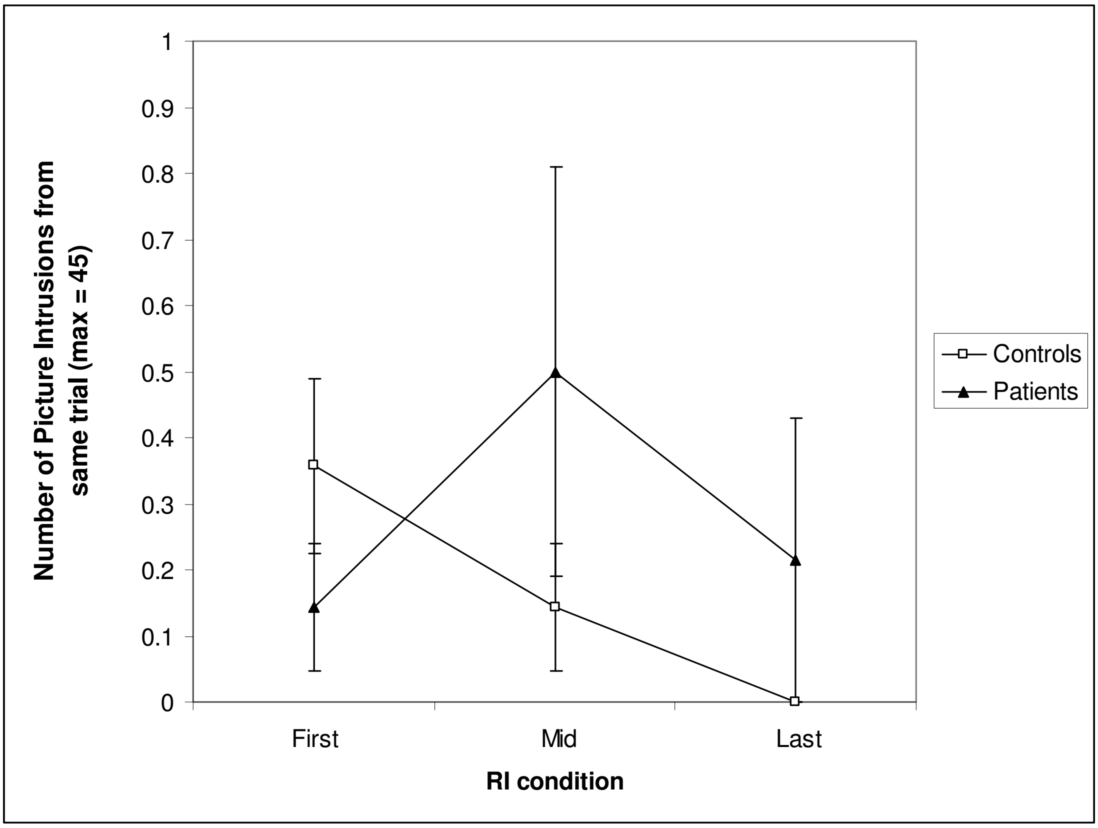


Figure 6.16. Group mean picture intrusions from same trial as a function of RI Condition. Error bars = SEM.

When considering picture intrusions from any of the trials (including the practise trial), i.e. measure (b), the total number of picture intrusions increased in both groups: A total of 38 picture intrusions at Delayed recall in the patient group and a total of 20 picture intrusions at delayed recall in the control group. As for measure (a) Patient P10 showed a large amount of picture intrusions, contributing 21 out of the 38 pictures and thus raising the Group mean somewhat.

A mixed factors ANOVA on total picture intrusions with within subjects Factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects Factor Group (Patients vs. Controls) with Greenhouse-Geisser correction following a significant Mauchsley test of sphericity revealed no significant difference in total picture intrusions between the groups or between the RI Conditions. No Group x RI Condition interaction was observed either. A further ANOVA with additional between subjects Factor RI Condition Order (order 1, i.e. *Min RI – Last RI – Mid RI –First RI* vs. order 2, i.e. *First RI – Mid RI – Last RI – Min RI*) further revealed that RI Condition Order had no significant effect on total number of picture intrusions, nor did it significantly interact with either Group or RI Condition.

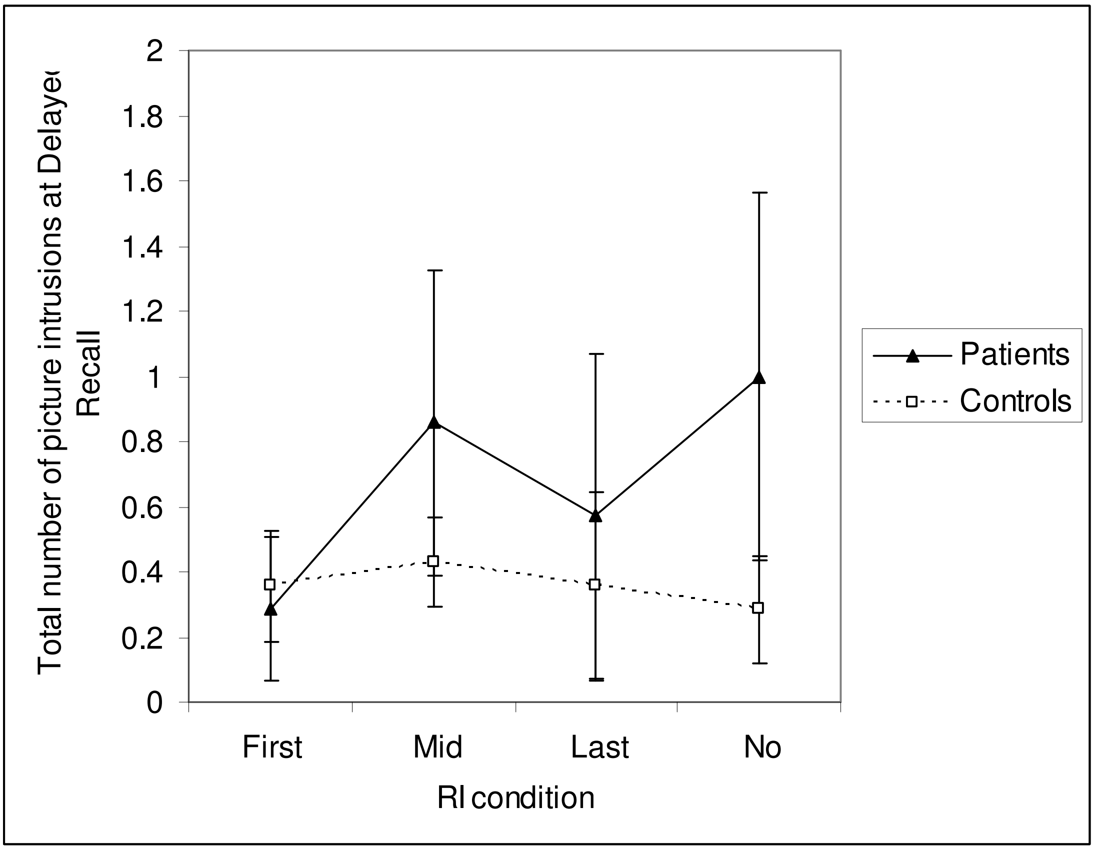


Figure 6.17. Group mean picture intrusions from any trial at delayed word list recall as a function of RI Condition. Error bars = SEM.

Total number of Intrusions at Immediate recall were also examined as above. The total number of picture intrusions at Immediate recall was 9 for the patient Group and 3 for the Control group.

An ANOVA such as the one conducted for Delayed Recall showed no significant differences in the number of picture intrusions at immediate recall between the groups or the RI Conditions. Moreover, no significant Group x RI Condition was obtained. Order of RI Condition did not significantly affect the number of picture intrusions at immediate recall either in any way.

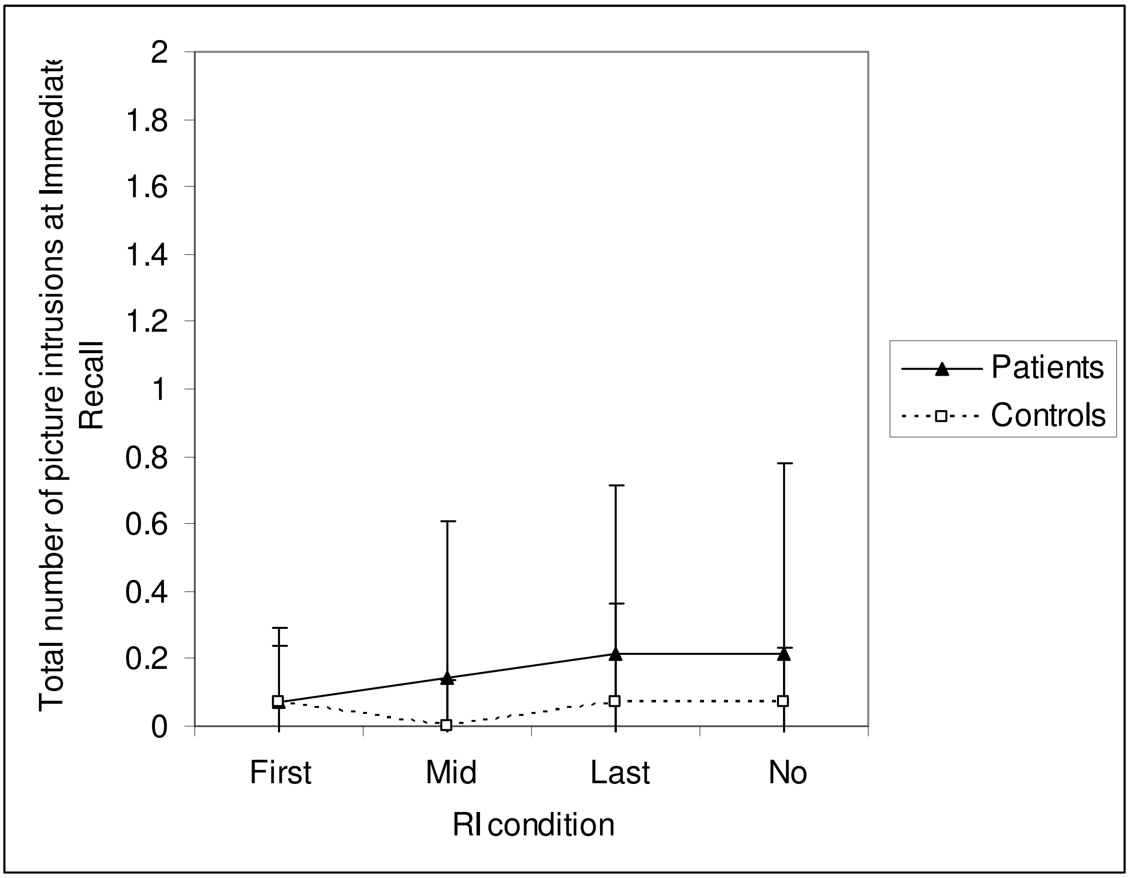


Figure 6.18. Group mean picture intrusions from any trial at immediate word list recall as a function of RI Condition. Error bars = SEM.

6.2.3.4 <u>Word intrusions (PI)</u>

The number of intrusions at immediate and delayed recall by words presented in prior trials (within the present Experiment) was computed for each RI Condition for each participant.

The total number of word intrusions from previous trials at delayed recall was 24 for the patient group and 31 for the control group.

A mixed factors ANOVA on number of word intrusions from previous trials at delayed recall with within subjects factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls) revealed no significant effects. Order of RI Conditions did not have a significant effect on the number of word list intrusions either as evinced by a second ANOVA with additional between subjects factor RI Condition Order.

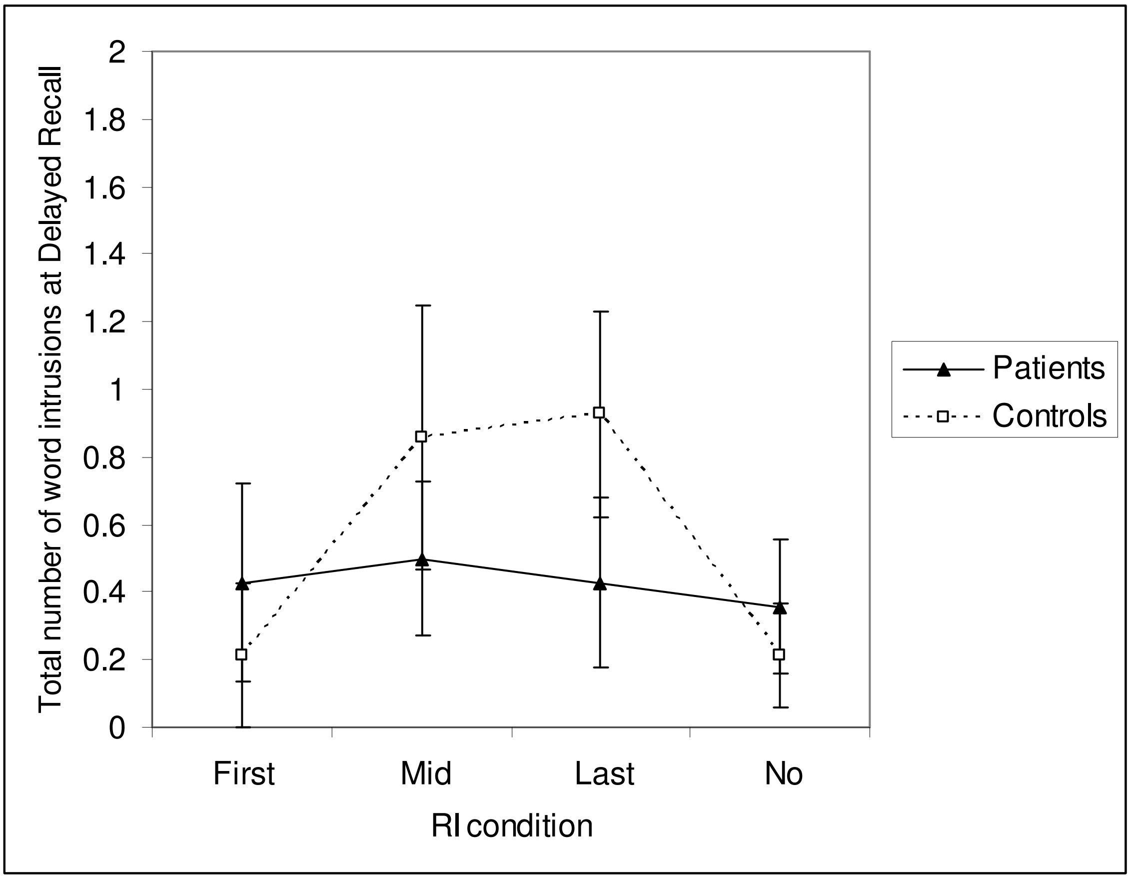


Figure 6.19. Group mean Total word intrusions (PI) at delayed word list recall. Error bars = SEM.

The total number of word intrusions from previous trials at immediate recall was 6 for the patient group and 14 for the control group.

A mixed factors ANOVA on number of word intrusions from previous trials at immediate recall with within subjects factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Patients vs. Controls) revealed no significant effects. Order of RI Conditions did not have a significant effect on the number of word list intrusions either as evinced by a second ANOVA with additional between subjects factor RI Condition Order.

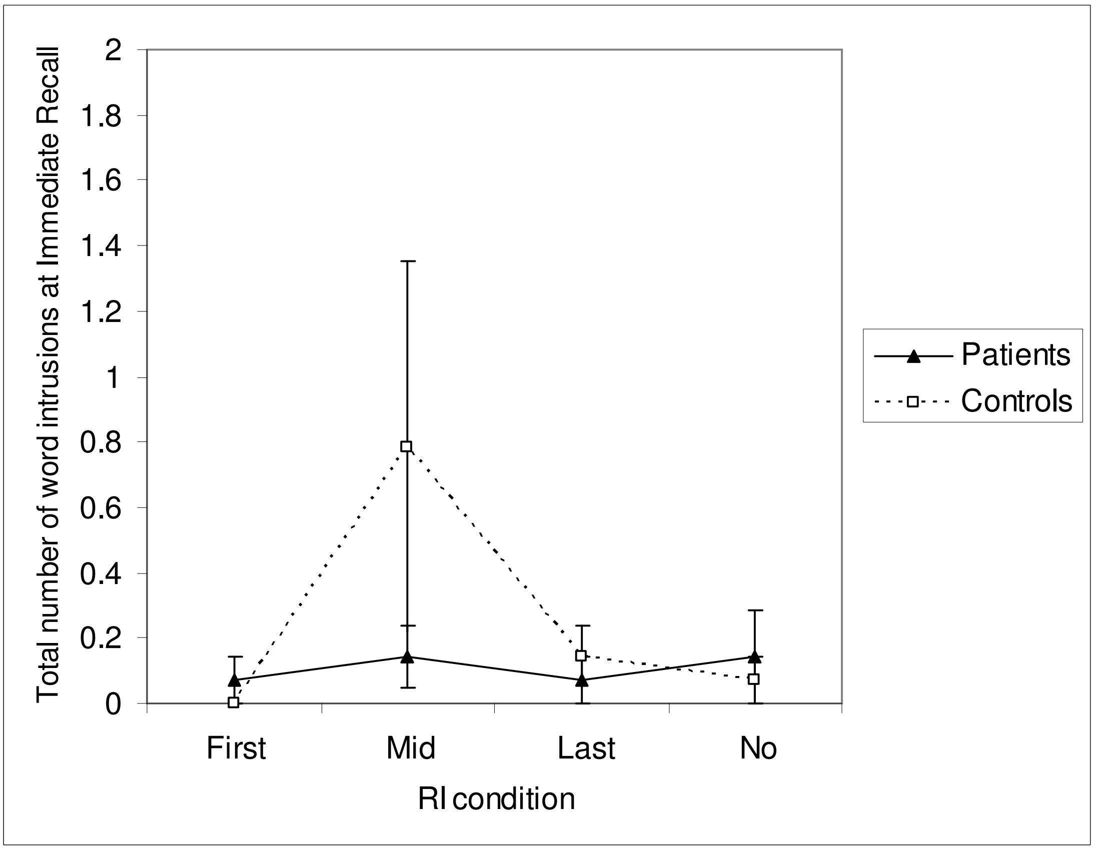


Figure 6.20. Group mean Total word intrusions (PI) at immediate word list recall. Error bars = SEM.

6.2.4 Discussion

The aim of Experiment 5(a) was to examine whether or not *onset time* of RI within a delay interval would affect proportion retention in a sample of patients with aMCI and if so, whether a *temporal gradient of RI* would be elucidated.

The results of Experiment 5(a) reveal that temporal onset of RI within the delay interval did indeed have a significant effect on proportion retention in this sample of patients with aMCI: Proportion retention was significantly higher following the Last RI Condition than the First RI Condition and Mid RI Condition, thus demonstrating a *temporal gradient of RI*. Such findings were also made for the neurologically intact control group, albeit to a much lesser degree, as evinced by the highly significant Group x RI Condition interaction.

Firstly, the aMCI finding provides strong evidence that these patients were able to retain word list stimuli even in the presence of RI *if* such RI occurred following a period of minimal RI as opposed to immediately following immediate recall.

The difference in retention following First RI and Last RI is especially apparent in the 8 patients who failed to remember any of the presented words following First RI. Two of these patients went from 0 proportion retention in the First RI Condition to 0.3 proportion retention in the Last RI Condition, three went from 0 proportion retention in the First RI Condition to 0.4 proportion retention in the Last RI Condition, one went from 0 proportion retention at First RI to 0.6 proportion retention at Last RI and two went from 0 proportion retention at First RI to 0.67 proportion retention at Last RI. Such results strongly suggest that even patients whose retention of verbally presented material is 0 following First RI, are able to retain verbal material in LTM *if* given sufficient time of minimal RI immediately following the learning episode.

Such results in turn strongly suggest that the benefit of minimal RI cannot simply underlie explicit STM maintenance, at least not in the present patient sample. If this were the case, proportion retention should have been similarly poor following First RI, Mid RI and Last RI, as RI would have interrupted explicit STM maintenance to the same degree, irrespective of RI onset time.

There was the slim possibility that the significant difference in proportion retention following Last RI and First RI and Last RI and Mid RI could have been the result of explicit STM maintenance during picture naming in the Last RI but not the First RI and Mid RI Condition. However, the replication of a significantly higher proportion retention in the Last RI than First RI and Last RI than Mid RI Conditions following *exclusion* of any participants who tried to rehearse the to-be-retained material during any of the RI Conditions revealed that such hypothesis is highly unlikely for either group.

It thus strongly appears that the benefit of Minimal RI in the present aMCI sample (as well as the neurologically intact controls) underlies improved LTM performance as opposed to improved STM performance. More specifically, the present findings closely map onto the predictions posed by the consolidation hypothesis (Müller and Pilzecker, 1900; Dudai, 2004) of an effect of the *temporal onset of RI* on memory retention. Thus, there is strong evidence for the notion that the present patients are (still) capable of some consolidation, but only when they are given sufficient time of Minimal RI shortly after the learning of to-be-retained material, i.e. during the time when new memories are postulated to be most fragile and vulnerable to disruption (Dudai, 2004).

However, prior to discussing the present findings with respect to such consolidation hypothesis and predictions, it is important to consider two alternative LTM hypotheses of the present findings:

6.2.4.1 Lack of interference at LTM **retrieval in Last RI**?

It could be argued that consolidation may be intact in these patients irrespective of RI Condition, but that First RI greatly interferes with the LTM *retrieval* of to-be-retained material. However, firstly, while the RI material in the present Experiment did contain single words, as did the to-be-retained material, such words were presented visually and in association with visually presented pictures, rather than verbally as was the case for the to-be-retained words. Thus, it is unlikely that the RI material was similar enough to the to-be-retained material to lead to interference at LTM retrieval (see Chapter 2 for a discussion on how similar material must be to be classified as similarity RI). However, assuming for a moment that the RI material utilised in the present Experiment was sufficiently similar to the to-be-retained material for it to interfere at LTM retrieval, it would appear unclear as to why such interference should have been so much greater in the First RI than the Last RI Condition.

It may be argued that RI material occurring immediately following presentation and immediate recall of to-be-retained material (i.e. First RI) could interfere at retrieval of the to-be-retained material due to its close temporal and contextual proximity to the to-be-retained material at encoding (c.f. Mensink & Raajmakers, 1988). However, it would appear likely that RI material occurring just prior to delayed recall of the to-be-retained material (i.e. Last RI) should also interfere with retrieval of the to-be-retained material. Indeed given that context is postulated to fluctuate over time (Mensink & Raajmakers, 1988) it would be predicted that the retrieval context would be more closely associated with the encoding context of the RI material than that of the to-be-retained material RI, which could consequently lead to interference from RI material at retrieval of to-be-retained material (Mensink & Raajmakers, 1988; Anderson and Bjork, 1994).

In fact, in the early work on immediate versus delayed RI in neurologically intact participants an inverted U was found for retention following early, middle and late RI when such RI was highly similar to the to-be-retained material (see Wixted, 2004).

Thus, if interference at retrieval had been the culprit in the present Experiment, one would have expected such inverted U and hence poor retention to appear following both the First RI and the Last RI Conditions with better retention following the Mid RI Condition.

Of course it may be claimed that the inverted U is particular to retrieval interference in the neurologically intact population and hence that aMCI patients may show a different pattern of retrieval interference such as the pattern observed in the present Experiment.

It was thus reasoned that if indeed a difference in retrieval interference was the cause of the differences in retention following First and Last RI, less instances of intrusions from the RI material should have occurred in the Last RI than the First RI Condition.

However, the results revealed that intrusions from RI material were very infrequent and more importantly, that they were randomly distributed across delayed recall of the three RI Conditions with no trend of a lower concentration in the Last RI Condition. Such was also the case when all RI material intrusions, i.e. including those from other conditions (PI) were counted as intrusions. Moreover as indicated in the results, word list intrusions from previous trials (PI) were also randomly distributed across the three RI trials. While one cannot exclude the possibility that the greater performance in No RI retention than Last RI retention could have at least been partially augmented by a lack of interference at retrieval in the No RI Condition, there appears to be little support for a retrieval based hypothesis for the greater retention following the Last RI than the First RI Condition.

Moreover, if the patients' deficit were a heightened susceptibility to interference at the LTM retrieval level, one would expect such patients to also present with retrograde memory retrieval problems, i.e. as argued more generally by opponents of a retrieval deficit in anterograde amnesia (c.f. Squire, 1980, Squire, 1982, Curran and Schacter, 2000; Squire 2006, Wilson, 1987).

6.2.4.2 Facilitated consolidation due to less demanding Picture naming in Last RI?

Given the above evidence against a retrieval based LTM enhancement, it appears very likely that indeed, the significantly heightened proportion retention following Last RI than First RI was (at least to a great extent) the product of facilitated LTM consolidation and hence that the cognitive process underlying the benefit of Minimal RI in at least the present aMCI sample is uninterrupted consolidation. Thus, the present findings provide stronger evidence for the in Chapter 5 proposed consolidation hypothesis of the benefit of Minimal RI in at least some patients with anterograde amnesia.

However, while the findings in this study closely mapped onto the *time based* predictions posed by the consolidation hypothesis put forward by Müller and Pilzecker (1900) and modern neuroscience (c.f. Dudai, 2004), there is the possibility that the facilitation of consolidation in the Last RI Condition in the present study may have not been the product of the temporal onset of RI per se.

Thus, it could be argued that the significantly larger proportion retention in the Last RI than the First RI or Mid RI Condition could have been the product of a less cognitively demanding RI period. Indeed, Müller and Pilzecker (1900) speculated whether degree of mental effort of an RI task may have an effect on proportion retention of to-be-retained material.

However, the lack of a significant difference in Total RT or Score for the three picture lists in the pilot study assessing naming only, suggests that no such differences in task demand should have been present in the experiment.

Moreover, even though the initial analysis on Naming score in the main Experiment revealed a significantly higher naming score for the list presented in the Last RI Condition than the First RI Condition, the various subsequent analyses performed provided no evidence for a relationship between naming score and proportion retention.

It thus appears very unlikely that an effect of degree of cognitive demand of RI may have masqueraded as an effect of temporal onset of RI.

6.2.4.3 Facilitated consolidation due to delay in RI onset time

Having provided evidence against an explicit *STM maintenance hypothesis*, a *retrieval hypothesis* and a *mental effort based consolidation hypothesis* of the findings of significantly improved proportion retention following delayed RI onset in the present sample of aMCI patients (and controls), it appears highly likely that such finding can be explained via the time based consolidation theory originally proposed by Müller and Pilzecker (1900) and adopted by modern neuroscience.

Such in turn provides further strong evidence for the in Chapter 5 proposed *consolidation hypothesis* of the benefit of Minimal RI in at least some patients with anterograde amnesia.

With particular respect to aMCI, the present findings imply that such patients (still) have some capacity for LTM consolidation, but that they are only able to consolidate new information when encoding of such new information is immediately followed by a period of Minimal RI, hence, when the period during which memories are most fragile is devoid of any disruption. Such in turn strongly suggests that diversion RI has a highly detrimental effect on *consolidation* in patients with aMCI. Given that diversion RI is almost always present in everyday life, it would not be surprising to find that people with some spared consolidation ability yet a heightened susceptibility to diversion RI should show a severe anterograde amnesia in every day life.

In fact, recent research on errorless learning in MCI patients by Akhtar et al. (2006) supports the notion that MCI patients may (still) be more capable of LTM formation than it may appear. MCI patients and elderly controls were given the word stem of a list of words, which they were either told (Errorless Learning) to learn or asked to guess up to three times (Errorful learning) and then learn. This learning phase was followed by three cued recall trials, which again were followed by a five minute conversation filled delay interval and subsequent delayed recall. The study showed that patients with MCI performed significantly better at delayed recall following errorless than errorful learning. Moreover, the authors conducted an analysis of inter-trial performance (i.e. analysis of specific words learned and retained across the cued recall trials) using the measures gained access (words recalled that were not recalled in the previous trial) and lost access (words recalled in the previous trial but not the current trial). According to Woodard et al. (1999) and Moulin et al. (2004) lost access is a measure of consolidation. It was shown that both the MCI patients and controls benefited from errorless learning to the same extent in terms of acquisition. However, even when the errorless condition was utilised the MCI patients nevertheless performed significantly worse at acquisition than the controls. However, the analysis of lost access (i.e. the amount of forgetting) elucidated that while the patients with MCI showed significantly more forgetting than the controls following errorful learning, their forgetting rate was equal to that of the controls following the errorless condition. The authors thus argue that errorless learning may ameliorate consolidation as opposed to acquisition of new material. Such finding may thus provide further evidence that patients with MCI are in fact better at forming Long Term Memories than it appears. In fact there is reason to hypothesise that errorless learning may in fact lead to a benefit at delayed recall due to *preventing of RI*. It will hence be of great interest to further investigate the underlying cognitive processes that allow for the benefit of errorless learning, and in particular whether or not the reduction of RI may be a key player.

Moreover, given the present findings of (a) some uninterrupted consolidation during Minimal RI as well as (b) a temporal gradient of RI, it will be of future interest to establish whether there is a duration of Minimal RI that leads to a maximum benefit of Minimal RI, i.e. whether proportion retention plateaus once a certain duration of Minimal RI has been reached.

Indeed, while the present experiment indicated a steady increase in proportion retention in the aMCI patients with increasing RI onset delay, the maximum onset delay utilised was limited to six minutes. It is thus plausible that a longer onset delay could lead to even better retention than did the Last RI Condition in the present study. The current experiment provides tentative data that indeed retention may be increased following a nine minute Minimal RI period. However, given that no RI was interpolated within this nine minute delay period, it cannot be excluded that proportion retention could have been augmented to some extent by explicit STM maintenance in at least some participants. Future work should thus include a nine minute Minimal RI interval as used in the present experiment, as well as a nine minute delay interval that is immediately followed by RI in order to examine whether or not the higher retention following the nine minute interval is the product of a longer duration of Minimal RI or possible rehearsal. Such should also be done for longer intervals such as 30 minutes or an hour. The aMCI data by Della Sala et al. (2005) very tentatively suggests that an hour long period of Minimal RI may not be greatly more beneficial than a six minute period of Minimal RI. Indeed, the mean proportion retention of 0.55 following the one hour Minimal RI period in Della Sala et al.'s (2005) study does not differ substantially from the proportion retention of 0.46 following the six minute Minimal RI period (i.e. the Last RI Condition). However, given that the studies differed in the type of to-be-retained material (prose passages in the Della Sala et al. 2005 study) such comparison may not be very reliable.

6.2.5 Conclusion

The present experiment demonstrated that a sample of aMCI patients performed significantly better at delayed recall when RI onset time was delayed than when RI occurred at the start of the delay interval. Moreover, a *temporal gradient of RI* was revealed, suggesting that in aMCI patients proportion retention improves with increasing delay in RI onset time. Such findings are of great interest as they provide further strong evidence for a *consolidation hypothesis* of the benefit of Minimal RI in at least some patients with anterograde amnesia. Moreover, they demonstrate that patients with aMCI may (still) be more capable of forming new Long Term Memories than been previously assumed.

6.3 <u>Experiment 5(b): Apparent improved consolidation in aMCI following Minimal Retroactive Interference (II)</u>

6.3.1 Aims of Experiment 5(b)

Given the findings of some consolidation of word list stimuli during Minimal RI in the aMCI sample tested in Experiment 5(a) the aim of the present Experiment was to examine whether these patients would continue to remember such material shortly following completion of Experiment 5(a).

6.3.2 Methods

6.3.2.1 <u>Participants</u>

The participants were the same patients and controls who had participated in Experiment 5(a).

6.3.2.2 Materials and Procedure

Following completion of Experiment 5(a) each participant was initially asked to recall and describe what the testing session had consisted of. Such was done in order to (a) assess their general memory of the Experiment as a whole and (b) distract them from the previously recalled word list.

Participants were then asked to try to verbally recall any of the (60) words they had been presented with during duration of the Experiment.

A 'post experiment proportion retention from Delayed recall' (Post Exp_DR) score was computed for each participant.

Post Exp_DR=

(Total Post Experimental Recall/Total Delayed Recall in Experiment 5(a))

6.3.3 Results

A one way ANOVA on Post Exp_DR with between subjects factor Group (Patients vs. Controls) was set up. The Levene's Test of Homogeneity of Variance was insignificant indicating that the assumptions for such ANOVA were not violated.

The ANOVA indicated that there was no significant difference in Post Exp_DR between the aMCI group and the controls. Group means and SEMs for Retention from DR are depicted in Figure 6.21.

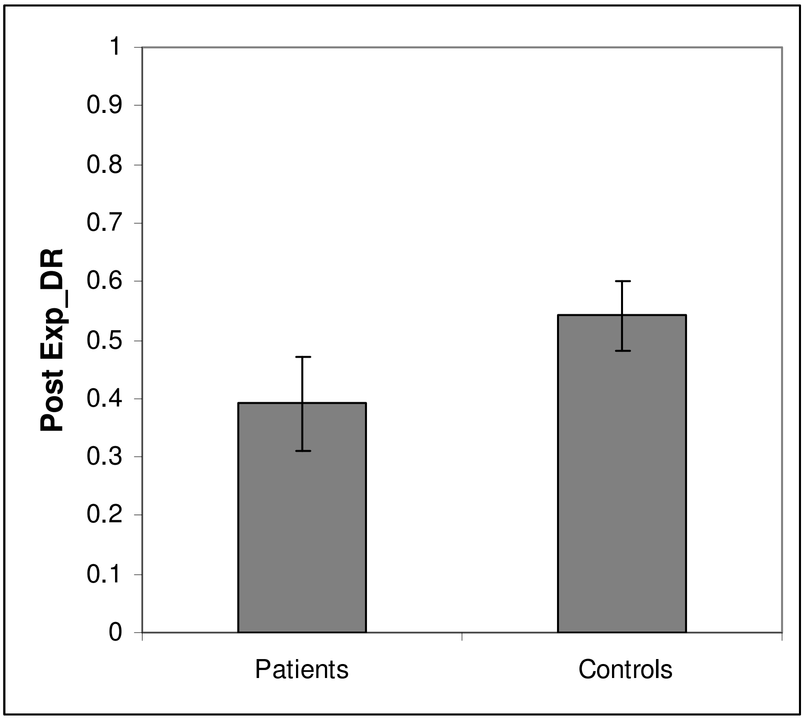


Figure 6.21. Proportion retention of words from DR by the patient and control group. Error bars = SEM.

Words correctly recalled following the experiment were subsequently coded in terms of the RI Condition they had been presented in to derive the proportion retention from DR as a function of RI Condition for each participant (i.e. post experiment proportion retention from DR for the No RI, the Last RI, the Mid RI and the First RI Conditions separately). When DR was 0 for a participant for any of the RI Conditions no post experimental retention score 'from DR' was given for that participant in that particular condition.

In order to examine post experimental retention of word list material from Delayed Recall for the two groups, group means and SEMs for each RI Condition were computed and plotted (see Figure 6.22). Note that a mixed factors ANOVA could not be run due to missing data for post experimental retention from First RI DR and Mid RI DR which was the result of some patients' 0 DR in either or both the First RI and Mid RI Conditions.

In order to assess whether the two groups differed in post experimental retention from DR in any of the four RI Conditions, a one way ANOVA with between subjects factor Group (Patients vs. Controls) was run on the four RI Conditions. No significant Group difference was obtained for post experimental retention from DR for any of the four RI Conditions.

In order to examine whether post experimental retention from DR differed significantly between the four conditions in the control group a within subjects ANOVA was conducted with Factor RI Condition (First vs. Mid vs. Last vs. No). No significant differences were shown.

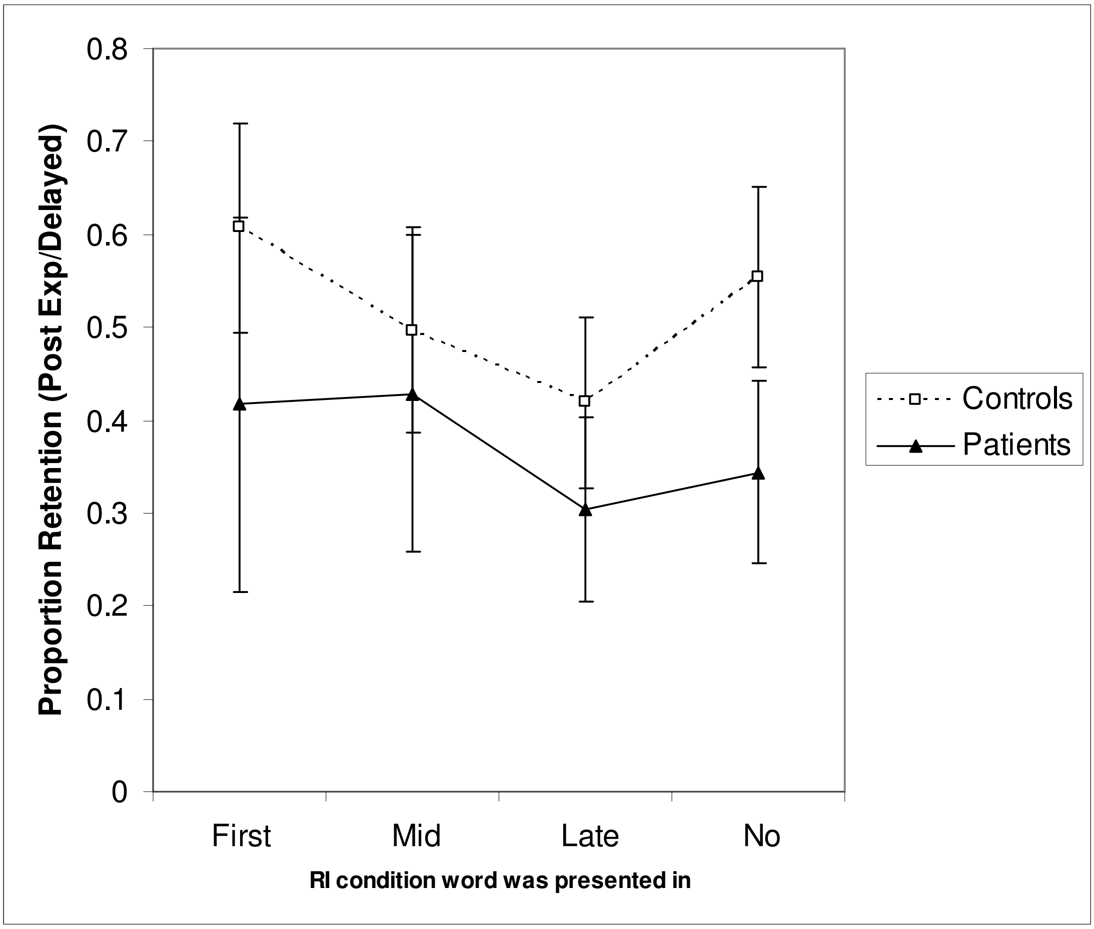


Figure 6.22. Proportion retention of words from DR as a function of RI Condition by the patient and control group. Error bars = SEM.

Inspection of the individual participant data revealed large differences in proportion retention within groups. For example a patient recalling one word at delayed recall and retaining this after the experiment would have had a post experiment proportion retention of 1 (100%) while another patient recalling one word at delayed recall yet showing 0 recall at post experimental recall would have had a proportion of 0. Such small differences in word recall yet large difference in proportion retention scores were thus likely to give a misrepresentation of actual post experimental retention.

It was thus decided to examine the raw post experimental data, i.e. the number of words recalled correctly from each condition.

A mixed factors ANOVA on number of words recalled with within subjects factor RI Condition (First RI vs. Mid RI vs. Last RI vs. No RI) and between subjects factor Group (Patients vs. Controls) was set up. The assumptions for such ANOVA were not violated as indicated by a non significant Mauchleys' test of sphericity.
The ANOVA showed a significant main effect of RI Condition, $F(1, 26) = 2.755$, $p < 0.05$, as well as a significant main effect of Group, $F(1, 26) = 20.685$, $p < 0.001$. No significant Group x RI Condition interaction was found. The RI Condition main effect was further examined via a series of one way ANOVAs. These revealed significant differences in number of words recalled between the No RI and Last RI Conditions, $F(1, 26) = 4.789$, $p < 0.05$) and the No RI and Mid RI Conditions, $F(1, 26) = 5.506$, $p < 0.05$. No other significant RI Condition differences emerged. Group mean data for number of words recalled as a function of RI Condition is provided in Figure 6.23 below.

Moreover, Figures 6.24 – 6.31 provide raw individual participant data for Immediate recall, delayed recall and post experimental recall for each of the RI Conditions.

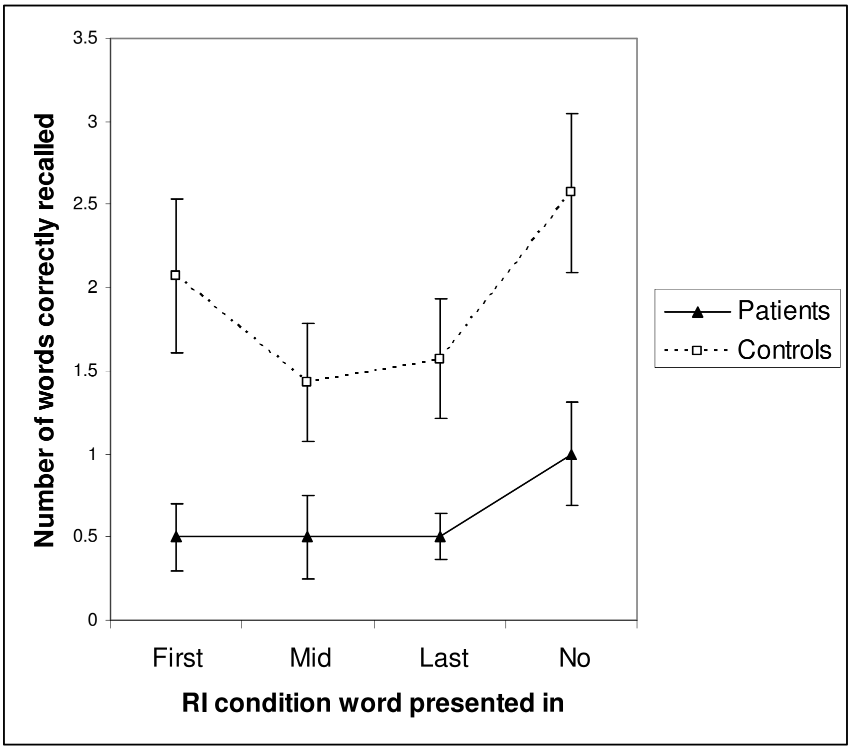


Figure 6.23. Number of words correctly recalled from list as a function of RI condition by the patient and control group. Error bars = SEM.

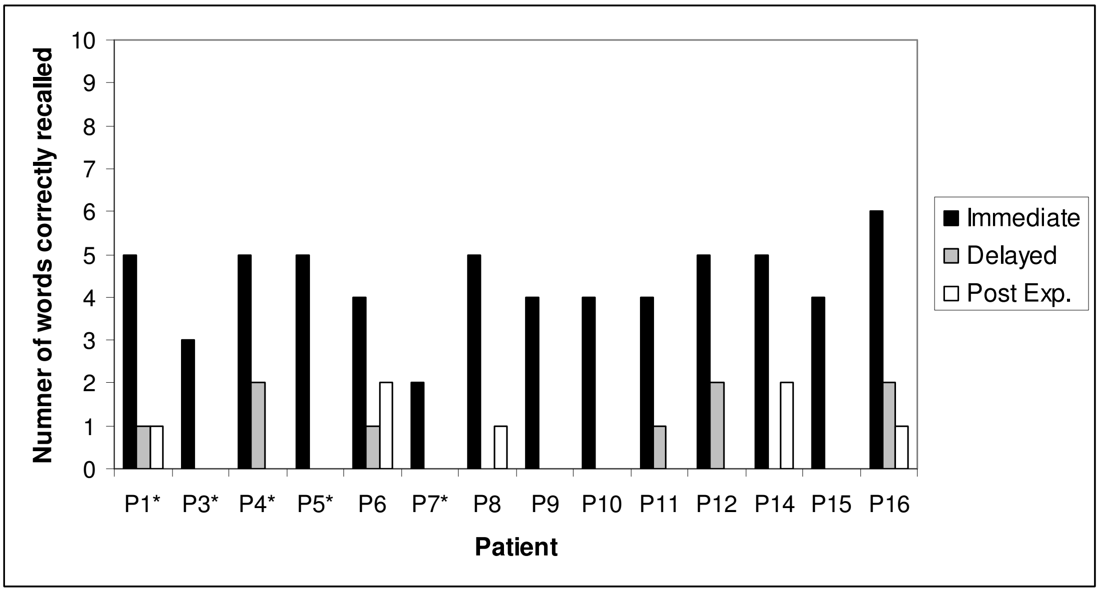


Figure 6.24. Number of words recalled correctly from the word list presented by each patient in the First RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Patients who tried to rehearse.

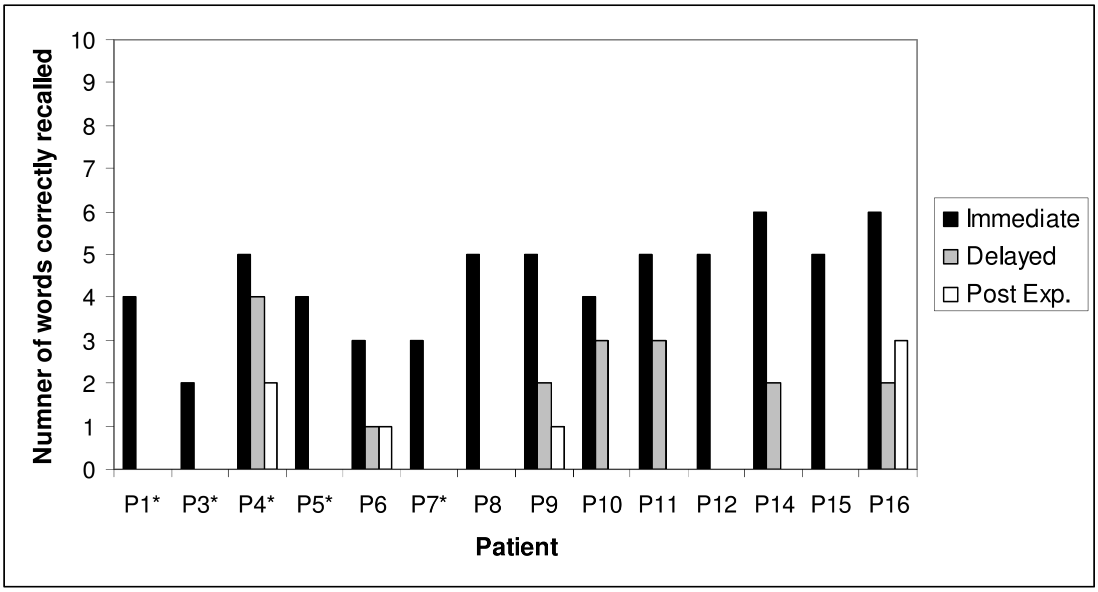


Figure 6.25. Number of words recalled correctly from the word list presented by each patient in the Mid RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Patients who tried to rehearse.

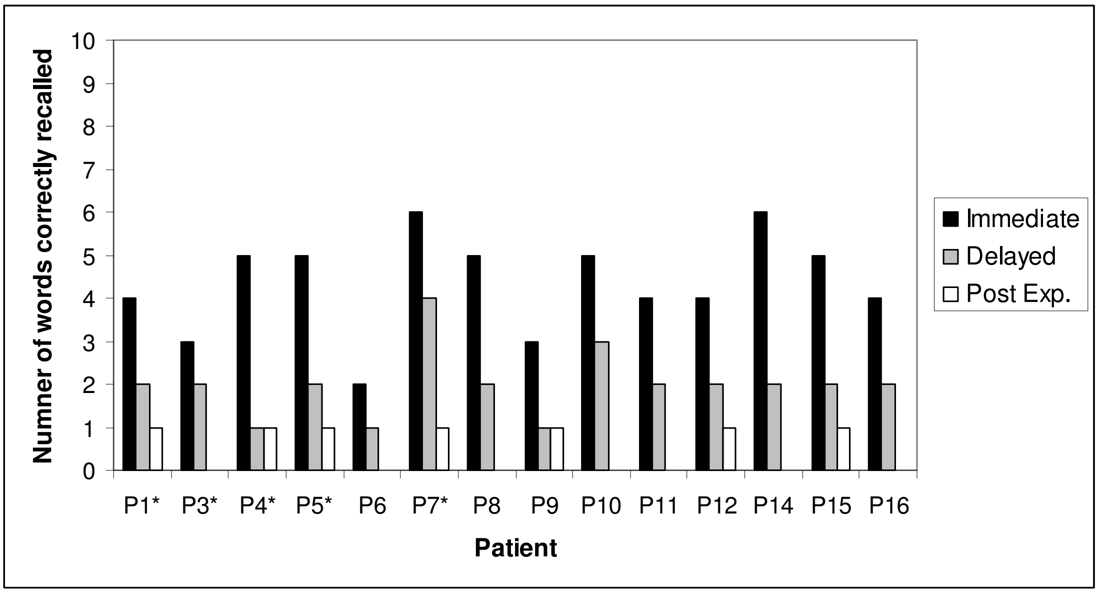


Figure 6.26. Number of words recalled correctly from the word list presented by each patient in the Last RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Patients who tried to rehearse.

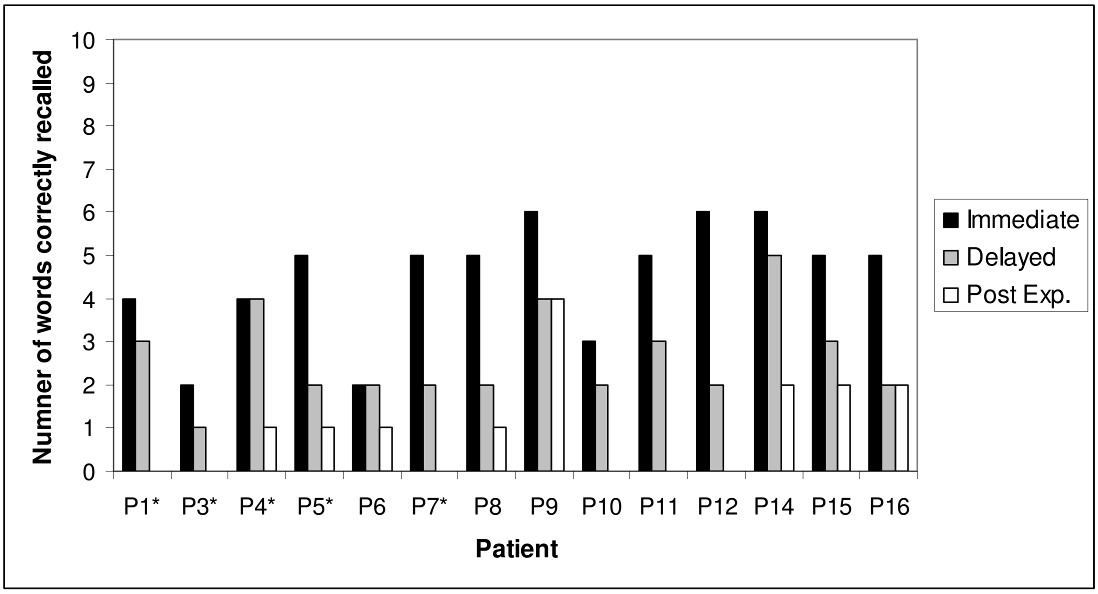


Figure 6.27. Number of words recalled correctly from the word list presented by each patient in the No RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Patients who tried to rehearse.

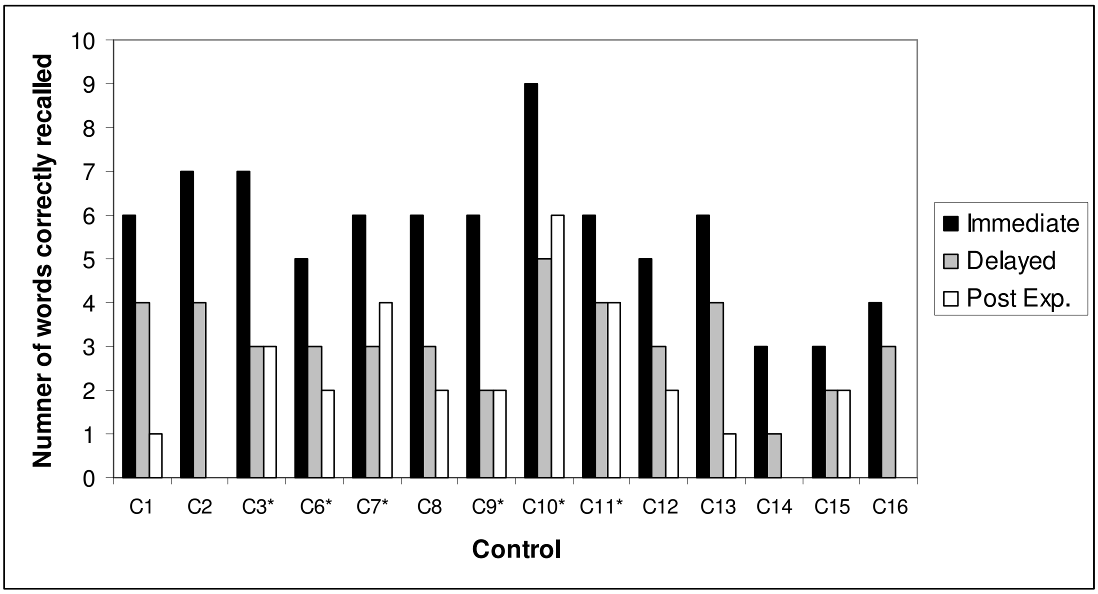


Figure 2.28. Number of words recalled correctly from the word list presented by each patient in the First RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Controls who tried to rehearse.

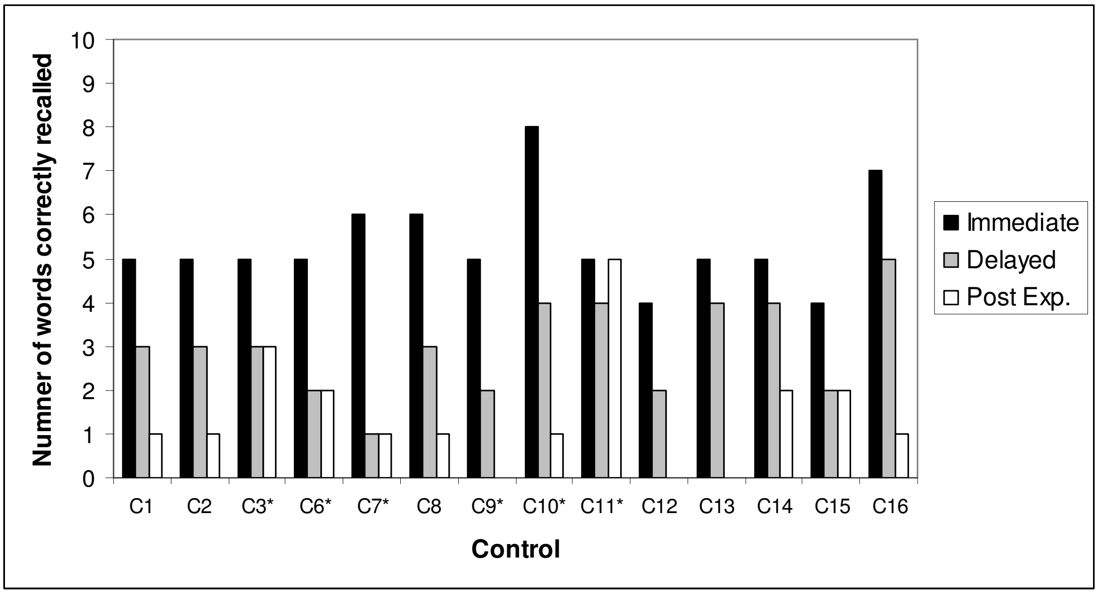


Figure 6.29. Number of words recalled correctly from the word list presented by each patient in the Mid RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Controls who tried to rehearse.

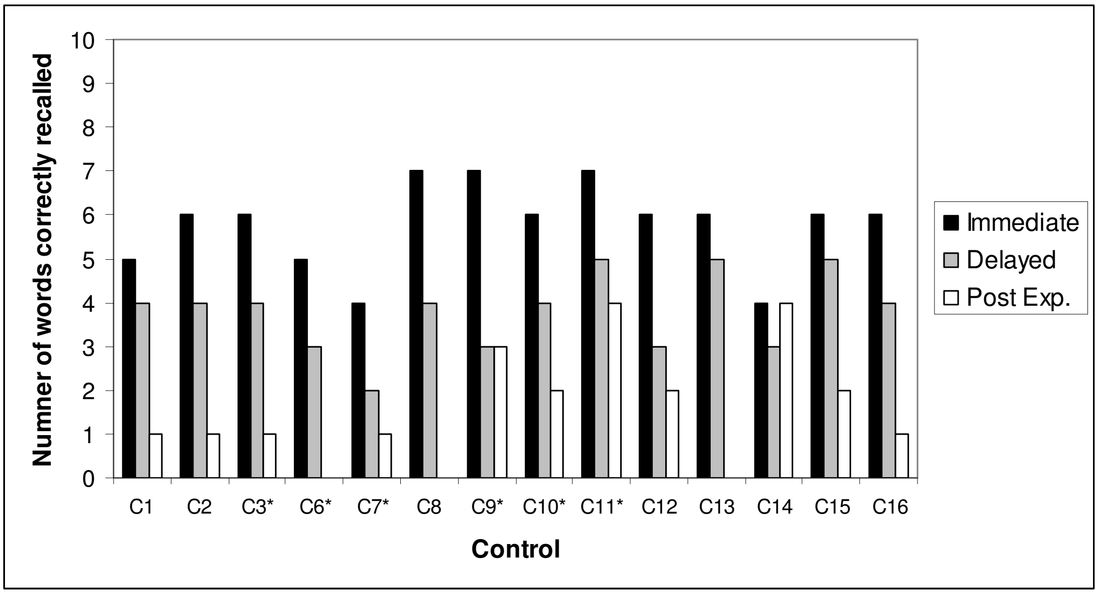


Figure 6.30. Number of words recalled correctly from the word list presented by each patient in the Last RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Controls who tried to rehearse.

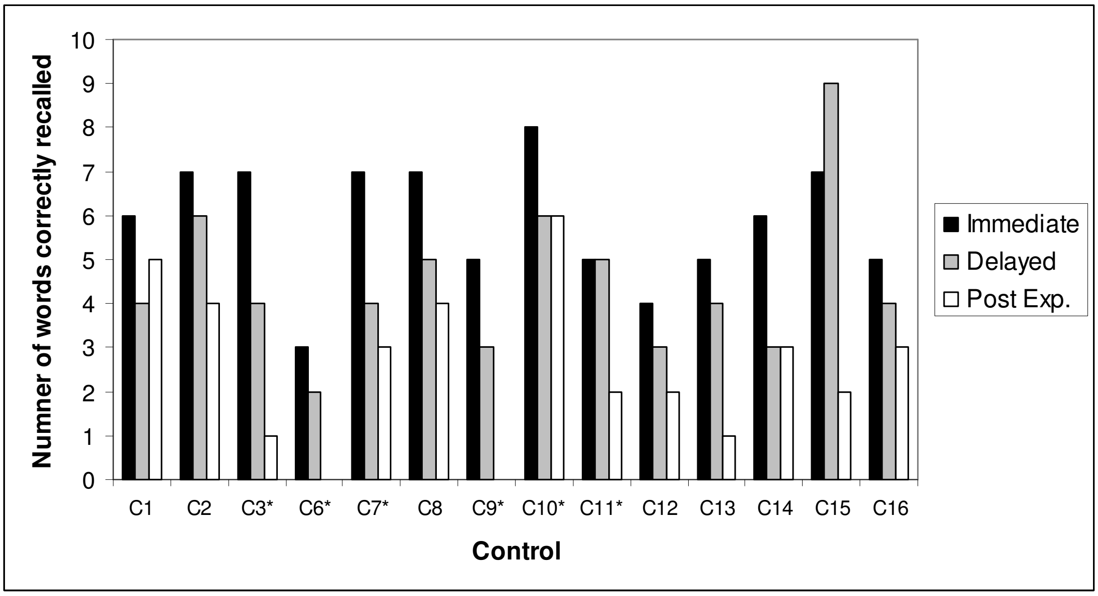


Figure 6.31. Number of words recalled correctly from the word list presented by each patient in the No RI Condition at Immediate recall, Delayed Recall and at Post Experimental recall. * = Controls who tried to rehearse.

It was also decided to inspect post experimental retention from DR of Last RI and No RI for the eight patients who in Experiment 5(a) had 0 proportion retention at First RI yet showed > 0 retention at DR of Last RI and No RI. A one way ANOVA was set up to examine whether or not this subgroup differed significantly from the controls in post experimental retention from No RI DR and/or from Last RI DR. Levene's test of homogeneity of variances was insignificant for both RI Conditions indicating that the assumptions for such ANOVA were not violated. The ANOVA showed no significant differences between the patients and controls for either post experimental retention from No RI DR or Last RI DR. The patient and control group means and SEMs for post experimental retention from No RI DR and Last RI DR are depicted in Figure 6.32.

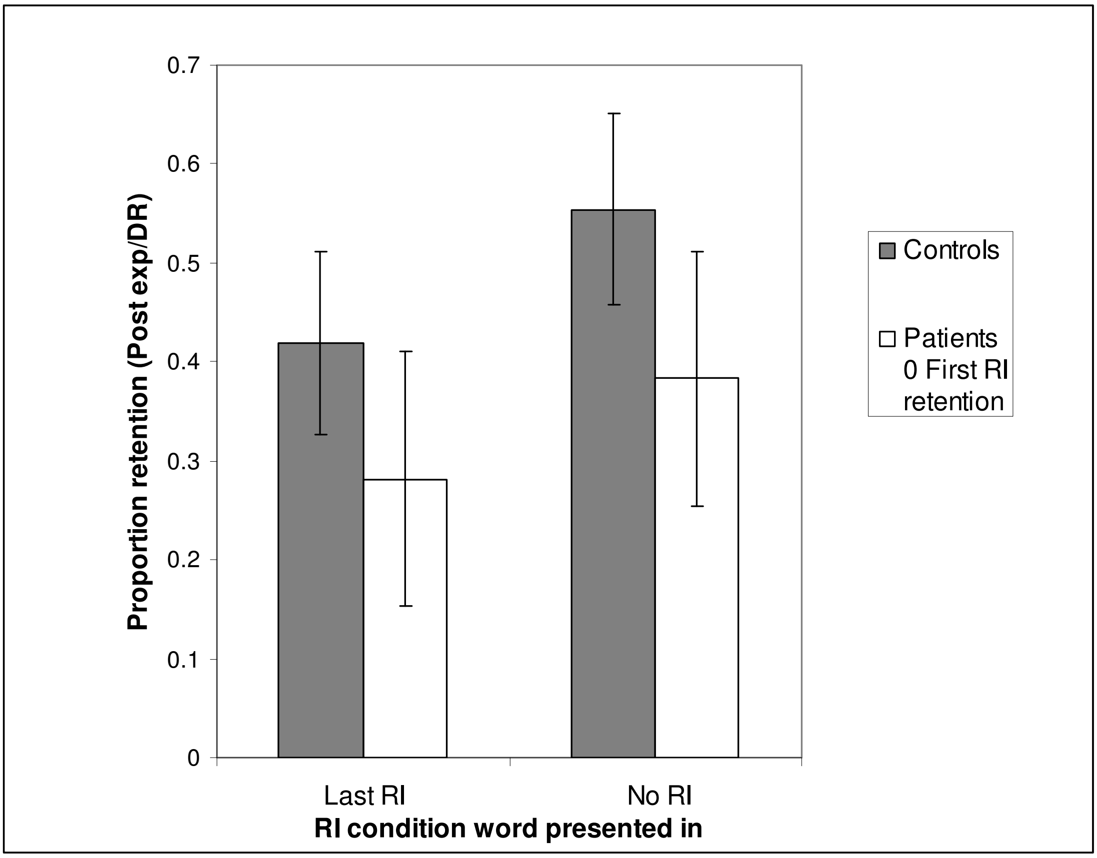


Figure 6.32. Subgroup of patients who performed 0 at Delayed recall of the First RI Condition and control group means and SEMs for post experimental retention from No RI DR and Last RI DR

6.3.4 Discussion

The aim of the present Experiment was to examine whether the patients taking part in Experiment 5(a) would continue to remember any of the word list material presented to them during Experiment 5(a) shortly following its completion. As a whole the data of the present experiment demonstrates that indeed the majority of aMCI patients within the sample were able to remember some of the material presented to them in Experiment 5(a).

In fact, the lack of a significant group difference between post experiment retention from DR overall (see Figure 6.21) and from DR of the four individual conditions of Experiment 5(a) strongly suggests that memory observed in

Experiment 5(a) was nearly as stable in the patients as in the controls when tested again in the present Experiment. However, it is possible that the large variability in post Experiment retention data may have led to a lack of power and thus an insignificant difference between the two groups. Nevertheless Figures 6.26 and 6.27 clearly indicate that 11 out of the 14 patients were able to retain at least some of the material from Delayed Recall of one of the No RI or Last RI Conditions following completion of Experiment 5(a).

The apparent LTM benefit of Minimal RI is particularly evident in the subgroup of patients whose First RI delayed recall in Experiment 5(a) was 0: Despite such 0 proportion retention following First RI, all of these patients were able to retain at least some of the verbal material following No RI and Last RI in Experiment 5(a). More importantly, with particular respect to the aim of the present experiment, six out of these eight patients still showed some retention of such verbal material from the No RI or Last RI Conditions following the Experiment. For example patients P9 and P15, who showed 0 retention following First RI, were able to retain 66.67% and 60% respectively following No RI (see Experiment 5(a), Table 6.7). Following the Experiment Patient 9 retained 100% of what he had retained following No RI and Patient 15 retained 66.7% of what she had retained following No RI. Such extended retention of verbal material following Minimal RI is very noteworthy given these and the other amnesic patients' very poor delayed recall following First RI.

In fact the ANOVA including only this subgroup suggests that there was no significant difference between this subgroup and the controls in post experimental retention from No RI or Last RI DR, a finding that is indeed remarkable given these amnesic patients' performance following First RI.

Moreover, the finding of such extended retention from Experiment 5(a)'s No RI Condition provides further strong evidence against an explicit STM maintenance hypothesis of the benefit of Minimal RI. Indeed, if patients had merely performed well following the No RI Condition due to STM maintenance, none of the recalled material should have been retained following delayed recall of the No RI Condition, i.e. once patients were distracted by further testing. However, as demonstrated by

Figure 6.27, eight out of the 14 patients still showed some retention of word list material from the No RI Condition of Experiment 5(a).

With respect to the in Experiment 5(a) elucidated benefit of delayed RI, Figure 6.23 suggests that temporal onset of RI might no longer have an effect on retention at post experimental recall, a finding that could support a retrieval account of the benefit of delayed RI. However, the raw data depicted in Figures 6.24 – 6.27 indicate a trend for more patients to retain word list material from the Last RI condition (seven patients) than the First RI (five patients) and Mid RI (four patients) conditions. Such trend thus provides further tentative evidence for a consolidation account of the benefit of Minimal RI and delayed RI in patients with aMCI.

Nonetheless, while the majority of patients (11/14) showed some extended retention from the No RI and /or the Last RI Condition of Experiment 5(a), it is important to highlight that three patients (P3, P10 and P11) did not show any extended retention from any of the four RI Conditions of Experiment 5(a). Examination of these three patients' neuropsychological data did not reveal any obvious deviation from the other 11 patients apart from an apparent lower performance at delayed prose recall in P3.

It could be possible that the order of presentation might have played a role in the lack of post experimental retention in P3. P3 was in order 1, meaning that No RI and Last RI occurred first and second in Experiment 5(a). Thus perhaps the subsequent trials disrupted further consolidation of the No RI and Last RI word list material in this patient. However, P1, P4, P5 and P7 were also presented with the conditions in order 1 yet all showed some post experimental retention from either or both No RI DR and Last RI DR.

Moreover, P10 and P11, the other patients who did not show any post experimental retention from DR of any RI Conditions, were presented with the RI Conditions in order 2, and should have thus been at an advantage as the No RI and Last RI would have been followed by less disruption. It thus appears unlikely that order of conditions led to the lack of extended retention in patients P3, P10 and P11.
Table 6.7 in Experiment 5(a) indicates that P3, but not P10 or P11, tried to rehearse some of the word list material during some of the RI periods. It is thus possible that

P3's retention at delayed recall in Experiment 5(a) may have been the product of explicit STM maintenance as opposed to consolidation. If this were the case such would certainly explain P3's lack of extended retention in the present Experiment. However given that P10 and P11 reported that they did *not* rehearse the word list material during the RI periods, yet showed some retention following Mid RI and Last RI (and even First RI in the case of P11) in Experiment 5(a), it appears unlikely that these patients failed to show any extended retention due to a sole explicit STM maintenance benefit of Minimal RI. It thus remains unclear as to why these two (or possibly three) patients only showed relatively short term benefits of Minimal RI while the other patients were able to benefit from Minimal RI over an extended period of at least up to 1.5 hours (i.e. the approximate delay interval between the first trial of Experiment 5(a) and the present Experiment).

It may be postulated whether P10 and P11 (and possibly P3) might differ from the other patients in terms of the two hypothesised types of consolidation, i.e. synaptic and systems consolidation (Dudai, 2004). Thus, as tentatively speculated in Chapter 5 there may be the possibility that Minimal RI could only allow for uninterrupted *synaptic* consolidation in some patients with the consequence that the benefit of Minimal RI would be relatively short lived. However, with particular regard to the present patient sample this would imply that the other 11 aMCI patients should show a long lasting benefit of Minimal RI. However, as no one year follow up has been conducted on this patient sample as yet, such prediction cannot be tested or verified via the present data.

It will thus be vital for future aMCI RI studies to include further post experimental delayed recalls, following increasing intervals such as one hour, a few hours, a day, a week. Given the apparent individual differences in extended retention, such future work could also investigate whether differences in the duration of extended retention from Minimal RI might be related to the severity of aMCI. Thus it could be hypothesised for example that patients in the earlier stages of aMCI may show longer retention following Minimal RI, possibly due to some intact systems consolidation as well as a benefit of Minimal RI at the synaptic consolidation phase. However, patients in the later stages of aMCI may have impaired systems consolidation, thus showing only relatively short-lived benefits of Minimal RI. In line with such reasoning it will also be of interest to examine recent pre-morbid retrograde memory in patients with aMCI, as such could provide further information as to the functioning of the hypothesised systems consolidation in such population.

6.3.5 Conclusion

The present Experiment demonstrated that following completion of Experiment 5(a) the majority of patients taking part in Experiment 5(a) still showed retention of at least some of the material they had previously recalled following Minimal RI or delayed RI. As demonstrated in Experiment 5(a), the majority of these patients performed at floor following RI that occurred at the start of the delay interval in Condition 5(a). The present findings of extended retention from Minimal RI/delayed RI in such patients thus greatly strengthen the in Experiment 5(a) provided evidence for a consolidation hypothesis of the benefit of Minimal RI in this aMCI sample. Furthermore, the present findings further demonstrate that patients with aMCI may (still) be more capable of forming new Long Term Memories than been previously assumed. Nonetheless it remains to be established via future research how durable such new Long Term Memories are in patients with aMCI.

Chapter 7: Retroactive Interference and healthy Ageing

7.1 Experiment 6: Comparing the effects of Minimal RI, RI and delayed RI in the healthy Elderly and Young

7.1.1 Introduction

The study by Della Sala et al. (2005) and the results of Experiment 5 demonstrate a substantial benefit of Minimal RI in patients with aMCI, strongly suggesting that at least some of the severe anterograde memory deficit seen in such patients is explained by a greatly heightened susceptibility to diversion RI. Furthermore, the findings of a benefit of *delayed* RI in Experiment 5 provided strong evidence that Minimal RI allows for some uninterrupted consolidation of newly encoded information to take place in such patients, indicating that their heightened susceptibility to diversion RI is likely to be associated with an impairment affecting the consolidation process.

Experiment 5 further showed that the age and education matched neurologically intact controls also benefited significantly from both Minimal RI as well as delayed RI, albeit to a much lesser extent that did the aMCI patients. Such findings are relevant for two reasons. Firstly, they provide further support for a benefit of Minimal RI and hence a small, yet detrimental effect of diversion RI in the neurologically intact population (Müller and Pilzecker, 1900; Experiment 1). Secondly, they indicate that such benefit of Minimal RI is likely to underlie uninterrupted consolidation in neurologically intact individuals as well (Müller and Pilzecker, 1900, see their Experiment 34 provided in Chapter 2).

Nonetheless, as highlighted above (and indicated in Table 6.4 of Experiment 5(a)), the neurologically intact elderly showed a significantly *smaller* benefit of Minimal RI and delayed RI than the elderly diagnosed with aMCI. Such finding thus demonstrates a clear cognitive *difference* in memory function between the neurologically intact elderly and the elderly with aMCI.

Nonetheless, it cannot be told from the results of Experiment 5 whether such cognitive difference in memory function in the neurologically intact elderly and elderly with aMCI is a *qualitative* difference or a *quantitative* difference.

Thus, given that anterograde memory also declines to a small extent in neurologically intact elderly, it may be that ageing as a whole is associated with an increase in susceptibility to diversion RI. If such were the case, aMCI could represent a greatly exaggerated degree of such 'normal' age related increase in diversion RI susceptibility. This would render the observed difference in RI susceptibility between the elderly neurologically intact and patient groups a *quantitative* difference.

On the other hand, it is plausible that the susceptibility to diversion RI observed in the neurologically intact population does not vary across the lifespan, and hence that the anterograde memory decline associated with normal ageing is related to different cognitive factors. If this were the case, the observed difference in RI susceptibility between the elderly neurologically intact and patient groups would be a *qualitative* difference in as much as it would not be predicted to deviate from the difference in RI susceptibility between neurologically intact *young* and aMCI patients.

The question of whether the difference in degree of susceptibility to diversion RI in the neurologically intact elderly and the elderly with aMCI is of quantitative or qualitative origin is relevant for two reasons: Firstly, the question is important for the further theoretical understanding and cognitive modelling of aMCI, in particular with respect to diversion RI. Secondly and importantly, elucidation of the specific nature of the difference in RI susceptibility, in particular of a qualitative difference, could also have practical implications. Indeed, given the difficulty in distinguishing the very early stages of AD/aMCI from normal age related memory decline (Morris, 2006) the findings of a qualitative difference in RI susceptibility/benefit between neurologically intact elderly and elderly with aMCI could be relevant for future research on an early diagnosis tool.

Moreover, the question of whether normal age-related LTM memory decline may be related to an increased susceptibility to diversion RI is also of interest per se. In fact, it appears that such question has not been examined to date.

Indeed, while age-related increases in susceptibility to memory interference have been reported, such research has mainly focused on the effects of PI (c.f. Bowles and Salthouse, 2003, Hasher et al., 2002) and *similarity* RI in *working memory* (c.f. Hedden and Park, 2001; Hedden and Park, 2003; see also Kane and Hasher, 1995 for a review of both PI and (similarity) RI effects in ageing). Hedden and Park (2001) for example found that elderly participants were much more susceptible to similarity RI than were young participants in an AB-AC-type verbal associative memory working memory paradigm, suggesting a heightened impairment at the memory retrieval stage.

However, working memory research by Pucket and Stockburger (1988) suggests that elderly and young may not differ in terms of susceptibility to diversion RI. Their elderly and young participants were presented with to-be-retained word lists (titrated to individual memory span), which were followed by a matching task (lasting between 3s – 15s), in which the participants had to indicate whether two presented words (distractor type 1) or symbols (distractor type 2) were identical or not. Participants were strongly encouraged not to rehearse the to-be-retained material and were excluded from the subsequent analysis if they did rehearse. No differences in retention were found between the elderly and young, leading Pucket and Stockburger (1988) to conclude that there was ‘an absence of normal age-related proneness to short-term retroactive interference’.

Moreover, previous studies on the effects of healthy ageing on *LTM* have suggested that decreases in delayed recall in the elderly may not necessarily be due to increased forgetting over a temporal delay but due to impairments in initial memory acquisition (c.f. Trahan and Larrabee, 1992; Dunlosky and Salthouse, 1996; Tombaugh and Hubley, 2001; Davis et al., 2003). Indeed, it has been shown that when levels of acquisition are accounted for, by using a percentage retention measure, i.e. (retention score/acquisition score x 100) or by adding immediate recall

as a between subjects factor, retention does not appear to differ significantly between the young and elderly (c.f. Trahan and Larrabee, 1992; Tombaugh and Hubley, 2001; Davis et al., 2003). Furthermore, detailed research on gained and lost access of words in verbal learning has elucidated that the elderly show lower gained access than the young while lost access is comparable for the two groups (Dunlosky and Salthouse, 1996). Thus, while the elderly show reduced acquisition of words when compared to the young, they do not differ in terms of retention of gained, i.e. acquired material.
Nevertheless, the lack of an effect of age on retention does not appear to hold for all retention interval durations. Huppert and Kopelman (1992) for example reported that retention of visuospatial material did not differ between elderly and young participants following a 10 minute delay interval when acquisition differences were controlled for via longer stimuli exposure in the elderly group. However, when tested again following 24 hours and following one week, the elderly group showed significantly lower retention than the young group, hence showing an effect of age on the rate of forgetting over a longer duration. Evidence for such age related differences in forgetting rate following a longer duration were replicated by Tombaugh and Hubbley (2001) who elucidated that while retention of verbal material did not differ between the young and elderly following a standard 20 minute delay interval, the elderly did show significantly worse retention following 24 hours. However, age effects again ceased to be significant following such period. Davis et al. (2003) recently provided further evidence for such increased forgetting following 24 hours in their 76 to 90 year olds when only those participants matched for level and degree of acquisition were included in the analysis. However, as in the Tombaugh and Hubbley (2001) study, no significant difference was shown for forgetting following a 20 minute filled delay interval, even when only the matched participants were included in the analysis.

Thus, while the elderly appear to differ from the young in terms of initial memory *acquisition* and retention over *long* delay intervals (i.e. > 24 hours), they do not seem to differ from the young in terms of their ability to retain acquired material over *shorter filled* delay intervals (i.e. 10 – 20 minutes).

Given that detrimental effects of diversion RI are observed following short delay intervals (i.e. minutes) in both anterograde amnesiacs (Cowan et al., 2004;

Della Sala et al., 2005; Experiments 2 – 5) as well as neurologically intact individuals (Müller and Pilzecker, 1900; Skaggs, 1925; Experiment 1) such findings of no apparent age effect in forgetting rate over a short *filled* delay interval suggest that diversion RI susceptibility may not differ substantially between the elderly and the young, and hence that normal age related memory decline, at least that observable following short delays, may be unrelated to diversion RI. This in turn suggests that the difference in the benefit of Minimal RI and susceptibility to RI between the neurologically intact elderly and the aMCI patients in Experiment 5(a) may be a *qualitative* difference.

Nonetheless, in order to examine such hypothesis empirically, it is important to compare performance of the neurologically intact controls of Experiment 5(a) with that of neurologically intact young controls under identical experimental conditions.

7.1.2 Aim of Experiment 6

The aim of the present experiment was thus to run Experiment 5(a) and (b) on a sample of neurologically intact *young* participants and to subsequently compare their performance with that of the neurologically intact elderly participants who had taken part in Experiment 5(a) and (b). More specifically, the main aim was to examine whether or not the elderly and young would differ significantly in degree of benefit of Minimal RI. A second aim was to examine whether or not a temporal gradient would be revealed also in the young, and if so whether or not this would differ from that elucidated in the elderly.

7.1.3 Methods

7.1.3.1 Participants

12 young volunteers (6f/6m, mean age = 27.5 years, SD = 3.344, mean education = 16.58, SD = 0.996) participated in the study (Note that four further young participants took part in the present study but performed at ceiling (N=3) and Floor (N=1) and were thus excluded from the sample). Their demographic data as well as basic psychometric data is provided in Table 7.1. The data of these 12 young participants was compared with that of 12 of the 14 neurologically intact elderly who had taken part in Experiment 5(a) (10f/2m), mean age = 71.33, SD = 6.853, mean education = 10.25, SD = 4.957). These were selected to form the closest match with the 12 young in terms of years of education and Estimated IQ. Note however, that the two groups could not be matched perfectly for education due to substantial changes to the education regulations in Cuba where this data was collected.

	Elderly		Young		
	Mean	SD	Mean	SD	
Age	71.33	6.85	27.5	3.34	***
Education (years)	10.25	4.96	16.58	1	**
Estimated IQ (WAIS)	117.83	8.7	129	11.16	*
MMSE	28.42	1.38	29.33	0.65	*

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Table 7.1. Mean age, education, estimated IQ and MMSE for the young and elderly group.

7.1.3.2 Materials and Procedure

The materials and methods were identical to those described in Experiment 5 (a) and Experiment 5(b).

7.1.4 Results

7.1.4.1 <u>RI versus No RI</u>

A mixed factors ANOVA on proportion correct immediate recall with within subjects factor RI Condition (no RI vs. First RI) and between subjects factor Group (Young vs. Elderly) was run to examine the state of memory before a delay was imposed. The ANOVA revealed that proportion correct immediate recall did not differ significantly between the two conditions for either group. However, the ANOVA showed that the young group performed significantly better at immediate recall than the elderly group, $F(1, 22) = 9.599$, $p < 0.01$. Group mean Immediate recall proportion correct and SD was 0.49 (0.11) and 0.38 (0.1) for the young and elderly groups respectively. No RI Condition x Group interaction was obtained.

Given the significant Group difference in estimated IQ (see Table 7.1), a correlation on mean proportion correct immediate recall and estimated IQ was run in order to examine whether or not the Group difference in proportion correct immediate recall may have been affected by such Group difference in estimated IQ. However, no significant correlation was obtained, $r = .0292$, $p = 0.292$. Estimated IQ is plotted against mean proportion correct immediate recall in Figure 7.1.

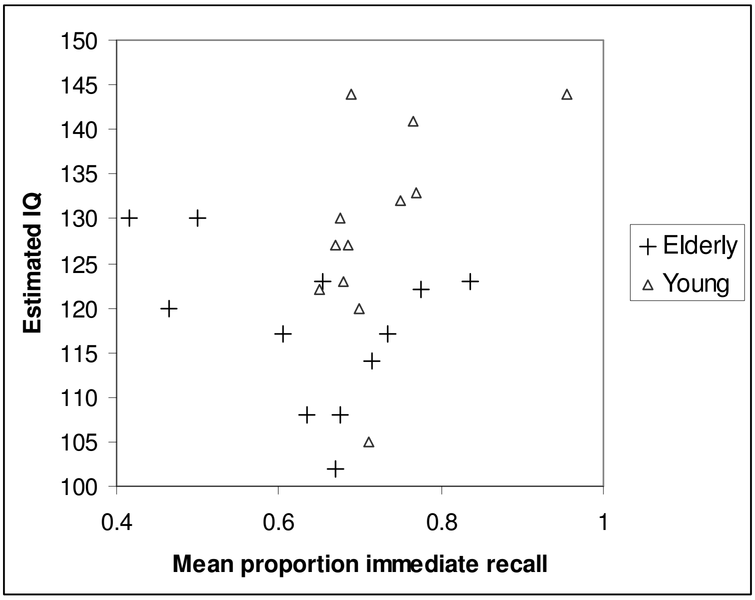


Figure 7.1. Estimated IQ plotted against mean proportion immediate recall.

As in the studies on amnesia by Della Sala et al. (2005) and Cowan et al. (2004) and the studies reported in the prior chapters retention at delayed recall was measured as the number of correct words recalled at delayed recall divided by the number of correct words recalled at immediate recall in the same condition (i.e. Delayed Recall/Immediate Recall).

A mixed factor ANOVA with within subjects factor RI Condition (No RI vs. First RI) and between subjects factor Group (Young vs. Elderly) showed a significant RI Condition main effect, $F(1, 22) = 19.615$, $p < 0.001$. No significant Group main effect or a RI Condition x Group interaction was shown, though the group difference approached significance, $p = 0.063$. However, two one way ANOVAs on proportion retention in the No RI and First RI Conditions with between subjects Factor Group (Elderly vs. Young) indicated no significant group differences in proportion retention for either RI Condition. It should be noted that a prior Levene's Test of homogeneity of variances was insignificant meaning that the assumptions for these two ANOVAs were not violated. Group means and SEMs are shown in Figure 7.2 below.

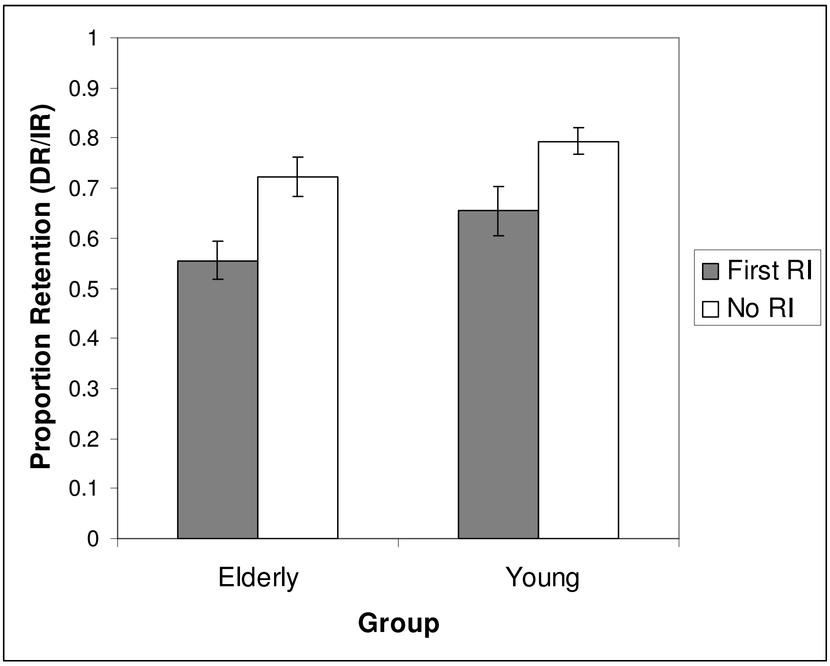


Figure 7.2. Mean Proportion Retention (DR/IR) as a function of Group and RI Condition. Error bars = SEM.

Given the significant Group difference in estimated IQ (see Table 7.1), it was decided to run a Pearson correlation on the difference in proportion retention between the MinRI and FirstRI condition (MinRI – FirstRI) and estimated IQ in order to examine whether the lack of a significant Group x RI Condition interaction may have been affected by a Group difference in estimated IQ. However, no significant correlation was obtained, $r = -.147$, $p = 0.493$. Estimated IQ is plotted against the difference in proportion retention between the Min RI and the First RI condition (Min RI – First RI) in Figure 7.3.

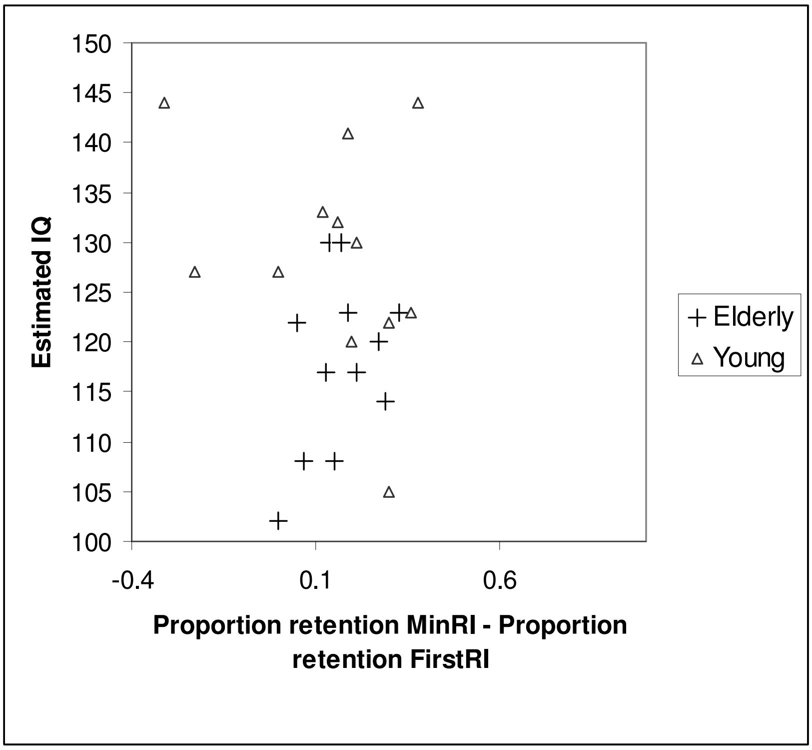


Figure 7.3. Estimated IQ plotted against the difference in proportion retention between the Min RI and the First RI condition (Min RI – First RI).

7.1.4.2 <u>Temporal gradient of RI</u>

A further set of ANOVAs was set up including the data from all four RI Conditions. A mixed factors ANOVA on proportion correct immediate recall with within subjects factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Young vs. Elderly) was run to examine the state of memory before a delay was imposed. The assumptions for such ANOVA were not violated as elucidated by an insignificant Mauchly's test of sphericity. The ANOVA revealed that proportion correct immediate recall did not differ significantly across the four conditions for either group. However, the ANOVA showed that the young group performed significantly better at immediate recall than the elderly group, $F(1, 22) = 17.323$, $p < 0.001$. Group mean Immediate recall proportion correct and SD was 0.49 (0.07) and 0.38 (0.06) for the young and elderly groups respectively. No RI Condition x Group interaction was obtained.

A mixed factor ANOVA on proportion retention (DR/IR) with within subjects factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Elderly vs. Young) was set up. As indicated by an insignificant Mauchly's test of Sphericity, the assumptions for this ANOVA were not violated.

The ANOVA showed a significant RI Condition main effect, $F (3, 66) = 6.398$, $p < 0.01$, and a significant Group main effect, $F (1, 22) = 4.654$, $p < 0.05$. However, no significant RI Condition x Group interaction was obtained. Group Mean Proportion Retention and SEMs are depicted in Figure 7.4. The RI Condition main effect was further examined by analysing each combination pair via a mixed factors ANOVA with within subjects factor RI Condition (No RI vs. Last RI, No RI vs. Mid RI, No RI vs. First RI, Last RI vs. Mid RI, Last RI vs. First RI and Mid RI vs. First RI) and between subjects Factor Group (Young vs. Elderly). These ANOVAs revealed that the significant main effect in the above ANOVA was the result of a significantly higher retention following the No RI than the Mid RI Condition, $F (1, 22) = 6.927$, $p < 0.05$, significantly higher retention following the No RI than the First RI Condition, $F (1, 22) = 19.615$, $p < 0.001$ (as indicated above) as well as a significantly higher proportion retention following the Last RI than the First RI Condition, $F (1, 22) = 7.149$, $p < 0.05$. No significant differences were shown between the remainder of the RI Condition pairs. These ANOVAs were subsequently repeated for each group separately. The significant differences between retention following the No RI and Mid RI Conditions, $F(1, 11) = 6.266$, $p < 0.05$, and the First RI and Last RI Conditions, $F(1, 11) = 6.137$, $p < 0.05$, were replicated in the Elderly group. However, no significant differences between any of the RI Conditions apart from the previously shown difference between the No RI and First RI Condition were shown for the young group.

The Group main effect was also further examined via four one way ANOVAs with between subjects factor Group (Elderly vs. Young) on proportion retention in the No RI, the Last RI, the Mid RI and the First RI Conditions. The Levene's Test of Homeogeneity of Variances was insignificant for all four RI Conditions thus indicating that the assumptions of neither ANOVA were violated. No significant group differences in proportion retention were revealed for any of the RI Conditions.

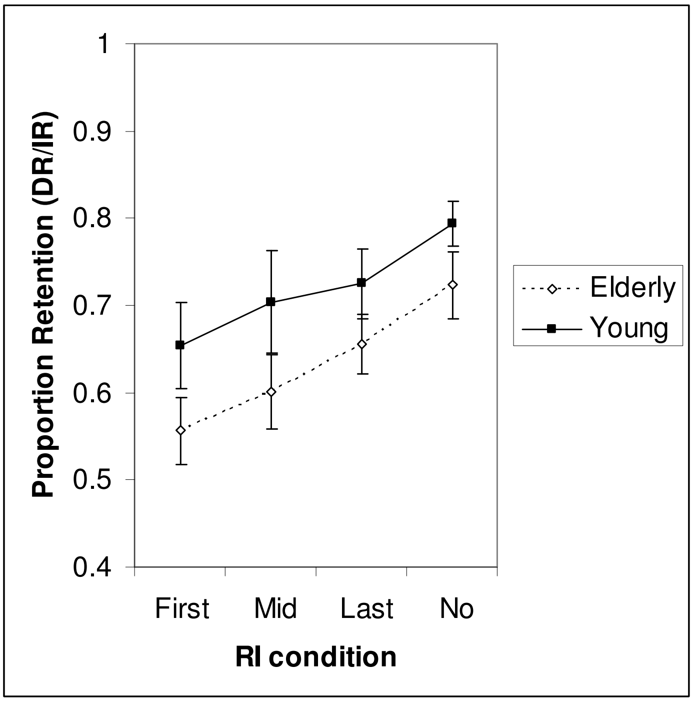


Figure 7.4. Mean Proportion Retention (DR/IR) as a function of Group and RI Condition. Error bars = SEM.

Given the lack of a significant effect of RI onset in the young group, the raw data was inspected further. It was revealed that in contrast to the majority of the young sample, four of the young participants showed better proportion retention following First RI than Last RI. Such was also the case in 2 out of the 12 elderly participants. In order to examine whether temporal onset did significantly affect proportion retention in the young participants who showed larger proportion retention following Last RI than First RI, it was decided to remove the four outliers from the data set temporarily and to run a within subjects ANOVA on proportion retention following First RI and Last RI in the young sample.

Prior to doing so it was important to establish whether or not the previously significant difference between these two conditions in the Elderly would remain following exclusion of the two elderly who showed larger proportion following First RI than Last RI, as well as whether a Group x RI Condition would emerge following removal of the six outliers.

Thus, a mixed factors ANOVA on proportion retention with between subjects factor Group (Elderly vs. Young) and RI Condition (Last RI vs. First RI) was set up. The ANOVA showed a significant RI Condition main effect, $F(1, 16) = 29.147$, $p < 0.001$, proportion retention being lower following First RI than Last RI. No Group main effect or Group x RI Condition interaction was found.

In order to examine whether both groups showed a significantly higher proportion retention following Last RI than First RI, two separate within subjects ANOVAs were run. These ANOVAs revealed that indeed, proportion retention was significantly higher following Last RI than First RI in both the elderly and the young sample, $F(1, 9) = 13.671$, $p < 0.01$, and $F(1, 9) = 15.369$, $p < 0.01$, respectively.
The proportion retention Group means and SEMs are shown in Figure 7.5 below.

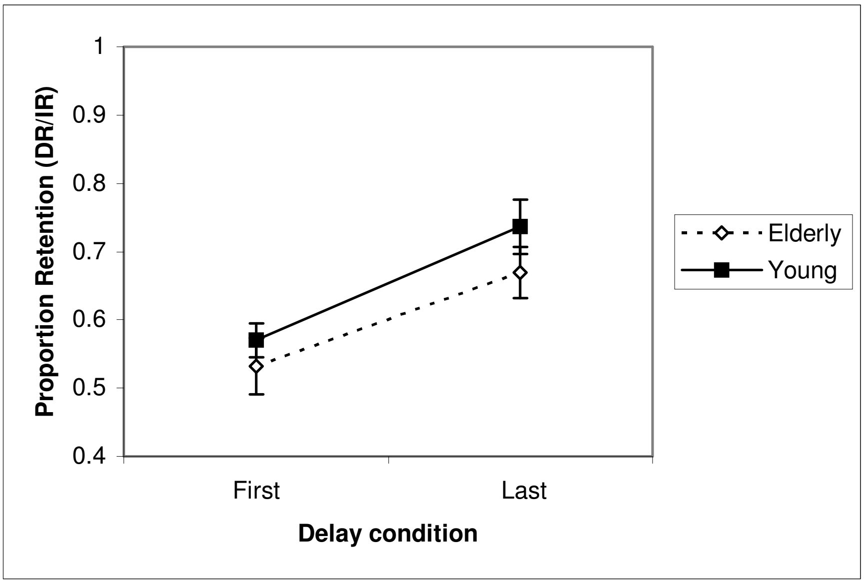


Figure 7.5. Group mean proportion retention (DR/IR) as a function of RI Condition.

7.1.4.3 RI task performance

RT

As in Experiment 5(a) performance in the picture naming task in the three RI Conditions was examined. A mixed factors ANOVA with within subjects factor RI Condition (Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Young vs. Elderly) with Greenhouse-Geisser correction due to a significant Mauchly's Test of Sphericity ($p < 0.01$) showed no significant difference in picture naming RT between the three RI Conditions and no RI Condition x Group interaction. However, a main effect of Group was obtained, $F(1, 21) = 11.913$, $p < 0.05$. This main effect was the result of significantly lower picture naming RT in the young than the elderly. RT group means and SEMs are shown in Figure 7.6.

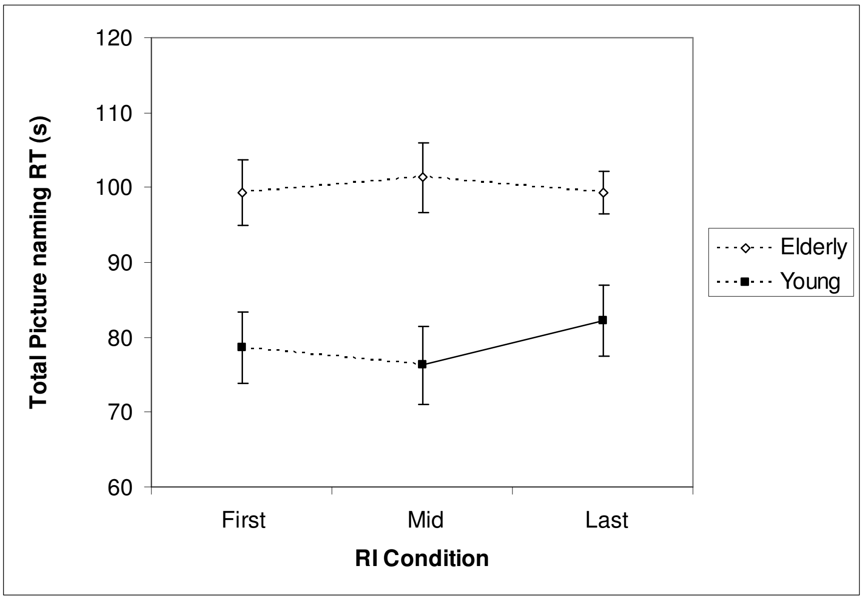


Figure 7.6. Group Mean Total Picture naming RT as a function of RI Condition. Error bars = SEM.

Naming scores

A mixed factors ANOVA on naming score with within subjects factor RI Condition (Last RI. Vs. Mid RI vs. First RI) and between subjects Factor Group (Young vs. Elderly) was set up. The assumptions for such ANOVA were not violated as indicated by an insignificant Mauchly's Test of Sphericity. The ANOVA revealed a significant difference in picture naming scores across the three RI Conditions, $F(2, 44) = 4.383$, $p < 0.05$. Moreover, the ANOVA showed a significant main effect of Group, $F(1, 22) = 9.232$, $p < 0.01$ and a significant RI Condition x Group interaction, $F(2, 44) = 4.255$, $p < 0.05$. Picture naming score group means and SEMs are shown in Figure 7.7.

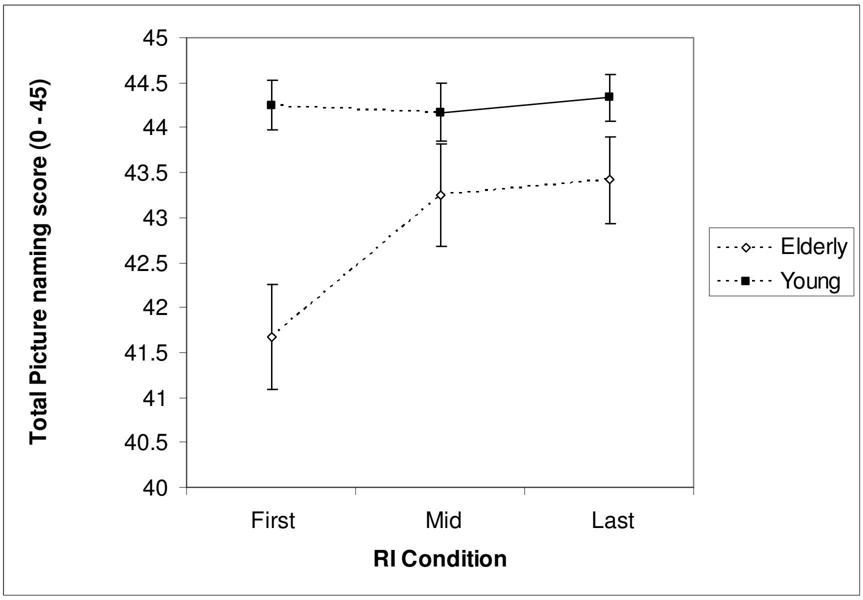


Figure 7.7. Group Mean Total Picture naming score as a function of RI Condition. Error bars = SEM.

A simple main effects analysis revealed that picture naming was significantly poorer in the First RI than the Last RI Condition, F (1, 22) = 10.278, $p < 0.01$. Furthermore the analysis showed a marginally significant difference in naming score between the Mid RI and First RI Conditions, F (1, 22) = 4.135, $p = 0.054$. No significant difference was obtained between the Last RI and Mid RI Conditions.

In order to establish the basis of the RI Condition x Group interaction a simple main effects analysis was undertaken. An insignificant Mauchly's Tests of Sphericity indicated that the assumptions for such ANOVA were not violated. This ANOVA on naming score showed that there was no significant effect of RI Condition in the young group while there was a significant effect of RI Condition in the elderly group. A further simple main effects analysis revealed that the basis of the RI Condition effect in the elderly was a significantly poorer naming score in the First Delay RI than the Last RI Condition and a significantly naming score in the First RI than the Mid RI Condition.

In order to assess whether there was an association between picture naming score and proportion retention, bivariate correlations were run for each group between picture naming score and proportion retention of each of the three RI Conditions. No significant correlations were obtained.

As in Experiment 5(a) individual slopes were computed for picture naming score and proportion retention over the three RI Conditions. Bivariate correlations were then run between the picture naming score slope and the Retention slope for each group. None of these correlations was significant.

Number of Picture-Word 'Stroop' effects

Inspection of the raw naming data for the incongruent stimuli revealed only a small number of picture-word stroop errors, i.e. instances in which the incongruent word as opposed to the actual picture name was voiced during picture naming.
In the young group a total of 2 stroop errors were found across the three trials. In the elderly control group a total number of 7 stroop errors was observed across the three trials.

In order to examine whether or not there was a significant difference in the number of picture-name errors between the three trials a mixed factors ANOVA was set up with within subjects Factor RI Conditions (First RI vs. Mid RI vs. Last RI) and between subjects Factor Group (Young vs. Elderly). The assumptions for such ANOVA were not violated as indicated by a nonsignificant Mauchley's test of sphericity.

No significant main effect was found for RI Condition or Group. Moreover, no RI Condition x Group interaction was shown.

	First RI	Mid RI	Last RI
Young	2	0	0
Elderly	3	2	2

Table 7.2: Total number of picture-name stroop errors made by the two groups in the three RI Conditions.

Subjective Picture naming feedback

Participant feedback was also checked for any possible links between subjective RI task difficulty ratings and proportion retention within each group. 9 out of the 12 Elderly stated that they found the picture naming task ‘very easy’. The remaining 3 said that they found the task ‘easy’. All 12 young participants stated that they found the picture naming task very easy.

7.1.4.4 Working memory rehearsal

As in Experiment 5(a) the participant feedback further revealed that some young and elderly participants tried to consciously rehearse the to-be-retained material while naming the pictures (i.e. during the RI task). It was thus decided to check whether the aforementioned significant RI Condition effect, the significant Group effect and insignificant RI Condition x Group interaction for both the No RI vs. First RI analysis and the analysis on all four RI Conditions would hold following exclusion of such participants.

As in Experiment 5(a) any participant stating that he or she had tried to rehearse during any of the trials was excluded. The remaining number of young and elderly participants following exclusion of rehearsers was 9 in each group.

In order to examine the effects of No RI versus First RI in the young and elderly a mixed factor ANOVA with within subjects factor RI Condition (No RI vs. First RI) and between subjects factor Group (Patients vs. Controls) was set up. As the ANOVA on the whole data set, this ANOVA showed a significant RI Condition main effect, $F (1, 16) = 9.077$, $p < 0.01$ and a significant main effect of Group, $F (1, 16) = 7.916$, $p < 0.05$. Moreover as was the case for the ANOVA on the whole data set, No RI Condition x Group interaction was shown.

In order to examine the effects of all four RI Conditions on proportion retention in the two groups following exclusion of the rehearsers a mixed factor ANOVA with within subjects factor RI Condition (First RI vs. Mid RI vs. Late RI vs. No RI) and between subjects factor Group (Young vs. Elderly) was set up. Prior to analysis the assumptions for such mixed factor ANOVA were checked via the

Mauchly's test of sphericity, which was insignificant, thus revealing that the assumptions for the planned ANOVA were not violated.

As was the case for the ANOVA on the whole data set, the ANOVA revealed a significant RI Condition main effect, $F(3, 48) = 2.914$, $p < 0.05$, and a significant Group main effect, $F(1, 16) = 9.162$, $p < 0.01$. No significant RI Condition x Group interaction was obtained.

It was further decided to re-run the above mixed factors ANOVA on proportion retention following First RI and Last RI for the sample of elderly and young participants who showed higher retention following Last RI than First RI *and* did not rehearse.

As the previous ANOVA including rehearsers and non-rehearsers, the present ANOVA showed a significant RI Condition main effect, $F(1, 11) = 26.574$, $p < 0.001$, with proportion retention being higher following the Last RI than the First RI Condition. Moreover, as previously, no Group main effect or Group x RI Condition was shown.

Two further within subjects ANOVAs revealed that both the young and the elderly participants showed significantly higher proportion retention following the Last RI then the First RI Condition, $F(1, 4) = 16.177$, $p < 0.05$, $F(1,7) = 11.818$, $p < 0.05$ respectively.

7.1.4.5 Intrusions at Word List recall

Picture intrusions at word List recall

As in Experiment 5 raw participant picture intrusion data was computed to derive 3 picture intrusion scores for each participant:

(a) Intrusions from same trial: Number of picture intrusions at delayed recall of the Last RI, Mid RI and First RI trials by pictures presented in the same trial (i.e. Last RI, Mid RI and First RI respectively). Thus while a Last RI picture falsely recalled at Last RI would be classified as 1 intrusion, a Last RI picture false recalled at First RI would not be counted as an intrusions.

(b) Intrusions from any trials at Delayed Recall: Total number of picture intrusions from any of the trials at delayed recall of the Last RI, Mid RI and First RI trials.

(c) Intrusions from any trials at Immediate Recall: Total number of picture intrusions from any of the trials at immediate recall of the Last RI, Mid RI and First RI trials.

Firstly measure (a) data was considered.

Inspection of the raw data showed that occurrence of picture intrusions from the same trial was very low, with a Total of 7 intrusions in the Elderly Group and a Total of 4 intrusions in the Young Group. These intrusions were observed in 6 of the Elderly and 3 of the Young participants.

A mixed factors ANOVA on measure a (Intrusions from same trial) with within subjects factor RI Condition (Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Elderly vs. Young) was carried out with Greenhouse- Geisser correction due to a significant Mauchly's test of spericity ($p < 0.001$).

The ANOVA revealed a significant RI Condition main effect, $F(2, 44) = 6.761$, $p < 0.05$. The basis of this main effect was a significantly larger number of picture intrusions in the First RI Condition than the Last RI Condition, $F(1, 22) = 9.791$, $p < 0.01$, and than the Mid RI Condition, $F(1, 22) = 5.037$, $p < 0.05$. No significant main effect of Group or a RI Condition x Group interaction was found. Group Picture intrusion means (measure a) as a function of RI Condition are depicted below in Figure 7.8.

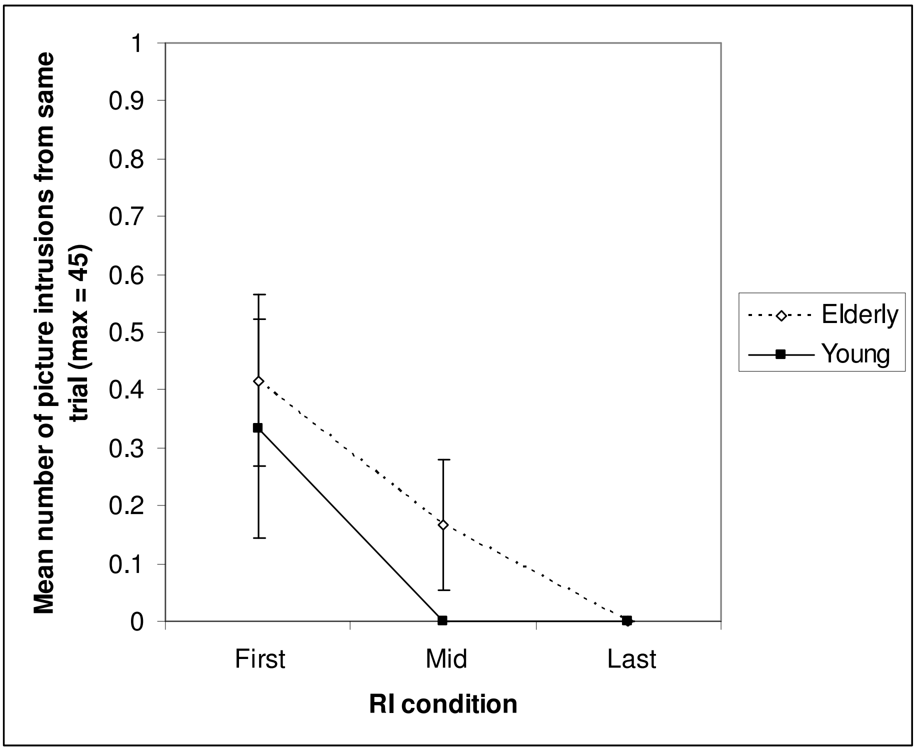


Figure 7.8. Mean number of picture intrusions from same trial as a function of Group and RI Condition. Error bars = SEM.

When considering picture intrusions from any of the trials (including the practise trial), i.e. measure (b), the total number of picture intrusions increased in both groups: A total of 19 picture intrusions at Delayed recall in the Elderly group and a total of 8 picture intrusions at delayed recall in the Young group.

A mixed factors ANOVA on total picture intrusions at DR with within subjects Factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects Factor Group (Patients vs. Controls) with Greenhouse-Geisser correction following a significant Mauchsley test of sphericity revealed no significant difference in total picture intrusions between the groups or between the RI Conditions. No Group x RI Condition interaction was observed either. Total picture intrusion group means and SEMs are shown in Figure 7.9.

A further ANOVA with additional between subjects Factor RI Condition order (order 1 vs. order 2) further revealed that RI Condition order had no significant effect on total number of picture intrusions, nor did it significantly interact with either Group or RI Condition.

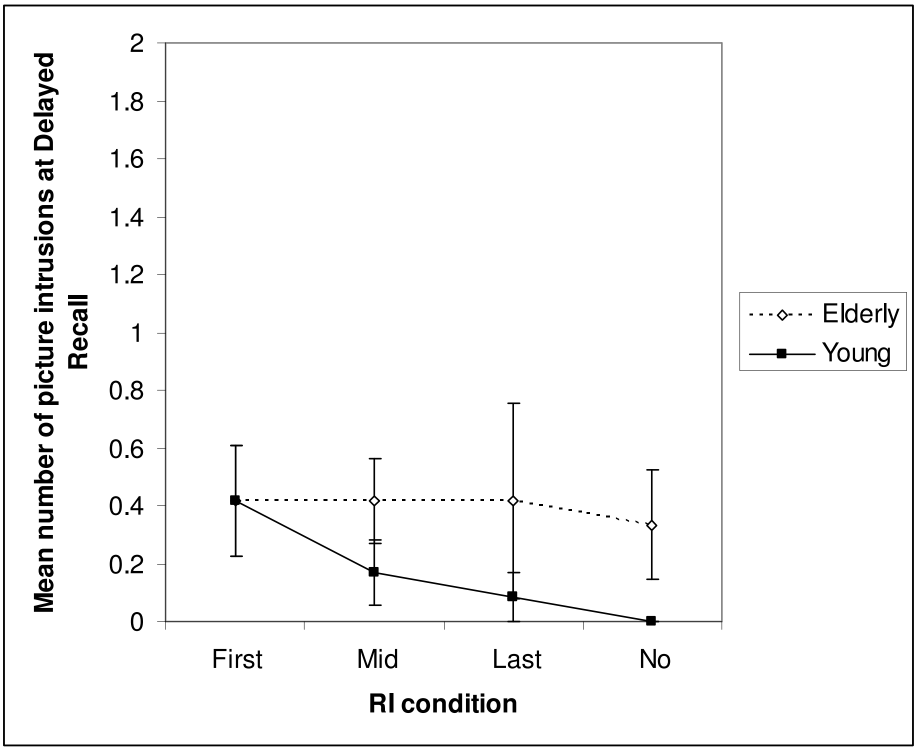


Figure 7.9. Mean number of picture intrusions (from any trial) at Delayed Recall as a function of Group and RI Condition.

In order to establish whether or not the main findings would hold when excluding the participants who showed picture intrusions, the above main ANOVA on proportion retention were repeated following exclusion of such participants.

First of all the ANOVA on proportion retention with within subjects factor RI Condition (First RI vs. No RI) and between subjects factor Group (Elderly vs. Young) was repeated with only those participants who showed 0 Picture intrusions at First RI. This resulted in a sample of 7 Elderly and 9 Young participants. The ANOVA showed a significant main effect of RI Condition, $F(1, 14) = 6.711$, $p < 0.05$, as well as a significant main effect of Group, $F(1, 14) = 5.126$, $p < 0.05$. No significant RI Condition x Group interaction was obtained. Thus the results of the main ANOVA on the full sample were replicated.

Secondly, the ANOVA on proportion retention with within subjects factor RI Condition (First RI vs. Mid RI vs. Last RI vs. No RI) and between subjects factor Group (Elderly vs. Young) was repeated with only those participants who showed 0 Picture intrusions in all of the three RI Conditions. This left a sample of 6 Elderly and 9 Young. The Mauchly's Test of Sphericity was insignificant indicating that the assumptions of this ANOVA were not violated. This ANOVA revealed no significant effects.

It was further decided to re-run the above mixed factors ANOVA on proportion retention following First RI and Last RI for the sample of elderly and young participants who showed higher retention following Last RI than First RI *and* showed 0 Picture intrusions in any of the three RI Conditions.

The ANOVA showed a significant RI Condition main effect, $F(1, 9) = 13.868$, $p < 0.01$, with proportion retention being higher following the Last RI than the First RI Condition. No further effects were found. In order to examine whether such findings were present in both groups, two within subjects ANOVAs were also run. These revealed that both the young and the elderly showed significantly higher proportion retention following the Last RI than the First RI Condition, $F(1, 4) = 8.778$, $p < 0.05$, $F(1, 5) = 6.616$, $p < 0.05$ respectively.

Word Intrusions (PI)

The number of intrusions at immediate and delayed recall by words presented in prior trials (within the present Experiment) was computed for each RI Condition for each participant. The total number of word intrusions from previous trials at delayed recall was 27 for the Elderly group and 4 for the Young group.

A mixed factors ANOVA on number of word intrusions from previous trials at delayed recall with within subjects factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Elderly vs. Young) was set up. The assumptions of this ANOVA were not violated as indicated by an insignificant Mauchly's Test of sphericity. The ANOVA showed a significant main effect of

Group, F (1, 22) = 5.454, $p < 0.05$, the basis of which was the larger number of word intrusions in the Elderly group. No further significant effects were obtained. Order of RI Conditions did not have a significant effect on the number of word list intrusions either as evinced by a second ANOVA with additional between subjects factor RI Condition order. Group mean number of word intrusions at the four RI Conditions are shown in Figure 7.10.

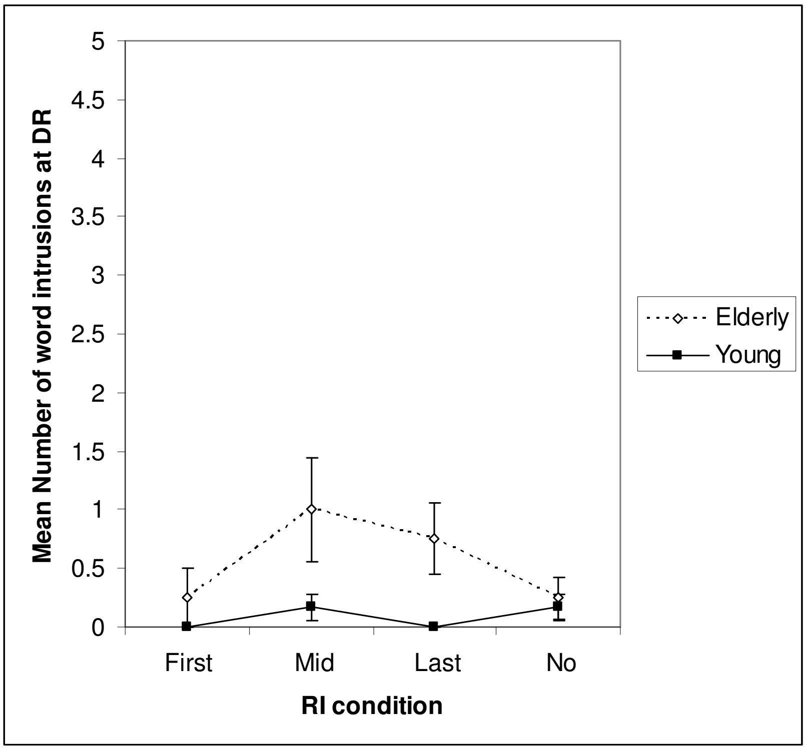


Figure 7.10. Mean number of word intrusions at DR as a function of RI Condition and Group.

The total number of word intrusions from previous trials at immediate recall was 5 for the Elderly group and 0 for the Young group.

A mixed factors ANOVA on number of word intrusions from previous trials at immediate recall with within subjects factor RI Condition (No RI vs. Last RI vs. Mid RI vs. First RI) and between subjects factor Group (Elderly vs. Young) was set up. Greenhouse-Geisser corrections were utilised due to a significant Mauchly's Test of sphericity, ($p < 0.01$). The ANOVA revealed a significant main effect of Group, the basis of which was a larger number of word intrusions in the Elderly Group. No further significant effects were obtained. Order of RI Conditions did not have a significant effect on the number of word list intrusions either as evinced by a second ANOVA with additional between subjects factor RI Condition order. Group mean number of word intrusions at the four RI Conditions are shown in Figure 7.11.

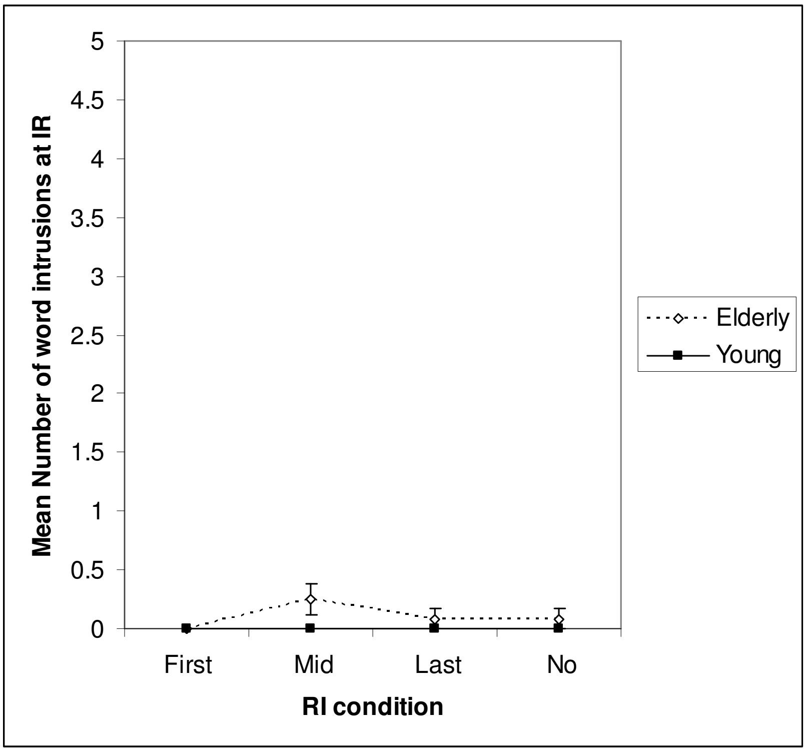


Figure 7.11. Mean number of word intrusions at IR as a function of RI Condition and Group.

7.1.4.6 Post experimental retention

As in Experiment 5(b) retention following the experiment was also examined in the present experiment.

The methods and procedure were the same as in Experiment 5(b).

As in Experiment 5(b) a ‘post experiment proportion retention from Delayed recall’ (Post Exp_DR) score was computed for each young participant.

Post Exp_DR=

(Total Post Experimental Recall/Total Delayed Recall)

A one way ANOVA on Post Exp_DR with between subjects factor Group (Patients vs. Controls) was set up. The Levene's Test of Homogeneity of Variance was insignificant indicating that the assumptions for such ANOVA were not violated.

The ANOVA indicated that there was no significant difference in Post Exp_DR between Elderly and Young. Group means and SEMs for Retention from DR are depicted in Figure 7.12.

As in Experiment 5(b), words correctly recalled following the experiment were subsequently coded in terms of the RI Condition they had been presented in to derive the proportion retention from DR as a function of RI Condition for each participant (i.e. post experiment proportion retention from DR for the No RI, the Last RI, the Mid RI and the First RI Conditions separately).

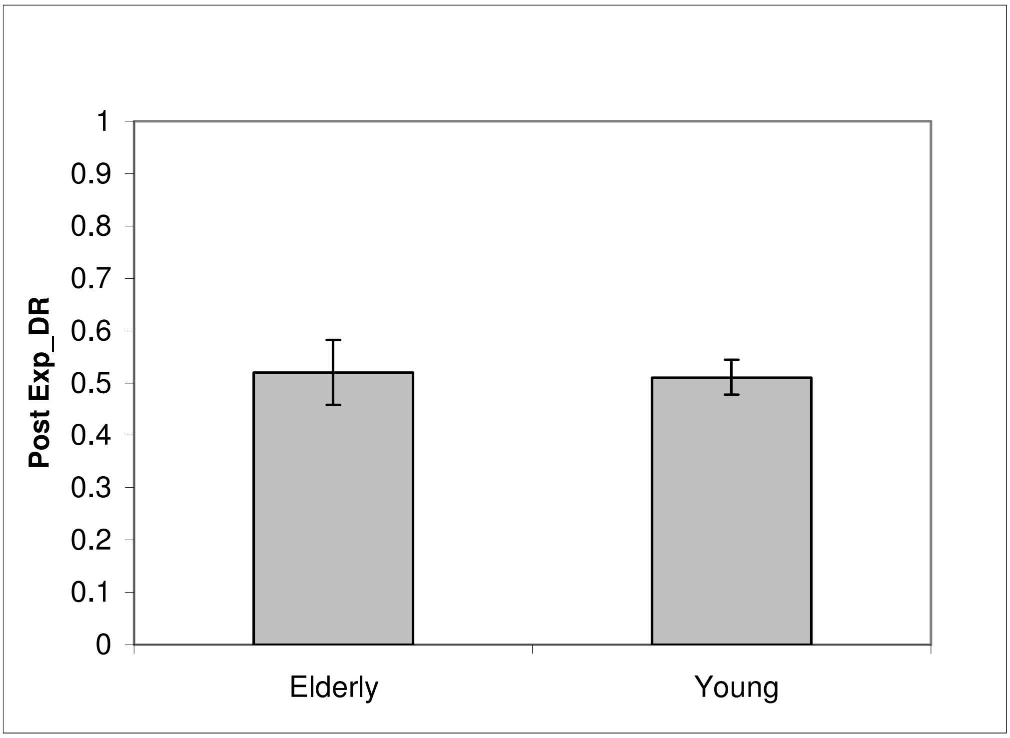


Figure 7.12. Proportion retention of words DR. Error bars = SEM.

In order to examine post experimental retention of word list material from Delayed Recall for the two groups, a mixed factors ANOVA on Post experimental retention from Delayed recall with within subjects factor RI Condition (First vs. Mid vs. Last vs. No) and between subjects factor Group (Elderly vs. Young) was set up. Mauchley's test of sphericity was significant, $p < 0.01$, indicating that the assumptions for this ANOVA were violated. An ANOVA with Greenhouse-Geisser correction was thus run. No significant main effects or an interaction were obtained in this ANOVA. The group means and SEMs are depicted in Figure 7.13 below.

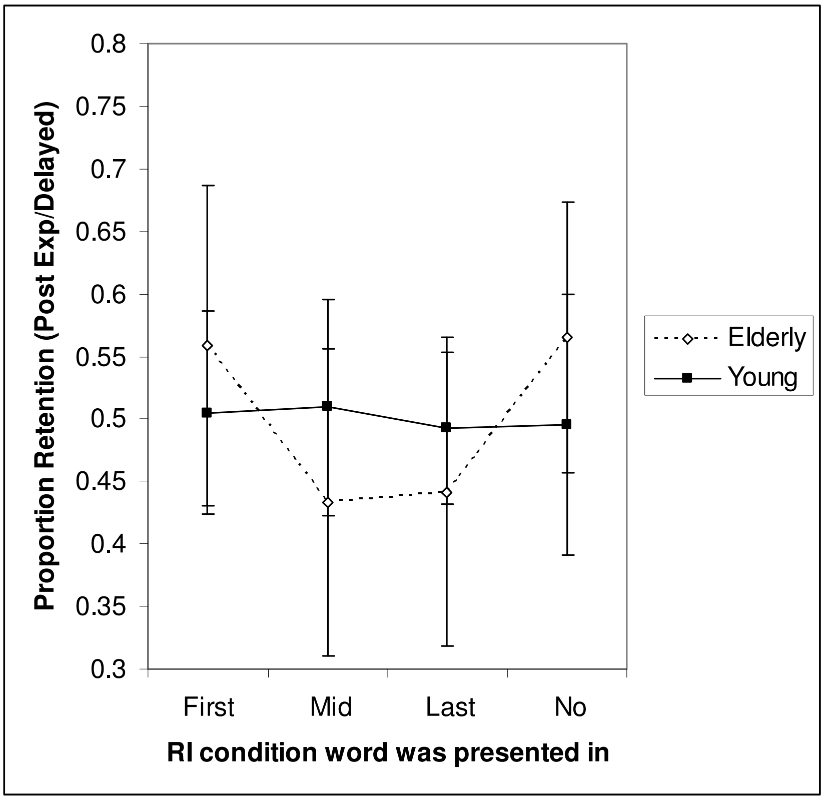


Figure 7.13. Group mean proportion Retention (Post Exp/Delayed) as a function of RI Condition.

7.1.5 Discussion

The results of the present experiment elucidate that while the elderly showed slightly lower retention than the young overall, they benefited from No RI to the same extent as did the young participants. Moreover the results show that the elderly and young also benefited to the same degree from delayed RI and thus that the temporal gradient of RI observed in this study was highly similar for both the elderly and young participants.

Most importantly then, these findings strongly suggest that the neurologically intact elderly were *no more* susceptible to RI than the neurologically intact young, strongly suggesting that specific age-related memory decline is likely to be unrelated to diversion RI.

Nonetheless, it is important to consider a potential alternative hypotheses for the lack of a difference in the benefit of Minimal RI between the elderly and young sample within this present study:

While somewhat unlikely, it could be argued that the First RI Condition in this experiment posed a larger cognitive demand on the young than the elderly. If so, the young may have performed more poorly at delayed recall following First RI than would have been expected if cognitive demand were equal for the two groups. Such in turn could have led to a larger benefit of Minimal RI in the young than would have been expected if cognitive demand were equal across the two groups. Such could in turn explain the absence of a group difference in the benefit of Minimal RI.
However, the results showed that in fact the young performed better at the First RI picture naming task than did the elderly, providing little evidence that the task was cognitively more demanding for the young than the elderly. Moreover, no differences were found in the number of 'stroop effects' (i.e. occasions in which the incongruent word as opposed to the actual picture name was voiced), indicating that the young were not more affected by such effects than the elderly.

Of course, it could be argued that the better performance in the young than the elderly at picture naming of the First RI Condition and the lack of a group difference in the number of stroop effects may actually indicate that the young concentrated harder on such task than the elderly and thus that perhaps the task did indeed pose more cognitive demand on the young than the elderly. Indeed, it could be hypothesised that the elderly focused less on picture naming during First RI due to attempted concurrent rehearsal of the to-be-retained material. Such would not only mean that the young participants may have performed worse than expected at delayed recall following First RI, but also that the elderly may have performed better than expected at delayed recall of First RI and hence that the absence of a group difference in the benefit of Minimal RI was in fact an experimental artefact.

However, firstly, no correlation was revealed between picture naming performance and proportion retention at delayed recall, demonstrating that even though the young performed better during the First RI picture naming task, such was unlikely to have had a detrimental effect on subsequent proportion retention. Moreover, the analysis of the data for the non-rehearsers for No RI and First RI replicated the previous findings of no significant group x RI Condition interaction, thus showing that when no rehearsal took place during First RI in either group, the two groups still did not differ in terms of the degree of benefit of Minimal RI.

Furthermore, the lack of a group difference in the number of picture intrusions at delayed recall of the First RI Condition further indicates that the young did not suffer from more similarity RI than the elderly, and hence that delayed recall performance at First RI in the young was unlikely to have been affected more by similarity RI in the young than the elderly.

Such argument is strengthened by the lack of a group x RI Condition interaction in the analysis on proportion retention at No RI and First RI when only those participants showing 0 picture intrusions at First RI were included.

Last but not least, at post experimental questioning all of the 12 young participants as well as 9 of the elderly stated that they had found the picture naming task ‘very easy’ while 3 of the elderly stated that they found it ‘easy’. Such subjective feedback thus provides further evidence that the picture naming task was equally perceived to be undemanding by both the young and the elderly.

Considering the evidence against the aforementioned alternative hypothesis as a whole, it appears very unlikely that the similar degree of benefit of Minimal RI in the elderly and young observed in the present experiment can be explained by group differences in the performance of the First RI Condition picture naming task.

Moreover, while the two groups differed significantly in estimated IQ, the lack of a significant correlation between estimated IQ and the difference in proportion retention between the Min RI and First RI condition (i.e. the benefit of minimal RI) suggests that it is further unlikely that the similar benefit of Minimal RI observed in the elderly and young participants can be explained by group differences in estimated IQ.

Such in turn suggests that the similar degree in the benefit of Minimal RI in the elderly and young is likely to be genuine as opposed to an experimental artefact caused by unmatched RI task performance or levels of estimated IQ.

Nonetheless, given that the benefit of Minimal RI appears to underlie *uninterrupted consolidation* in the elderly, it was of further importance to establish whether such was also the case for the young controls sample. Thus, even if the degree of the benefit of Minimal RI does not differ between the elderly and young, it would be difficult to argue that the benefit of Minimal RI did not differ between the young and the elderly if the cognitive processes underlying the benefit of Minimal RI in the young underlay a cognitive process other than uninterrupted consolidation. For such reason it was important to examine whether or not the temporal onset of RI also had an effect on proportion retention in the young.

7.1.5.1 Temporal gradient of RI

The sample size was relatively small for an analysis of a temporal gradient of RI, (i.e. for the comparison of First RI, Mid RI and Last RI). Indeed, the analysis of retention following these three RI onsets showed insignificant differences between the First RI, Mid RI and Last RI Conditions in the young. Nonetheless, Figure 7.2 does show a trend for a temporal gradient of RI in the young. Importantly, Figure 7.2 suggests that the slope of such temporal gradient was very similar to that of the elderly participants.

Moreover, as reported above, four young and two elderly participants showed higher proportion retention following the First RI Condition than the Last RI Condition. Given the small sample size it is plausible that such data may have occluded a significant temporal gradient of RI in this young sample. Indeed, the findings of significantly higher proportion retention following Last RI than First RI in both the young and the elderly, yet no Group x RI Condition interaction following the exclusion of these six participants tentatively suggests that the young, too, benefit from a delay in RI, and that such benefit is very similar to that observed in the elderly (see Figure 7.5). Nonetheless, while the six excluded participants may have been outliers, in as much as they may have not represented the young population, one cannot rule out the possibility that in general some young individuals may not show a temporal gradient of RI or indeed that some may show an opposite effect as did these six participants. Thus, more research on a larger young sample is required to examine whether these tentative findings of a temporal gradient of RI as well as a similar temporal gradient of RI in the young and elderly hold.

In the interim it is tentatively suggested that the benefit of Minimal RI also underlies some uninterrupted consolidation in the young and thus that the benefit of Minimal RI is not only quantitatively but also qualitatively comparable in the elderly and young.

Nonetheless, prior to concluding that the apparent higher retention following Last RI than First RI in the young did indeed underlie the temporal onset of RI, and thus improved consolidation, it is important to briefly consider the three alternative hypotheses for such finding that were proposed in Experiment 5(a)(please refer to the discussion of Experiment 5(a) for detailed arguments against them):

(1) Explicit STM maintenance during Last RI but not First RI
(2) Lack of interference at LTM retrieval in Last RI
(3) Facilitated consolidation due to less demanding picture naming in Last RI

(1) Explicit STM maintenance during Last RI but not First RI (see discussion of Experiment 5(a) in Chapter 6)

As discussed in Experiment 5(a) there is the possibility that proportion may have been better following Last RI than First RI due to explicit STM maintenance during Last RI but not First RI.

Given that the young subgroup of participants with larger proportion retention following Last RI than First RI still showed significantly higher proportion retention following the Last RI than the First RI Condition *even* following removal of those participants who tried to rehearse during any of the RI Conditions, it appears highly unlikely that the RI Condition effect in the young can be explained by explicit STM maintenance during Last RI but not First RI.

(2) Lack of interference at LTM retrieval in Last RI (see discussion of Experiment 5(a) in Chapter 6)

As argued in Experiment 5(a) there is the chance that perhaps interference at retrieval was lower in the Last RI than the First RI Condition.

While the analysis of the picture intrusions did reveal a slightly larger amount of intrusions in the First RI than the Last RI Condition, the subsequent analysis revealed that proportion retention at Last RI was still significantly larger than that following First RI even when only those young participants showing no picture intrusions were included. Moreover, instances of PI in the young group were very rare and certainly not concentrated in the First RI Condition.

Thus, there appears little evidence for a retrieval account for the significantly higher proportion retention following Last RI than First RI in the young sample.

(3) Facilitated consolidation due to less demanding picture naming in Last RI

As argued in Experiment 5(a) it could be possible that while Last RI allows for better consolidation of to-be-retained material than does First RI, such may be the product of a less demanding picture naming task during Last RI than First RI as opposed to the later temporal onset of RI in the Last RI Condition.

However, the analysis of picture naming data revealed no significant differences in the young group in either picture naming RT or picture naming score between the First RI and Last RI Conditions. Furthermore, no significant correlations between performance on picture naming and proportion retention were found in the young group. Thus, it appears highly unlikely that the findings of significantly higher proportion retention following Last RI than First RI can be explained by such alternative consolidation hypothesis.

Overall then there appears to be little evidence for either an explicit *STM maintenance hypothesis*, a *retrieval hypothesis* or a *mental effort based consolidation hypothesis* of the findings of significantly improved proportion retention following Last RI than First RI in the subgroup of young participants who showed better retention following Last RI than First RI. It thus appears highly likely that, as is the case for the elderly participants, such finding in the young can be explained via the time based consolidation theory originally proposed by Müller and Pilzecker's (1900) and adopted by modern neuroscience.

The finding of (a) no difference in the degree of benefit from Minimal RI between the elderly and young and (b) no apparent difference in the cognitive process underlying such benefit of Minimal RI in the elderly and young strongly suggest that the benefit of Minimal is not only quantitatively but also qualitatively comparable in the elderly and young.

Such finding is interesting as it suggests that age related memory impairment, i.e. any forgetting above and beyond that observed in the younger population, is unlikely to be associated with diversion RI.

Indeed, the results of significantly poorer immediate word list recall in the elderly than the young participants in the present experiment provide further tentative evidence for the notion that age related memory decline may be associated with impairments at initial memory acquisition (Trahan and Larrabee, 1992; Dunlosky and Salthouse, 1996; Tombaugh and Hubley, 2001; Davis et al., 2003). However, the results indicate that even when controlling for reduced acquisition in the elderly by using a proportion retention measure (DR/IR), retention following the nine minute delay interval was still slightly, if not significantly lower overall in the elderly than the young sample. Given the significantly higher number of word intrusions (PI) in the elderly than the young, it could be tentatively hypothesised that the slightly lower overall proportion retention in the elderly than the young may have been the consequence of such increased PI, and thus that the elderly may also show some retrieval deficit. Given the findings of an apparent heightened susceptibility in the elderly to similarity RI and PI (c.f. Bowles and Salthouse, 2003, Hasher et al., 2002; Hedden and Park, 2001; Hedden and Park, 2003; see also Kane and Hasher, 1995) such hypothesis does not seem unreasonable.

The lack of a difference between the elderly and young at the second delayed recall following the experiment suggests that memory of acquired word list material was just as stable in the elderly as it was in the young following such longer delayed recall. Nonetheless, given the previous research findings on accelerated forgetting in the elderly over longer delay intervals (Huppert and Kopelman, 1992; Tombaugh and Hubbley, 2001; Davis et al., 2003), it cannot be ruled out that the elderly taking part in this study may have shown poorer retention than the young following a longer delay interval such as a day or a week.

Nonetheless, the most relevant finding in this study is that of an apparent *lack* of an age-specific increase in *diversion RI susceptibility*.

Indeed, such finding is interesting with respect to the further cognitive understanding of age related memory decline. Moreover and with particular regard to the main aim of this experiment, this finding suggests that the substantially increased susceptibility to diversion RI in the aMCI patients in Experiment 5(a) is likely to be specific to aMCI rather than representing an exaggerated type of age-related increase in diversion RI susceptibility. Thus, it is tentatively hypothesised that while elderly people in general are likely to present with normal age-related memory deficits, possibly associated with impaired acquisition, retrieval and or accelerated forgetting, elderly people with aMCI present with an additional specific memory impairment that is associated with a *severely increased susceptibility to diversion RI*.

Hence, with particular reference to the question posed in the introduction of this chapter regarding a *qualitative* or *quantitative* difference in diversion RI susceptibility in the neurologically intact elderly and the elderly with aMCI, the answer appears to be that such difference is likely to be a *qualitative* one.

While, given the limited number of participants in the present study, it will be of substantial importance to examine whether such findings hold in a larger sample of elderly and young neurologically intact individuals, the present tentative findings could prove fruitful for future research on a potential early diagnosis tool for differentiating between normal age-related memory impairment and that of the early stages of aMCI and thus AD.

7.1.6 Conclusion

In conclusion, the findings of the present study indicate that both the young and elderly benefit from Minimal RI to the same extent. Moreover, the findings suggest that the temporal gradient of RI is highly similar for the two age groups. Thus it appears that normal age related memory decline is not associated with an increased susceptibility to diversion RI. Such finding is important with respect to the previous findings of greatly increased susceptibility to diversion RI as well as temporal gradient of RI in patients with aMCI. Indeed, it appears that the memory deficits in this patient group are qualitatively as opposed to quantitatively different from those in the normal elderly. Such findings are not only of interest in terms of the cognitive modelling of forgetting in normal ageing and aMCI but may also lead to a future means of differential diagnosis between normal ageing and the very early stages of aMCI/AD.

Chapter 8: Neural correlates of the benefit of Minimal Retroactive Interference

8.1 Introduction - Experiments 7 and 8

The studies on RI by Cowan et al. (2004) elucidated that focal brain injury patients with anterograde amnesia associated with a range of lesions *sparing* the temporal lobes/hippocampus (see Figures 8.1 and 8.2) showed greatly increased retention of to-be-retained material following Minimal RI than RI, indicating a large benefit from Minimal RI and thus a substantially larger susceptibility to RI in such patients than neurologically intact individuals.

In contrast, no benefit of Minimal RI was found in the other two patients, both of whom presented with temporal lobe lesions, which included the hippocampus bilaterally in one patient. Indeed, these two patients were unable to recall any material following the delay interval irrespective of whether this contained RI or Minimal RI. It was thus tentatively suggested that an intact temporal lobe may be required for a benefit of Minimal RI to emerge in patients with anterograde amnesia.

Further and possibly more precise evidence for such hypothesis comes from Della Sala et al's (2005) RI study on aMCI as well as a small sample of patients with early AD. While the aMCI patients were able to benefit from Minimal RI, no such benefit was observed in the small sample of patients with early AD (Della Sala et al., 2005). One of the main differences between these two patient groups lies in their hippocampal volume: AD patients show substantially greater hippocampal atrophy than do patients with aMCI (c.f. Dickerson et al. 2001). Della Sala et al.'s (2005) findings thus tentatively suggests that a relatively intact hippocampus may be required for a benefit of Minimal RI to emerge in patients with anterograde amnesia.

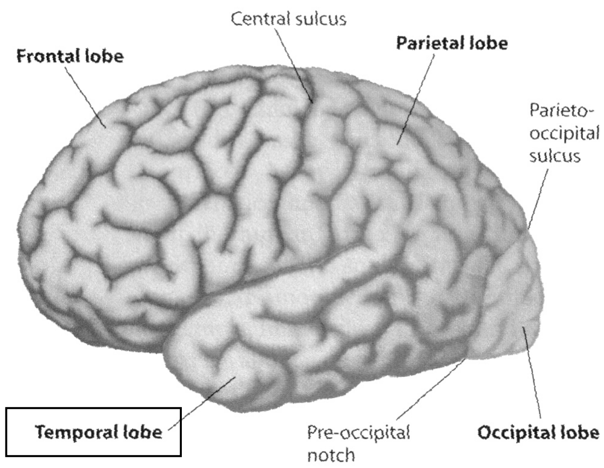


Figure 8.1. The temporal lobe within the human brain (taken from Gazzaniga, Ivry and Mangun, p. 46)

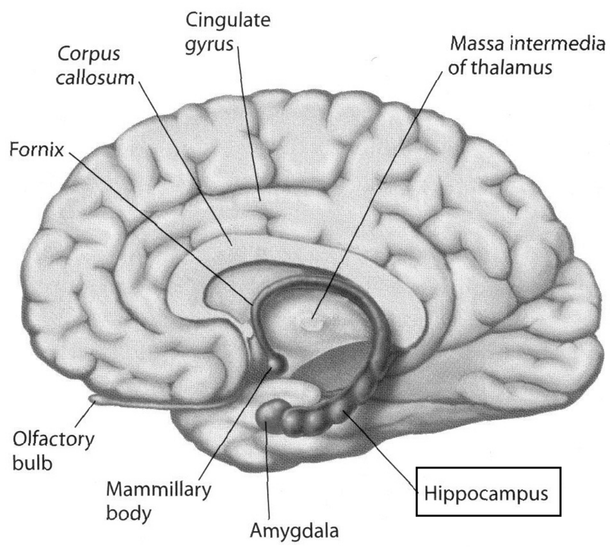


Figure 8.2. The hippocampus within the human brain. (taken from Gazzaniga, Ivry and Mangun, p. 59)

Cowan et al.'s (2004) and Della Sala et al.'s (2005) tentative findings and hypothesis of a requirement for an intact temporal lobe/hippocampus for a benefit of Minimal RI to emerge in patients with anterograde amnesia are of particular interest regarding the underpinning of the cognitive processes underlying the benefit of Minimal RI (see Chapters 5,6 and 7). Indeed, while the two studies elucidated that a benefit of Minimal RI was present in some patients with anterograde amnesia, the cognitive processes underlying such benefit were relatively unknown and tentative only, meaning that no precise predictions could be made regarding potential neural correlates of the benefit of Minimal RI.

However, the more recent findings of some apparent 'uninterrupted' LTM consolidation (reported in Chapters 5, 6 and 7) makes the search for the neural correlates of the benefit of Minimal RI somewhat more streamlined. Indeed, given the notion of an important role of the temporal lobe, especially the *medial* temporal lobe including the *hippocampus* in human declarative LTM consolidation (c.f. Squire, 1992; Squire and Alvarez, 1995; Alvarez and Squire, 1994; Squire et al., 2004), a 'temporal lobe/hippocampus' hypothesis of the benefit of Minimal RI would appear to fit the cognitive findings rather well. Thus, if, as strongly suggested by Experiments 3, 4(a), 4(b) and 5, Minimal RI allows for some LTM consolidation to take place in these severely amnesic patients, and the temporal lobe/hippocampus is of vital importance to LTM consolidation, then a patient whose temporal lobe/hippocampus were damaged extensively, should not be able to consolidate new information, whether RI is present or minimal.

However, so far the aforementioned tentative hypothesis of a requirement of an intact temporal lobe/hippocampus for a benefit of Minimal RI in focal brain injury patients with anterograde amnesia rests on a very small pool of patients with a broad range of aetiologies, lesions and with somewhat large individual differences with respect to the degree of the benefit of Minimal RI. The latter is also true for the RI study on aMCI patients by Della Sala et al. (2004). Indeed, while the variance in aetiology was greatly minimised by testing such defined subcategory of amnesia, and while all patients showed a benefit of Minimal RI, the patients within the sample nevertheless showed somewhat large individual differences in the degree of the benefit of Minimal RI (ranging from a difference in proportion retention following RI and Minimal RI of 0.08 to 0.56). As the aetiology of the patients entering the study was the same it is unclear why such patients differed somewhat in the degree of benefit of Minimal RI. One possibility is that the benefit is not simply present or absent according to whether or not the temporal lobe/hippocampus is damaged, but that it varies in degree according to the extent of temporal lobe/hippocampal damage. If such were the case, it could be hypothesised that the patients differed in extent of hippocampal atrophy. Indeed, given the fact that a large proportion of patients with aMCI gradually progress to AD (Petersen et al., 1999), and that such progression involves volumetric hippocampal decline, it is possible that the individual differences in the degree of benefit from Minimal RI in the study by Della Sala et al. (2004) were at least partially related to individual differences in the extent of hippocampal atrophy.

The two studies to be reported subsequently (Experiment 7 and 8) were set up to further investigate (a) whether or not an intact temporal lobe/hippocampus is required for patients with anterograde amnesia to benefit from Minimal RI and/or (b) whether or not the extent of the temporal/hippocampal lesion, as opposed to the mere presence/absence of such lesion may affect the benefit of Minimal RI, in particular its magnitude.

8.2 Experiment 7: Neural correlates of the benefit of Minimal RI in neurological patients (1) – Lesion locus and the presence/absence and extent of a benefit of Minimal RI in focal brain injury patients

8.2.1 Aims of Experiment 7

The aims of Experiment 7 were to further examine any associations between the presence/absence of the benefit of Minimal RI and lesion site in a sample of focal brain injury patients with anterograde amnesia. In particular, the aim was to examine whether or not the tentative hypothesis of a lack of a benefit of Minimal RI in patients with temporal/hippocampal lesions would hold.

8.2.2 Method

8.2.2.1 Participants

The participants in this Experiments were the same as those entering Experiment 2(a) (See Tables 4.1a and 4.1b for a full description of these patients' demographic and neuropsychological test scores). P4 also participated in the Cowan et al. (2004) study.

8.2.2.2 Procedure

This Experiment was an exploratory analysis, in which the patients' benefit of Minimal RI data was examined in relation to their known lesion sites.

8.2.3 Results

Table 8.1 shows aetiology, known lesion site as well as absence or presence or a benefit of Minimal RI for each patient entering Experiment 2(a).

Of largest importance and relevance to the present experiment is the finding that a benefit of Minimal RI was found in each of the four patients with temporal lobe lesions (PA, PB, PH and PI). The table further shows that two of these patients with temporal lobe lesions had known lesions to the hippocampus (PB, see MRI, Figure 5.2.a and Figure 5.2.b; and PA). No benefit of Minimal RI was observed in PJ who had a known lesion in the right frontal lobe. Note that while patients PF (bilateral frontal lesion) and PK (diffuse atrophy with no focal lesion) did not show a benefit of Minimal RI either in Experiment 2(a), they did show some improved retention following Minimal RI in Experiments 4(a) and/or 4(b) meaning that their lesions cannot be associated with a lack of a benefit overall.

Given the apparent benefit of Minimal RI in patients with temporal lobe lesions in the present study but not in the study by Cowan et al. (2004), it was decided to investigate whether there were any potential differences in the *degree* of benefit from Minimal RI in the present patients with temporal lesions and non-temporal lesions. The underlying reasoning was that an intact temporal lobe may still be required for a benefit of Minimal RI to emerge, but that less extensive damage to such region could nevertheless allow patients to benefit from Minimal RI, albeit to a lesser extent.

Degree of benefit was computed for each patient by subtracting mean proportion retention in the RI (tone detection) condition from that of the Minimal RI Condition. This degree of benefit data is provided in Table 8.1 for each patient.
Observation of this data in Table 8.1 indicates no largely apparent differences in the degree of the benefit of Minimal RI between the temporal and non-temporal patients benefiting from Minimal RI.

Patient	Benefit (Y/N)	Aetiology	Known lesion sites	Degree of benefit
PA	Y	s	LO, LHip, LTh	0.25
PB	Y	Limbic Encephalitis	LRT(medial), LRHip	0.38
PC	Y	probable Limbic Encephalitis	Normal	0.4
PD	Y	probable birth asphyxia	Normal	0.52
PE	Y	h	LP	0.538
PF	N*	an	LRF	0
PG	Y	h	RTh	0.22
PH	Y	h	LRF, LT, RP	0.68
PI	Y	h	LT, RF	0.69
PJ	N	h	RF	0
PK	N*	an	Diffuse atrophy, non focal lesion	0

Benefit (Y/N): based on the presence/absence of a benefit in Experiment 2(a).
Aetiology: an = anoxia, h = head injury, s = stroke.
Lesion site: L = left, R = right, F = frontal, Hip = hippocampus, O = occipital, P = parietal, T = temporal, Th = thalamus, according to MRI.
* depicts patients who showed no benefit during Experiment 2(a) but showed signs of a benefit in Experiments 3(b) or 4(b). Degree of benefit: calculated as the difference between each individual patient's mean proportion retention following Minimal RI and that following RI (tone detection)

Table 8.1. Aetiology, known lesion sites, presence/absence of benefit of Minimal RI and degree of benefit of Minimal RI for each of the patients examined in the present Experiment.

In order to test this statistically a one-way ANOVA with between subjects Factor Lesion Group (Non-temporal vs. Temporal) was run on the degree of benefit data of patients showing a benefit from Minimal RI (i.e. those patients who did not benefit from Minimal RI were excluded for this ANOVA). Levene's Test of homogeneity of variance was insignificant indicating that the assumptions for such ANOVA were not violated.

The ANOVA showed no significant difference in degree of benefit between the two lesion groups. This is illustrated in Figure 8.3.

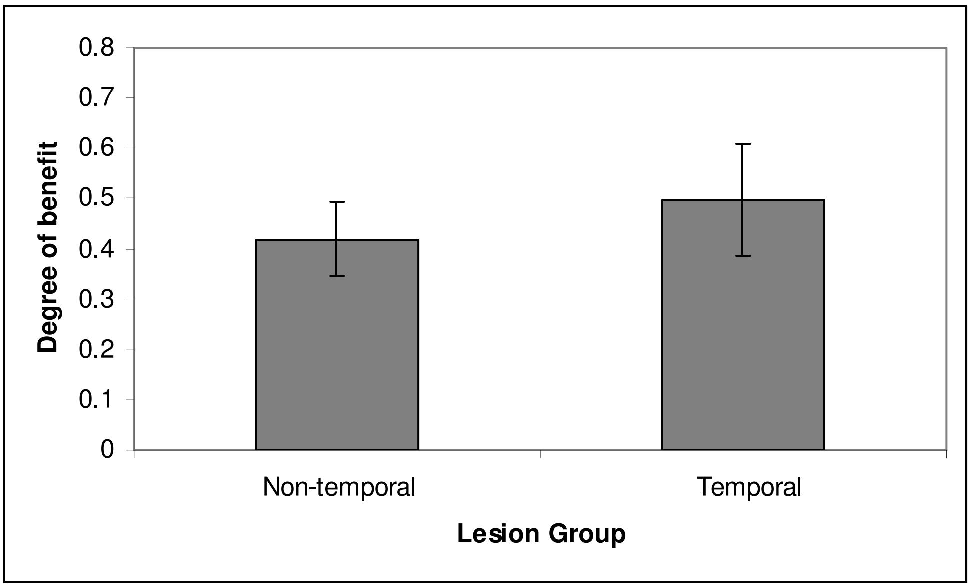


Figure 8.3. Lesion Group mean degree of benefit. Error bars = SEM.

Nonetheless, Table 8.1 did elucidate a smaller degree of benefit from Minimal RI in the two patients with known lesions to the hippocampus than in the two patients with more general temporal lesions. It was thus decided to split the Temporal group into two groups, a Temporal group and a Hippocampus group and to re-run the above ANOVA with this additional group.

As in the previous ANOVA the assumptions of this ANOVA were not violated, as indicated by an insignificant Levene's Test of Homogeneity of Variance. Nonetheless, given the very small and unequal sample sizes it was decided to also apply a Welch corrected ANOVA. The main ANOVA revealed a trend towards significance of Group, $F(2, 7) = 5.212$, $p = 0.06$. Such trend was confirmed by the

Welch corrected ANOVA, F (2, 2.008) = 18.023, p = 0.052. The data is shown in Figure 8.4 below.

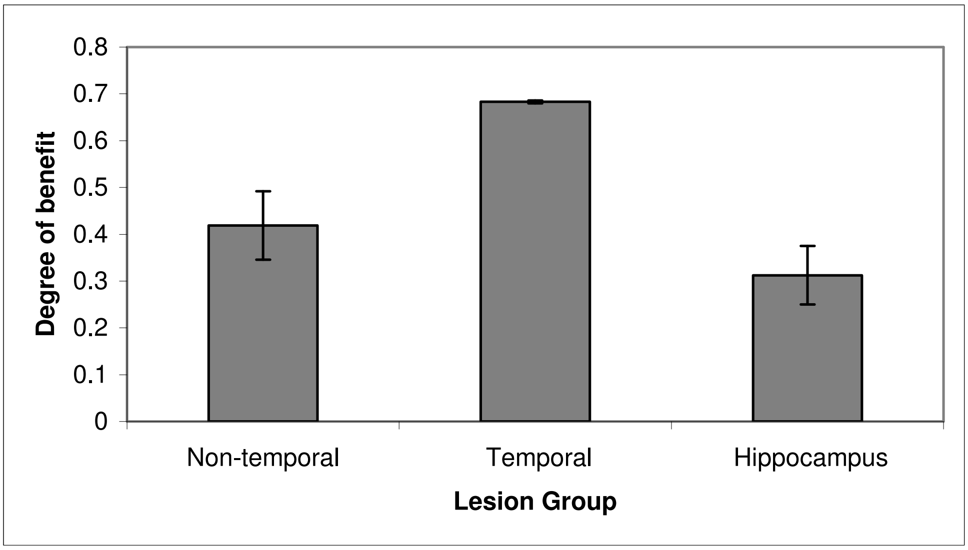


Figure 8.4. Lesion Group mean degree of benefit. Error bars = SEM.

8.2.4 Discussion

The aim of this Experiment was to further examine any associations between focal brain injury patients' lesion sites and the presence and absence of a benefit of Minimal RI. A more specific aim was to investigate whether or not Cowan et al.'s (2004) findings of an absence of such benefit of Minimal RI in patients with temporal lesions would hold in a further sample of anterograde amnesia patients.

Firstly, the results showed that all four patients with temporal lesions entering Experiment 2(a) were able to benefit from Minimal RI. Moreover, the results showed that on average the patients with temporal lesions benefited as much from Minimal RI as did those patients whose lesions did not encroach on the temporal lobe. Such finding thus clearly contrasts with that by Cowan et al. (2004). Indeed, even though the present study contained only a small sample of patients with temporal lobe lesions (N = 4), the findings suffice to demonstrate that a *fully* intact temporal lobe *cannot* be essential for a benefit or Minimal RI to emerge in patients with anterograde amnesia.

Interestingly, the results showed a trend towards significance in the degree of benefit of Minimal RI between the patients with general temporal lobe lesions and those with specific hippocampal lesions. It is important to note however, that given the very small sample size such analysis and its results may not be very reliable. Nonetheless, from visual inspection of the means it does appear that the two hippocampal patients appeared to benefit less from Minimal RI than the two temporal patients whose lesions did not appear to encroach on the hippocampus (as indicated by MRI). However, it is important to highlight that while the mean degree of benefit of the two hippocampal patients was somewhat lower than that of the two temporal patients, both hippocampal patients in fact performed highly in one Minimal RI trial (proportion retention = 0.75 and 0.5 for patients PB and PA respectively) and 0 in the other, meaning that their mean proportion retention and thus their computed degree of benefit may have been underestimations of their actual ability to benefit from Minimal RI. Nonetheless, given the somewhat stable proportion retention across the Minimal RI trials in patients PH and PI, it is possible that the large variability in benefit in the two hippocampal patients may itself indicate some difference in the ability to benefit from Minimal RI in the two groups. Thus, as stated above when referring to Della Sala et al.'s (2005) aMCI findings, further specific research on the hippocampus and its atrophy in relation to the benefit of Minimal RI is required (this will be the topic of the Experiment 8).

There are a number of possible explanations for the contrasting findings of the Cowan et al. (2004) study and the present study. These shall be discussed subsequently.

(a) The temporal lobe is not required for the benefit of Minimal RI in patients with anterograde amnesia

It is possible that the temporal lobe is *not* required for the benefit of Minimal RI in patients with anterograde amnesia. If this were the case there could be at least three possibilities for why the two temporal patients tested by Cowan et al. (2004) showed no benefit of Minimal RI. Firstly, these two patients may have other unknown lesions in a structure or structures that are required for a benefit of Minimal RI to emerge. Such structures would be predicted to have been spared in the other four patients, as well as the patients benefiting from Minimal RI in the present study. However, it should be highlighted that one of Cowan et al.'s (2004) patients who did not benefit from Minimal RI (their Patient 4), also took part in the present study (PH), in which he showed a benefit of 0.68. If indeed an unknown lesion had explained his lack of a benefit in the previous study, he should have also shown such a lack of benefit in the present study, unless there has been some functional reorganization, meaning that another structure is *now* able to benefit from Minimal RI.

A second possibility is that the lack of a benefit in Della Sala et al.' (2005) two temporal patients was not related to an anatomical lesion but to a cognitive problem such as for example high distractability, which could have led to diversion RI even during Minimal RI, for example via highly distracting thoughts. However, as argued above, if such was a persistent problem, PH should have also failed to benefit from Minimal RI in the present study.

However, it could be possible that such a cognitive factor, i.e. distracting thoughts or another distraction outwith the experimenters' control, could have led to the lack of a benefit of Minimal RI during that particular testing occasion. Thus, the patients may have had the capacity to benefit from Minimal RI but were unable to benefit during Cowan et al.'s (2004) study for an unknown 'temporary' reason. Evidence for such hypothesis may be gleaned from Experiments 2(a), 2(b), 4(a) and 4(b), which revealed that some patients who were able to benefit from Minimal RI did not always do so on all Minimal RI trials in the various experiments. Nonetheless, the patients in Cowan et al.' s (2004) study failed to benefit in all of the

Minimal RI trials in both the prose and the word list experiment reported by Cowan et al. (2004), rendering such a 'variability in benefit' hypothesis less probable.

(b) Some, but not all of the temporal lobe is required for the benefit of Minimal RI in patients with anterograde amnesia

A further potential explanation for the apparent disparity in the benefit findings in patients with temporal lesions in the Cowan et al. (2004) study and the present study could be that the temporal lobe, *albeit* not all of it, *is* required for a benefit to emerge. With respect to such potential hypothesis it is possible that patients PA, PB and PI, in the present study had less extensive damage to the temporal lobe than did the patient in the Cowan et al. (2004) study who did not participate in Experiment 2(a). Note, that such argument cannot be applied to PH who presumably should have shown the same extent of temporal damage in both studies.

However, in order to test this assumption empirically, future RI research on PH should include both further behavioral as well as structural data. In the absence of any structural changes to the temporal lobe in such patient it could be argued (as above) that some functional reorganization has allowed another structure to take over some memory function in PH, thus allowing him to benefit in Experiment 2(a). In light of such possibility it would also be of interest to retest Cowan et al.'s (2004) other temporal lobe patient in order to examine whether he may also be able to benefit from Minimal RI at this point in time. Such future work should also involve more recent structural data. Indeed, if this patient's previous lack of a benefit of Minimal RI is replicated, it will prove very interesting to compare extent of temporal damage in this patient and in the present patients (including PH) in order to examine the potential hypothesis that *extent* of temporal lobe/hippocampal damage may play a role in the absence/presence of a benefit of Minimal RI in patients with anterograde amnesia.

If at least some temporal lobe is required for a benefit of Minimal RI to emerge, and if extent of temporal lobe damage does play a role in the degree of benefit of Minimal RI one would predict that damage to the temporal lobe, even if not very extensive, should lead to a smaller degree of benefit in a patient with some temporal damage than in a patient with no temporal damage. However, the results of no difference in degree of benefit in the temporal and non-temporal patients in the present study did not match such prediction. However, it is important to highlight that the group mean of the non-temporal group may have been reduced by PG, who in fact was able to retain some material following RI and thus possibly showed less susceptibility to RI, at least to the type of RI utilized in Experiment 2(a). Moreover, as pointed out above, while PF and PK were excluded from the present analysis due to failing to benefit from Minimal RI, their apparent benefit of Minimal RI in further experiments indicates that they are indeed able to benefit to some extent. Such in turn means that their lesion sites cannot be translated into structures potentially required for a benefit to emerge. Only one patient, PJ, was unable to benefit from Minimal RI in all Minimal RI trials of Experiments 2(a) and 4(a). However, while such lack of a benefit differentiates him *cognitively* from the other patients taking part in Experiment 2(a), his lesion site, right frontal, does not do so. Indeed, right frontal lesions were also present in PH and PI, both of whom benefited from Minimal RI in Experiment 2(a), as well as in PF who showed a benefit in the later Experiment 4(a). It would thus be highly premature to argue, on the basis of this one patient (i.e. PJ), that the right frontal lobe was required for a benefit of Minimal RI to emerge in patients with anterograde amnesia.

It may be possible that PJ had a further unknown lesion that underlay his lack of benefit of Minimal RI. Furthermore, it could also be possible that his lesion was in a different part of the right frontal lobe or indeed more extensive than that of the other aforementioned patients with right frontal lesions. Moreover, given the apparent extensive interactions between the prefrontal cortex and the medial temporal lobes (Simons and Spiers, 2003), it is further plausible that PJ's specific frontal lesion obstructs a vital connection with the medial temporal lobe. Assuming for a moment that some intact temporal lobe is required for a benefit of Minimal RI to emerge, the consequence of such obstruction could mean that while the temporal lobe itself is spared, it may not be able to process incoming information irrespective of whether there is RI or Minimal RI, thus resulting in a lack of a benefit of Minimal

RI. Hence, such obstruction could have the same cognitive consequences as a severely damaged temporal lobe. Such hypothesis is speculative only at present.

Moreover, further research is also required to explain not only the neural correlates of the *benefit* of Minimal RI, but also the neural correlates of the apparent *heightened susceptibility* to RI in the somewhat varied range of patients studied by Cowan et al. (2004), Della Sala et al. (2005) as well as in the present study. Thus, it appears somewhat intriguing that lesions as diverse as those of the frontal lobe, the temporal lobe, the parietal lobe, the thalamus, as well as the hippocampus all appear to lead to a heightened susceptibility to RI. In line with the above speculation regarding interactions between various structures with the medial temporal lobe (Simons and Spiers, 2003), it could be argued that the non-temporal structures damaged in the patients tested by Cowan et al. (2004) and in the present research are all required for the filtering and structured input of to-be-retained information into the consolidation mechanism within the temporal lobe. Damage to such structures or their connections with the temporal lobe may thus lead to an overload of information into the temporal lobe, with the consequence of no consolidation taking place. In the absence of RI however the damage of such filtering mechanisms would not matter, as only the to-be-retained material would be entered into the temporal lobe system. In the case of not too extensive lesions to the temporal lobe or hippocampus itself, i.e. as may be the case in the present temporal patients as well as Della Sala et al.'s (2005) aMCI patients, susceptibility to RI could emerge as a product of impaired consolidation per se, possibly because such damage could render the consolidation system unable to process more than a few stimuli at a time. Under conditions of Minimal RI such damage to the temporal lobe/hippocampus would not be too detrimental as the consolidation system within the temporal lobe would have sufficient time and resources (during Minimal RI) to process the information.

While such hypothesis may explain the past and present findings of a benefit in Minimal RI and thus a susceptibility to RI in patients with lesions to the aforementioned structures, it is uncertain at present how such findings of a benefit of Minimal RI can be explained in the present two patients with apparent normal MRI scans (PC and PD).

8.2.5 Conclusion

The present study was undertaken to further explore potential associations between the presence/absence of the benefit of Minimal RI and lesion sites in focal brain injury patients with anterograde amnesia. Cowan et al.'s (2004) study tentatively indicated a requirement for an intact temporal lobe for a benefit of Minimal RI to emerge. While the present study did not provide further information as to the precise brain structure required for a benefit of Minimal RI to emerge in patients with anterograde amnesia, its results strongly suggest that a *fully* (structurally) intact temporal lobe is *not* required for such benefit to emerge. Given the behavioral evidence for a LTM benefit of Minimal RI and thus some uninterrupted consolidation, as well as the potential differences in the degree of benefit between patients with temporal lesions, it is tentatively hypothesized that the temporal lobe/hippocampus may indeed be required for anterograde amnesiacs to be able to benefit from Minimal RI, but that such benefit is not dependent on a fully (structurally) intact temporal lobe/hippocampus. Thus, the benefit of Minimal RI and its magnitude may not simply be present or absent depending on lesion site but may depend on *extent* of temporal/hippocampal lesion, at least in patients with damage to such structure. The latter will be the subject of the next Experiment.

8.3 Experiment 8: Neural correlates of the benefit of Minimal RI in neurological patients (2) – Degree of benefit of Minimal RI and hippocampal volume in aMCI patients

8.3.1 Aim of the Experiment

The aim of the present study was to specifically explore the aforementioned hypothesis of a potential association between hippocampal volume and the degree of the benefit of Minimal RI in anterograde amnesiacs.

8.3.2 Method

8.3.2.1 Participants

In order to minimize variations in aetiology and lesion site, only patients with aMCI (Petersen et al., 1999), a subcategory of anterograde amnesia as well as age and education matched controls were included in the study.

Ten patients and ten controls took part in this study. These were patients P1, P3, P4, P7, P8, P10, P11, P14, P15 and P16 as well as controls C1, C2, C3, C6, C9, C10, C12, C14, C15 and C16 from Experiment 5. Their individual demographic data and neuropsychological test scores are provided in Tables 6.2a and 6.2b. Table 8.2 below provides Group Means for the sample taking part in the present experiment. Note that the other four patients and four controls taking part in Experiment 5 were excluded from the present study because they were unwilling to undergo a structural MRI scan.

	Patients		Controls	
	Mean	SD	Mean	SD
Age	73.80	6.05	71.90	7.19
Education (years)	6.40	1.96	9.50	4.55
Estimated IQ (WAIS)	112.40	8.26	118.10	9.67
MMSE	26.80	1.81	28.10	1.29
CDR	0.50	0.00	0.00	0.00
Total Immediate Word List Recall	30.40	4.67	45.80	5.39 ***
Delayed Word List Recall	6.30	1.34	11.00	1.05 ***
Wor List Retention (%)	87.60	9.25	95.01	5.67 *
Immediate Prose Recall	6.82	1.07	7.77	0.34 *
Delayed Prose Recall	5.58	2.36	7.50	0.52 *
Digit span	5.20	0.92	5.80	0.63
Spatial span	4.40	0.97	4.80	0.63
Rey Figure Copy	32.05	3.86	34.20	2.10
Rey Figure Delayed Recall	11.50	3.67	16.70	1.77 **
Trail making A	85.10	28.85	57.50	21.21 *
Trail making B	278.50	75.28	146.20	66.53 **
Trail making B-A	193.40	66.88	88.70	60.59 **
Phonolog fluency	8.10	2.13	9.80	2.04
Semantic fluency	13.00	2.36	14.80	2.70
Token Test	32.40	1.70	33.65	1.18
Attentional Matrices	47.60	5.23	52.00	4.14

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Table 8.2. Demographic and neuropsychological data. Group means and SDs

8.3.2.2 Materials and Procedure

8.3.2.2.1 Behavioral Aspect of the Study:

The behavioral data for the present study was taken from Experiment 5 (please see Chapter 6 for materials and procedure of Experiment 5). As in Experiment 7, a degree of benefit score was computed for every participant by subtracting the proportion retention in the RI Condition (First RI in the specific case of Experiment 5) and the Minimal RI Condition, i.e.

Degree of benefit = Prop. Retention at Minimal RI – Prop. Retention at First RI

8.3.2.2.2 Structural MRI Aspect the Study:

MRI data acquisition

All ten patients and controls were scanned using a 1.5T Siemens Symphony MRI Scanner. High-resolution images were acquired (T1 sequence, high resolution structural image; 160 slices; voxel resolution = 1x1x1mm; Field of View (FOV) = 256 x 256 mm^2; TE/TR = 3.93ms/3000ms.)

Segmentation and labelling of anatomical brain structures

Traditionally segmentation of brain structures from MRI scans has been undertaken manually, i.e. by drawing around each region of interest (ROI) on every MRI slice via a pointing device such as a pc mouse. Given that such procedure has to be undertaken for each participant/patient individually, it can be exceedingly time-consuming (c.f. Collins et al., 1995). Moreover, manual segmentation is also subjective, thus prone to both inter- and intra-observer variability, and hence errors, which may render detection of subtle differences in structure volumes between groups somewhat difficult (Collins et al., 1999).

In order to minimise such pitfalls, recent advances have been made to develop *automatic* segmentation programs (c.f. Collins et al., 1995).
In the present study one of such programs, IBASPM[6], was utilised for the segmentation and labelling of brain structures. Automatic segmentation of an individual person's brain structures via IBASPM is achieved via the following procedure:

Firstly the MRI scan is normalised to the Montreal Neurological Institute (MNI) space (the average of 152 normal MRI scans). This is done in order to obtain the spatial transformation matrix, which provides the spatial correspondence between the voxels in the individual space (i.e. the individual scan) and the voxels in the MNI

[6] **I**ndividual **B**rain **A**tlas using **S**tatistical **P**arametric **M**apping Software (based on SPM99, SPM2 and SPM5) by Yasser Alemán-Gómez, Lester Melie-García, Pedro Valdés-Hernández, Cuban Neuroscience Centre, further details at http://www.thomaskoenig.ch/Lester/ibaspm.htm

space (see step 1 in Figure 8.5). In parallel the MRI scan is segmented into cerebral spinal fluid (CSF), gray matter and white matter (see step 1 in Figure 8.5).

The spatial transformation matrix is subsequently inverted to obtain the inverse correspondence between the MNI space and the individual space. The resulting inverted transformation is then applied to the MNI atlas (see step 2 in Figure 8.5) (which corresponds spatially to the MNI space and is constructed by manual or automatic segmentation of a group of brains) to provide an 'individual' atlas.

Thus, the MNI atlas (brain) is transformed to match the individual brain in shape and dimension by inverting the transformation that was previously required to normalise the individual scan to the MNI space.

Each individual gray matter voxel within the MRI scan is subsequently labelled based on the individual atlas. IBASPM then subsequently labels each structure.

ROIs and computation of ROI volumes

For each participant ROIs (the hippocampus, see Figure 8.6, as well as the other temporal lobe and non-temporal regions listed in Table 8.3 below) were subsequently measured in volume (left, right and bilateral) using IBASPM. Total intracranial volume was also measured by this means.

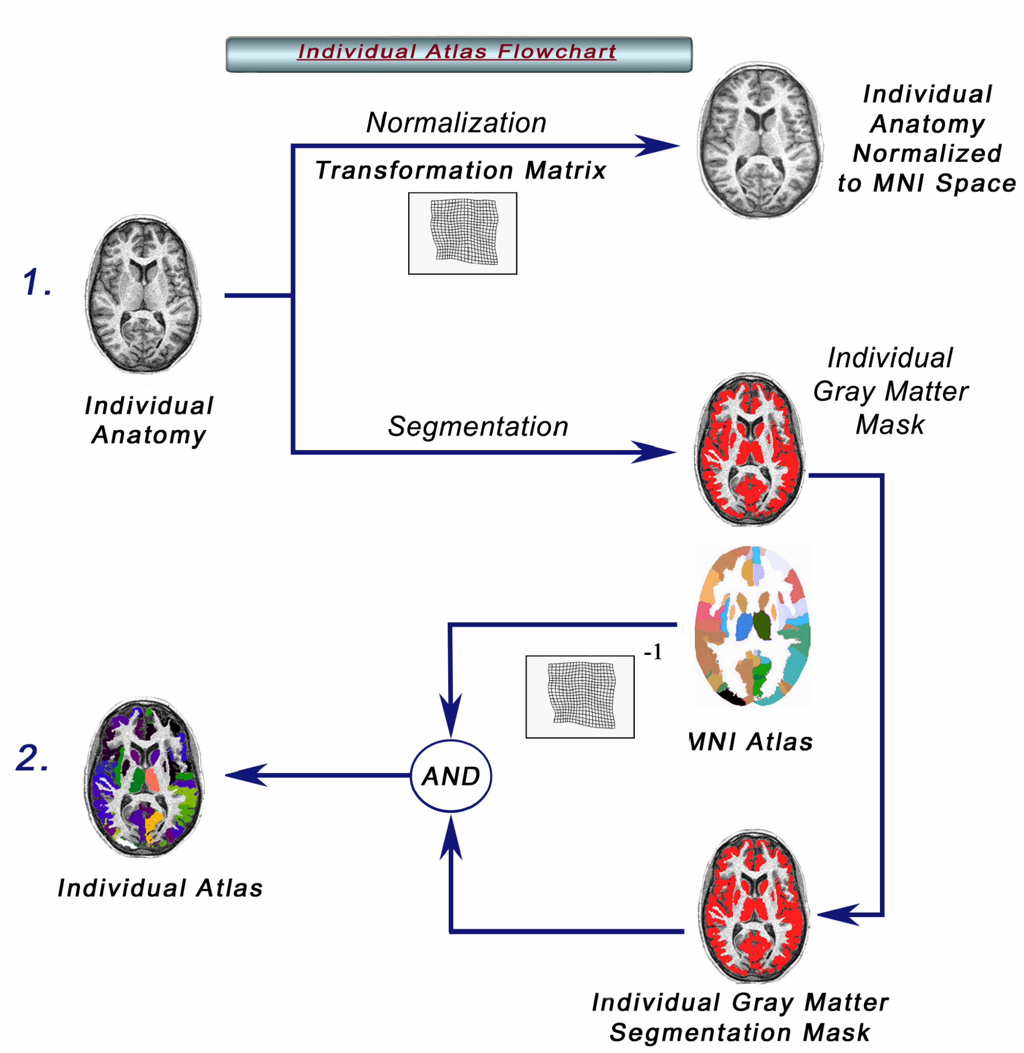


Figure 8.5. Automatic segmentation of brain structures using IBASM:

1. The MRI image is normalized to MNI space to obtain the spatial transformation matrix. Additionally, in this step MRI individual images are segmented into three different brain tissues: cerebral spinal fluid (CSF), gray matter and white matter.
2. Each individual gray matter voxel is labeled based on the MNI anatomical atlas (constructed by manual or automatic segmentation of a group of brains) and the transformation matrix obtained in the previous step.

(Figure and Figure caption by Yasser Alemán-Gómez, Lester Melie-García, Pedro Valdés-Hernández, Cuban Neuroscience Centre, further details at http://www.thomaskoenig.ch/Lester/ibaspm.htm)

Regions of interest (ROIs)	
Frontal Inf Orb	**Hippocampus**
Frontal Sup	Amygdala
Frontal Sup Orb	Parahippocampus
Occipital Inf	Temporal Inf
Occipital Sup	Temporal Med
Thalamus	Temporal Pole Med
Cerebellum	Temporal Pole Sup
Cingulum Ant	Temporal Sup

Table 8.3. Regions of Interest (ROIs) (temporal lobe regions including the hippocampus in the right hand column and non-temporal lobe regions in the left hand column) derived from the structural MRI scans. Volumes were acquired for each structure for the left and right sides independently as well as bilaterally (total of left and right).

Ant = anterior, Inf = inferior, Med = Medial, Orb = orbital, Sup = superior

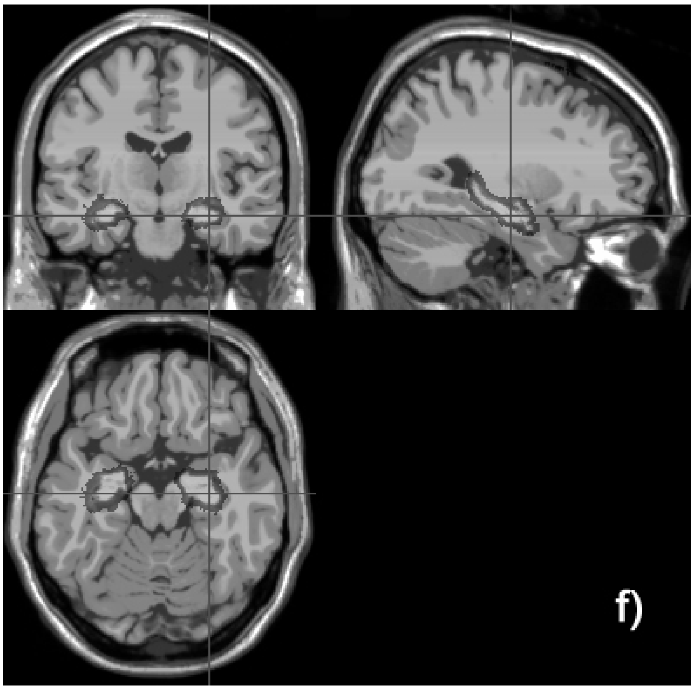


Figure 8.6. Region of the Hippocampus based on a group of 74 male subjects using IBASPM (image taken from http://www.thomaskoenig.ch/Lester/ibaspm.htm)

Normalisation of individual participants' ROI volumes

As in previous structural MRI studies on aMCI, Hippocampal Volume, as well as the volume of each of the other ROIs, was subsequently normalized to intracranial volume (by dividing ROI volume by the total intracranial volume) for each individual participant in order to correct for interpatient differences in headsize (c.f. Wolf et al., 2004; Jack et al., 1999).

8.3.3 Results

8.3.3.1 Group differences in volumes of ROIs

In order to firstly examine whether or not the patients and controls differed significantly in the left, right or bilateral volume of any of the ROIs, a series of one-way ANOVA's were set up (one one-way ANOVA for the left, the right and bilateral volume of each ROI).

The Levene's Test for Homogeneity of Variance was significant for the left cingulum, the left parahippocampus, the parahippocampus bilaterally and the left amygdala ($p < 0.05$), indicating that homogeneity of variance could not be assumed for these ROIs. It was thus decided to further run Welch-corrected ANOVAs for these ROIs.

The main ANOVAs revealed that the patients and the controls differed significantly in the volume of left superior Temporal Pole, $F(1, 19) = 6.316$, $p < 0.05$, the right superior Temporal Pole, $F(1, 19) = 6.474$, $p < 0.05$ and the superior Temporal pole bilaterally, $F(1, 19) = 9.407$, $p < 0.01$. The significant difference in each of these comparisons was the result of smaller ROI volumes in the patients than controls. Group means for these three structures are depicted in Figure 8.7. Moreover, a trend towards significant group differences in volume were also revealed for the right inferior Temporal Lobe, $F(1, 19) = 4.344$, $p = 0.052$ and the inferior Temporal Lobe bilaterally, $F(1, 19) = 4.419$, $p = 0.05$. Both were the result of a larger ROI volume in the patients than the controls. No other significant Group differences were obtained, including the hippocampus, for which Group Means and SEMs are depicted in Figure 8.8. The Welch-corrected ANOVA confirmed that the two groups did not differ significantly in any of the aforementioned ROIs with significant Levene's Tests of homogeneity of variance. Group means and SEMs for each ROI (left, right and left+right) are provided in Appendix E.

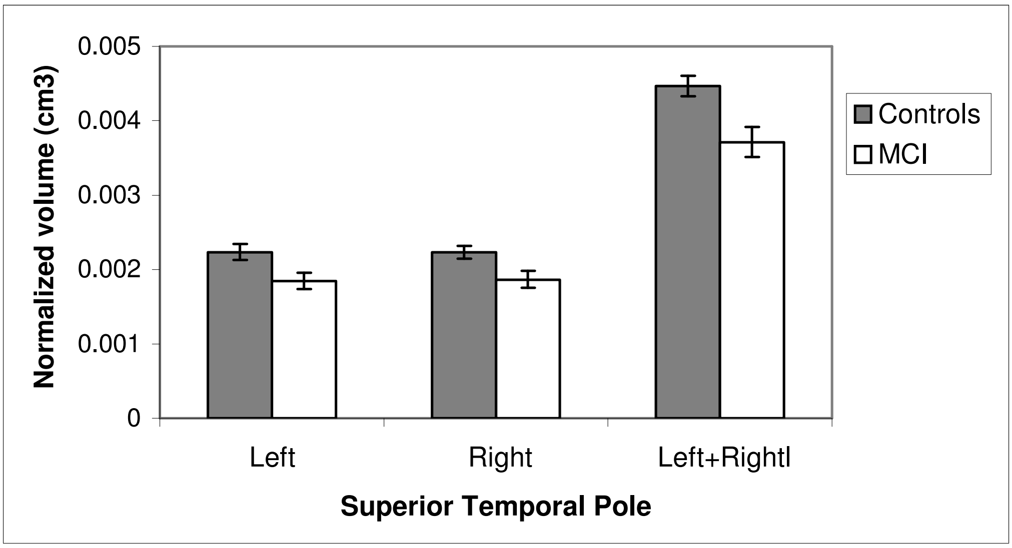


Figure 8.7. Group mean normalized volumes of the left, right and left+right superior temporal pole. Error bars = SEM.

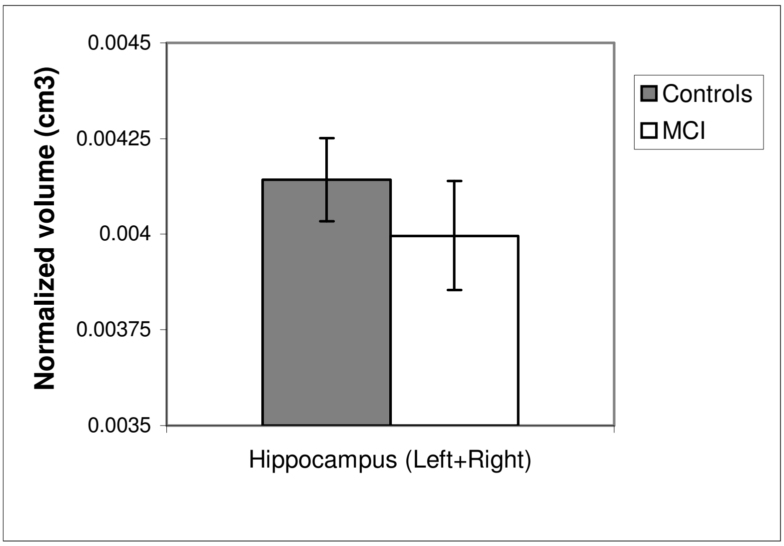


Figure 8.8. Group mean normalized volumes of the left+right hippocampus. Error bars = SEM. (Group difference non-significant).

8.3.3.2 Associations between the degree of benefit of Minimal RI and hippocampal volume in the aMCI sample

In order to firstly establish whether or not the previous findings of a benefit of Minimal RI in the patients with aMCI entering Experiment 5 were still present in this reduced sample, a mixed factors ANOVA with within subjects factor Delay Condition (No RI vs. RI) and between subjects factor Group (Patients vs. Controls) was run. The ANOVA showed a significant Delay Condition main effect, $F(1, 18) = 85.054$, $p < 0.001$ as well as a significant Group main effect, $F(1, 18) = 17.707$, $p < 0.01$. Moreover, a Delay Condition x Group interaction was shown, $F(1, 18) = 21.462$, $p < 0.001$.

A simple main effects analysis revealed that the basis of the Delay Condition x Group interaction was a significant Group effect in proportion retention following the RI Condition, $F(1, 19) = 42.515$, $p < 0.001$, but not following the Minimal RI Condition. Group means and SEMs are shown in Figure 8.9 below.

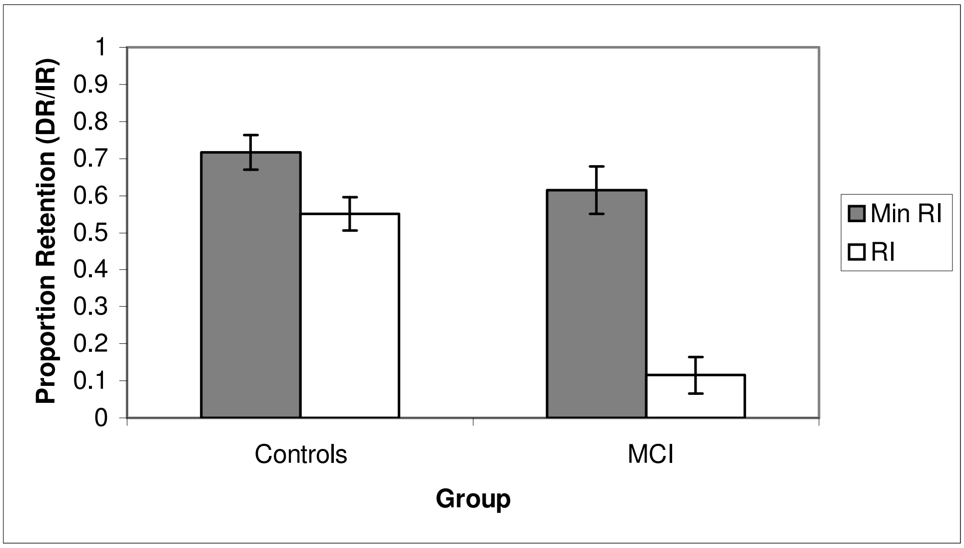


Figure 8.9. Group mean proportion retention as a function of Delay Condition (Minimal RI vs. RI). Error bars = SEM.

Having established that the findings of Experiment 5 held in the present sample, degree of benefit of Minimal RI was computed for each of the patients and controls included in the present study (see methods section). This data, alongside each participant's proportion retention following RI and Minimal RI, is shown in Table 8.4.

Patient	RI	Minimal RI	Benefit
P1	0.2	0.75	0.55
P3	0	0.5	0.5
P4	0.4	1	0.6
P7	0	0.4	0.4
P8	0	0.4	0.4
P10	0	0.67	0.67
P11	0.25	0.6	0.35
P14	0	0.83	0.83
P15	0	0.6	0.6
P16	0.33	0.4	0.07

Control	RI	Minimal RI	Benefit
C1	0.67	0.67	0
C2	0.57	0.86	0.29
C3	0.43	0.57	0.14
C6	0.6	0.67	0.07
C9	0.33	0.6	0.27
C10	0.56	0.75	0.19
C12	0.6	0.75	0.15
C14	0.33	0.5	0.17
C15	0.67	1	0.33
C16	0.75	0.8	0.05

Table 8.4. Individual participant proportion retention following Minimal RI and RI as well as the degree of benefit from Minimal RI (= *Prop. Retention at Minimal RI – Prop. Retention at First RI)*

In order to establish whether or not hippocampal volume was related to the degree of the benefit of Minimal RI in patients with aMCI, a Pearson correlation was run between the normalized volumetric data for the hippocampus (left, right as well as left+right) and the degree of benefit. No significant correlation was found.

Pearson correlations[7] were also run between the degree of the benefit and each of the other ROIs (left, right as well as left+right). The only significant correlation to emerge was that of the normalized volume of the left inferior orbital frontal area and degree of benefit of Minimal RI, $r = .643$, $p < 0.05$. The corresponding data is illustrated in Figure 8.10.

[7] The correlations reported in this chapter were not corrected for non-independent multiple comparisons.

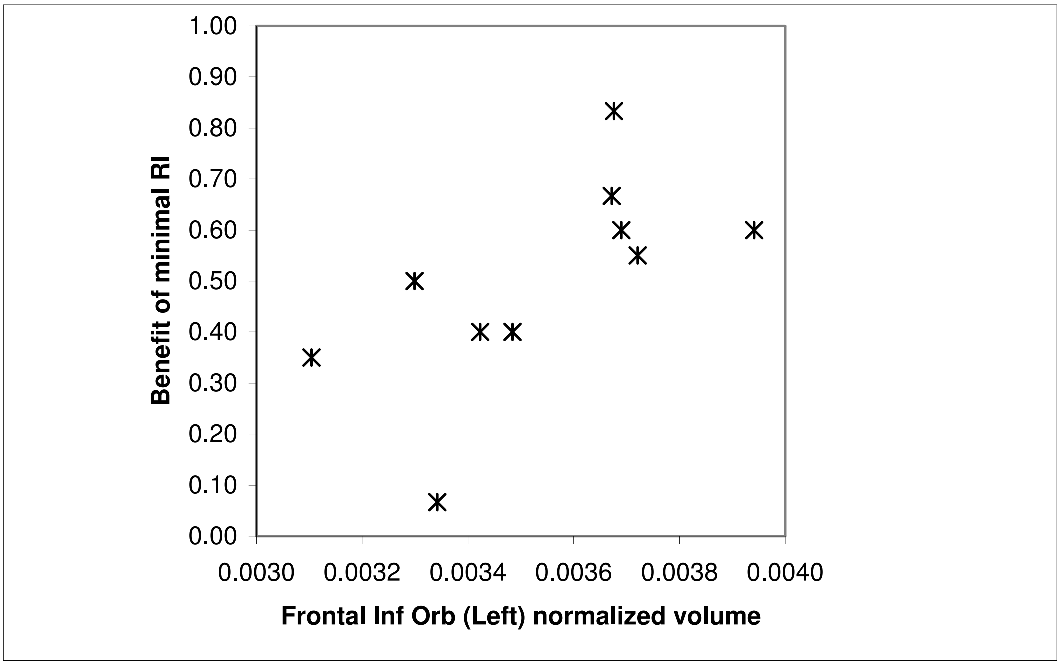


Figure 8.10. Patient degree of benefit from Minimal RI plotted against patient normalized volume of the left inferior orbital frontal area.

With regard to the hippocampus, inspection of scatterplots for each of the above three correlational analyses (see Figures 8.11 – 8.13) indicated a trend for a positive relationship between normalized hippocampal volume and degree of benefit, as well as an outlier for whom such relationship did not hold (P16, highlighted by a circle).

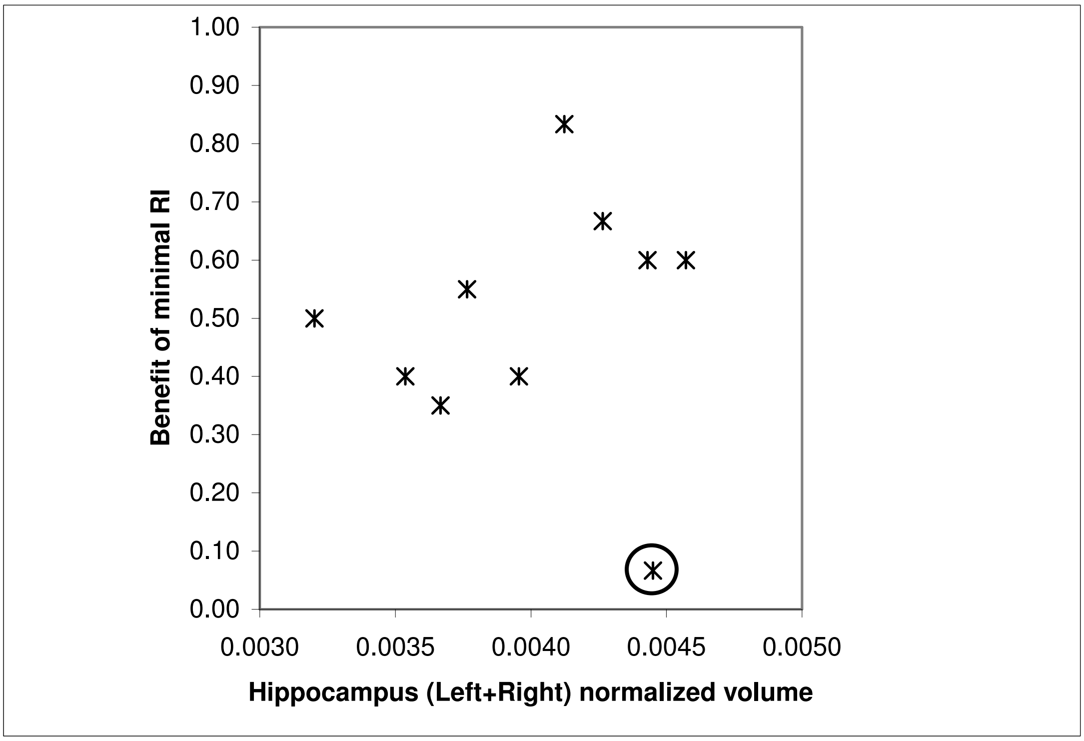


Figure 8.11. Patient degree of benefit from Minimal RI plotted against patient normalized volume of the left+right hippocampus.

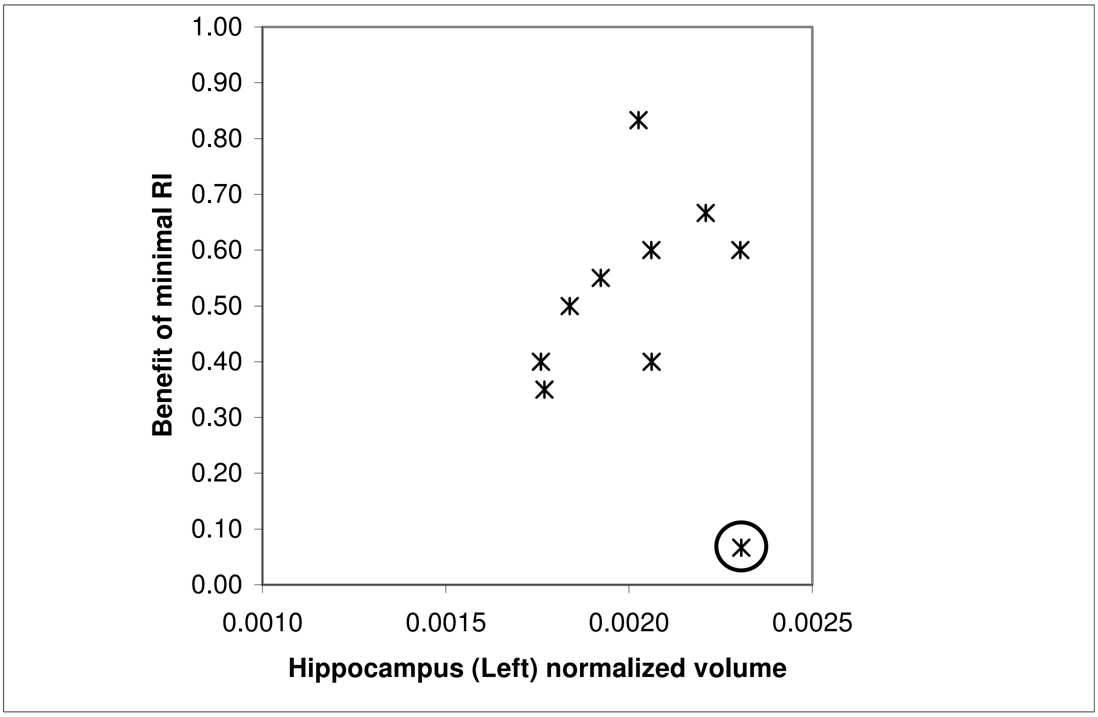


Figure 8.12. Patient degree of benefit from Minimal RI plotted against patient normalized volume of the left hippocampus.

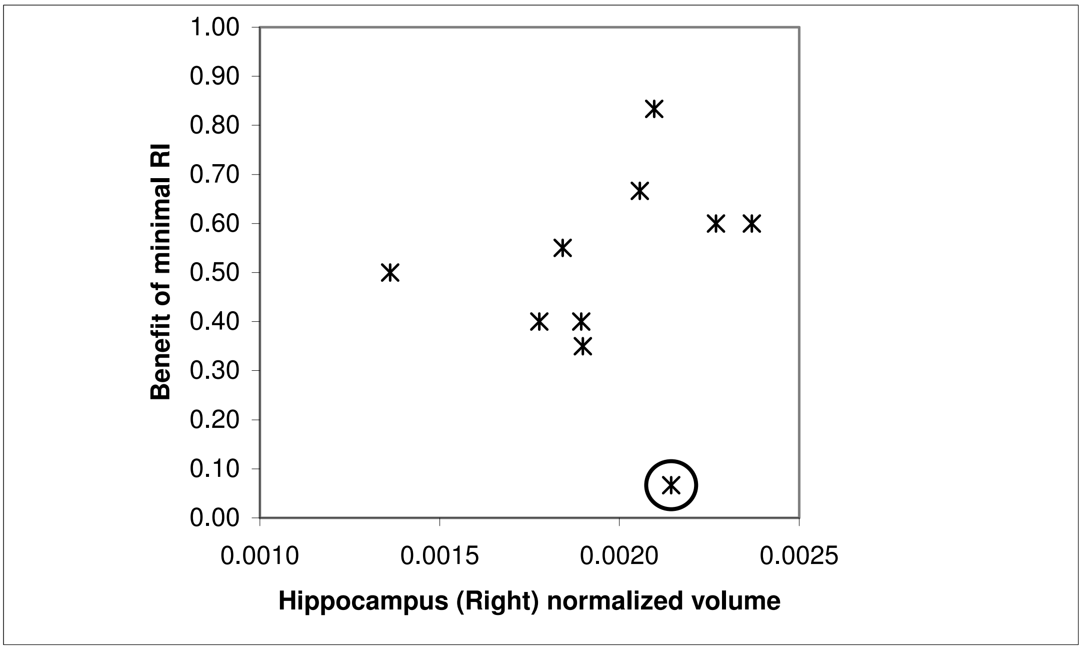


Figure 8.13. Patient degree of benefit from Minimal RI plotted against patient normalized volume of the right hippocampus.

Further inspection of the outlier P16 revealed that she was one of four patients who performed > 0 following the RI Condition indicating that this patient's memory impairment was not as severe as that of the six residual patients who scored 0 following RI. However, and more importantly, while the other patients scoring > 0 following RI nevertheless benefited somewhat from Minimal RI (benefits = 0.5, 0.6 ad 0.35 for P1, P4 and P11 respectively), P16 did not (benefit = 0.07) indicating that P16's memory impairment may not be associated largely with a susceptibility to RI and thus that P16's memory impairment may be qualitatively different from that of the remaining nine patients.

Before proceeding with the analysis without P16, Group differences in demographic, neuropsychological and corrected volumetric MRI data were reexamined following exclusion of P16 in order to ascertain that such exclusion had not altered the previously elucidated results to any large extent. The analyses were akin to the ones utilized above, i.e. one way ANOVAs.

The re-analysis elucidated that exclusion of P16 did not lead to any deviations from the previous comparisons in demographic and neuropsychological data shown in Table 8.2, (i.e. all significant Group differences were still significant and all insignificant Group differences were still insignificant). With respect to the normalized volumetric data, the re-analysis indicated that the patient sample still showed a significantly lower normalized volume of the superior temporal pole (left, right as well as left+right). Moreover, a significant group difference was now also obtained for the right medial temporal pole, $F(1, 18) = 4.645$, $p < 0.05$, the basis of which was a larger normalized volume in the patient than the control sample. Inspection of the raw data for the right medial temporal pole showed an outlier in the patient sample and that the Group difference for this structure was eliminated when this outlier was removed. The previously obtained trend towards significance in group differences in the right inferior Temporal Lobe and the left+right inferior Temporal Lobe were not present following exclusion of P16.

The aforementioned mixed factors ANOVA on proportion retention following the RI and Minimal RI Conditions in the patient and control sample was also re-run and showed no deviation from the previous results.

Repeating of the above Pearson correlations between normalized hippocampus volume (left, right and left+right) following exclusion of P16 revealed correlation coefficients $r = .567$, $p = 0.112$, for the correlation between the left hippocampus and the benefit, $r = .457$, $p = 0.217$, for the correlation between the right hippocampus and the benefit and $r = .544$, $p = 0.130$, for the correlation between the left+right hippocampus and the benefit. However, as indicated by the p-values, none of these correlations reached significance.

Nonetheless, given the apparent trend for an association between normalized hippocampal volume and degree of benefit in Figures 8.11 – 8.13, it was decided to split the degree of benefit data by degree, i.e. into those patients who showed a large benefit of Minimal RI and those patients who showed a small benefit of Minimal RI, and thus to compare normalized hippocampal volume for these two subgroups via a one way ANOVA.

Patients were divided into 'high' and 'low' benefitters by a median split on benefit scores. The median of the nine patients was 0.55 meaning that patients with benefit scores > 0.55 were classified as 'high' benefitters and those with benefit scores of < 0.55 as 'low' benefitters. This split led to four patients being classified as 'high' benefitters (P4, P15, P10, P14) and four patients being classified as 'low' benefitters P11, P7, P8, P3). One patient's (P1) benefit score was 0.55, i.e. the median. It was decided to classify her as a 'low' benefitter as there was less disparity between her benefit score and that of the lowest 'low' benefitters than her benefit score and that of the highest 'high' benefitter.

A subsequent one way ANOVA on degree of benefit with between subjects factor Benefitters (High and Low) revealed that the two formed groups did indeed differ significantly in degree of benefit of Minimal RI, $F(1, 8) = 13.552$, $p < 0.01$, (The Levene's test of homogeneity of variance was insignificant, indicating that the assumptions for such ANOVA were met). Figure 8.14 shows the degree of benefit means and corresponding SEMs for the two benefitter groups.

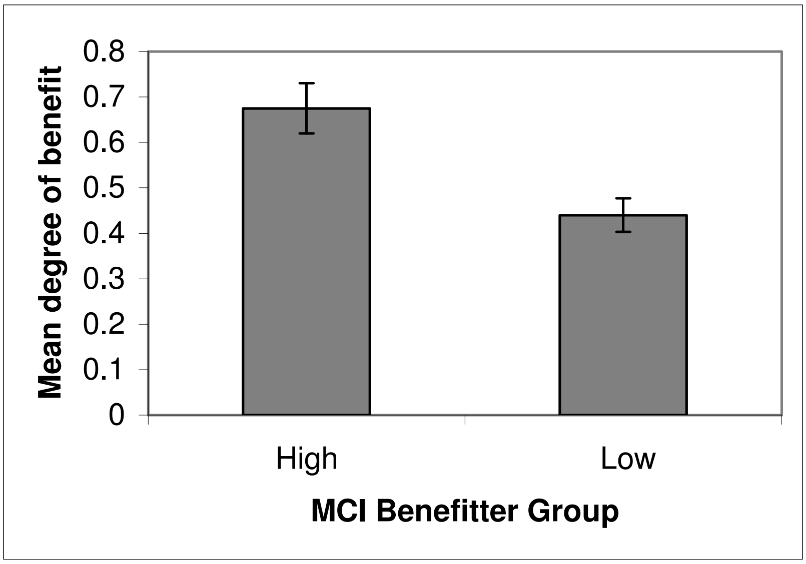


Figure 8.14. Degree of benefit from Minimal RI in the High and Low benefit patient groups.

In order to compare the two groups in normalized Hippocampus volume, one way ANOVAs were run for the Left Hippocampus, the Right Hippocampus and the

Left+Right Hippocampus, the between subjects factor being Benefitter group (High vs. Low). The Levene's Test of Homogeneity was insignificant for each of the three ANOVAs indicating that the assumptions of such ANOVA were not violated.

The ANOVAs revealed significantly higher normalized volumes in the high than the low benefitter group for the left hippocampus, the right hippocampus as well as the left+right hippocampus, $F(1, 8) = 10.759$, $p < 0.05$, $F(1, 8) = 11.459$, $p < 0.05$ and $F(1, 8) = 18.787$, $p < 0.01$ respectively. The hippocampus data for the two benefitter groups is depicted in Figures 8.15 and 8.16.

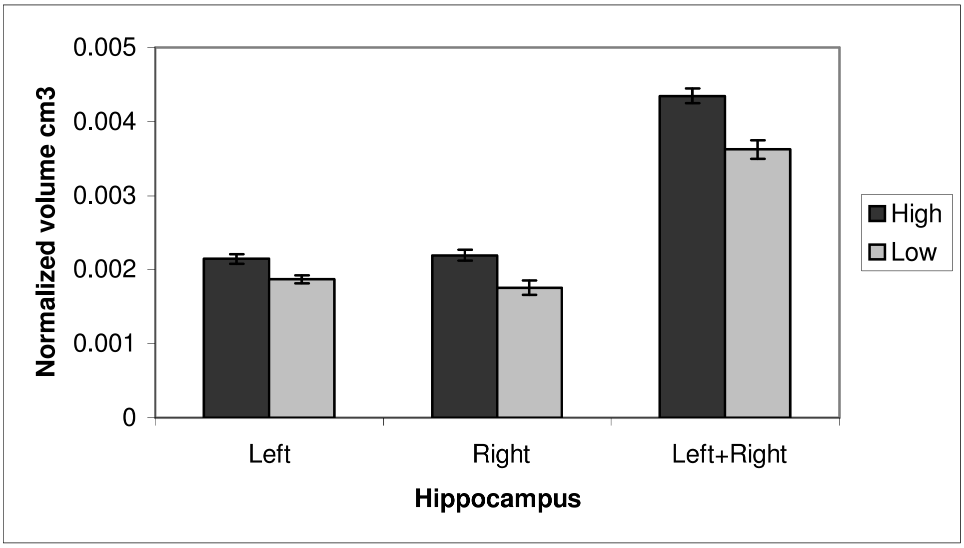


Figure 8.15. Normalized volume of the left, the right and the left+right hippocampus for the high benefitter and the low benefitter patient groups. Error bars = SEM.

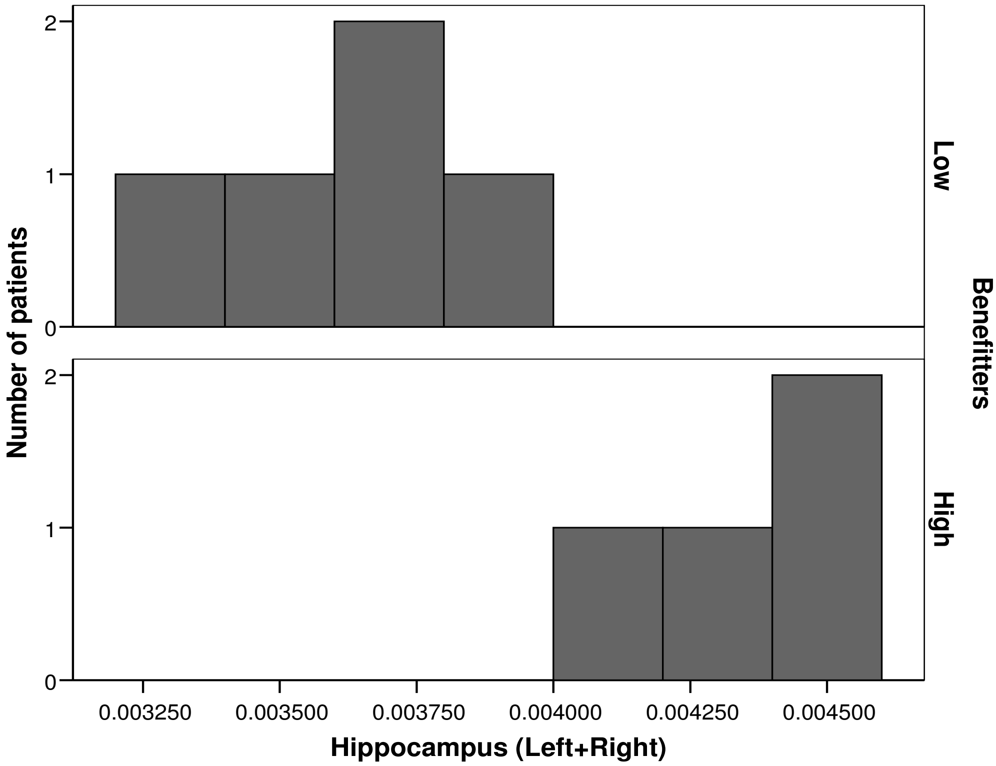


Figure 8.16. Distribution of normalized left+right hippocampus volume within the two benefitter groups.

In order to assess whether the two Benefitter groups differed in any of the aforementioned demographic variables, neuropsychological tests scores (see Table 8.2) or in proportion retention following Minimal RI and RI, a further set of one-way ANOVAs was run.

A significant group difference was found for age, with the high benefitters being significantly younger than the low benefitters, $F(1, 8) = 6.931$, $p < 0.05$ (Group means and SD = 69.75 (6.652) and 78 (2.236) for the high and low benefitters respectively)). No further significant group differences were found for any of the variables depicted in Table 8.2 or for proportion retention following Minimal RI or RI.

Given the significant group effect in age, the above ANOVAs on normalized hippocampus volume were repeated with the covariate 'age'.

These ANCOVAs indicated that, even after controlling for differences in age, the high benefitter group still had a significantly larger Left+Right Hippocampus and Right Hippocampus than the low benefitter group, $F(1, 8) = 8.216$, $p < 0.05$ and $F(1, 8) = 6.472$, $p < 0.05$ respectively. However, the previously significant group effect in normalized volume of the Left Hippocampus failed to reach significance when accounting for differences in age.

In order to examine whether or not the high and low benefitters differed with respect to normalized volume of any of the other ROIs, a further set of one way ANOVAs was run on each of these ROIs (Left, Right and Left+Right for each individual ROI). The Levene test of homogeneity was insignificant for all comparisons but that of Frontal Sup (Right) and Frontal Sup Orb (Left+Right). It was thus decided to run a one way ANOVA as well as a Welch corrected ANOVA on these two ROIs.

The main ANOVAs revealed a significant difference between the high and the low benefitters for the normalized volume of the Left Inferior Orbital Frontal region, $F(1, 8) = 6.862$, $p < 0.05$, and the right Thalamus, $F(1, 8) = 10.886$, $p < 0.013$.

A trend towards significant group differences were also obtained for the Left superior temporal region, $F(1, 8) = 5.557$, $p = 0.051$, and the Left+Right superior orbital frontal region, $F(1, 8) = 5.289$, $p = 0.055$. The basis of each of these differences was a larger volume for the high than the low benefitter group. No other significant differences were obtained. The Welch corrected ANOVAs confirmed that there was no significant group difference in the normalized volume of the Right superior Frontal region and also indicated that the near significant group difference in the normalized volume of the Left+Right superior orbital frontal region was not significant. However, when an ANCOVA was run on normalized volume of the Left Inferior Orbital Frontal region, the Right Thalamus and the Left superior temporal region with covariate age and between subjects factor benefitter Group (High vs. Low), the above significant Group differences in normalized volumes ceased to be significant.

Given the findings of (a) an association between the degree of benefit and the normalized volume of the hippocampus in the aMCI patients, (b) a significant difference in the degree of benefit between the aMCI patients and the controls (see Experiment 5), yet, (c) no significant difference in the normalized volume of the hippocampus between the aMCI sample and the control sample, it was decided to examine the degree of benefit data with respect to normalized hippocampus volume data in the controls, too.

In order to do so a Pearson correlation was run between the controls' normalized volumetric data for the hippocampus (left, right as well as left+right) and the degree of benefit. No significant correlations were revealed. Normalized volumetric data for the left+right hippocampus are plotted against the benefit of Minimal RI in Figure 8.17. Figure 8.18 shows the same control data as well as that of the aMCI sample. In order to assess whether or not the degree of benefit was associated with the normalized volume of any of the other ROIs provided in Table 8.3 in the control group, a further set of Pearson correlations was run on the left, right and left+right normalized volumetric data of each ROI and the degree of benefit or Minimal RI. No significant correlations were obtained.

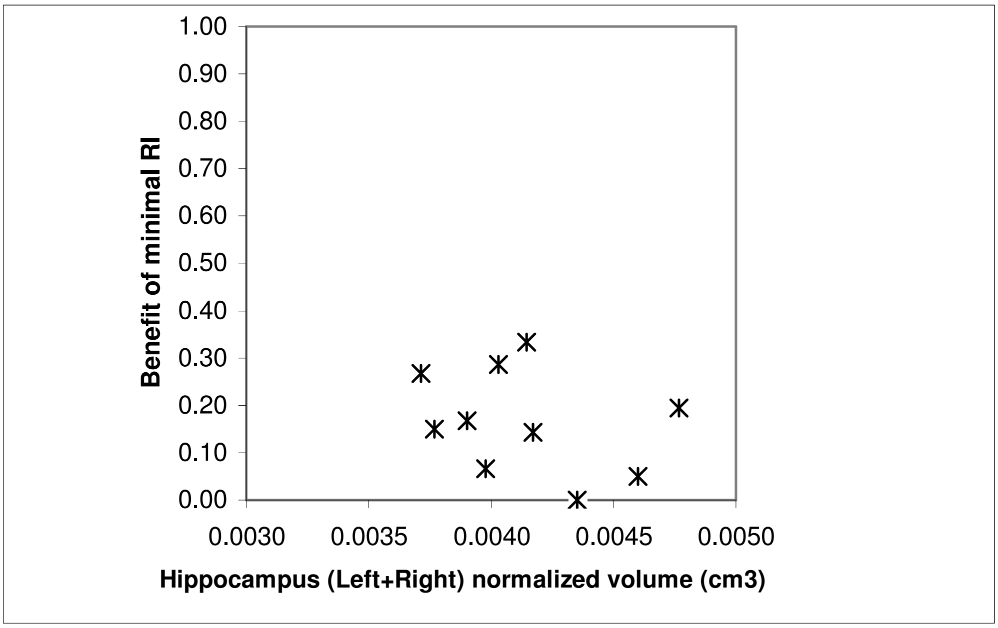


Figure 8.17. Control degree of benefit from Minimal RI plotted against control normalized volume of the left+right hippocampus.

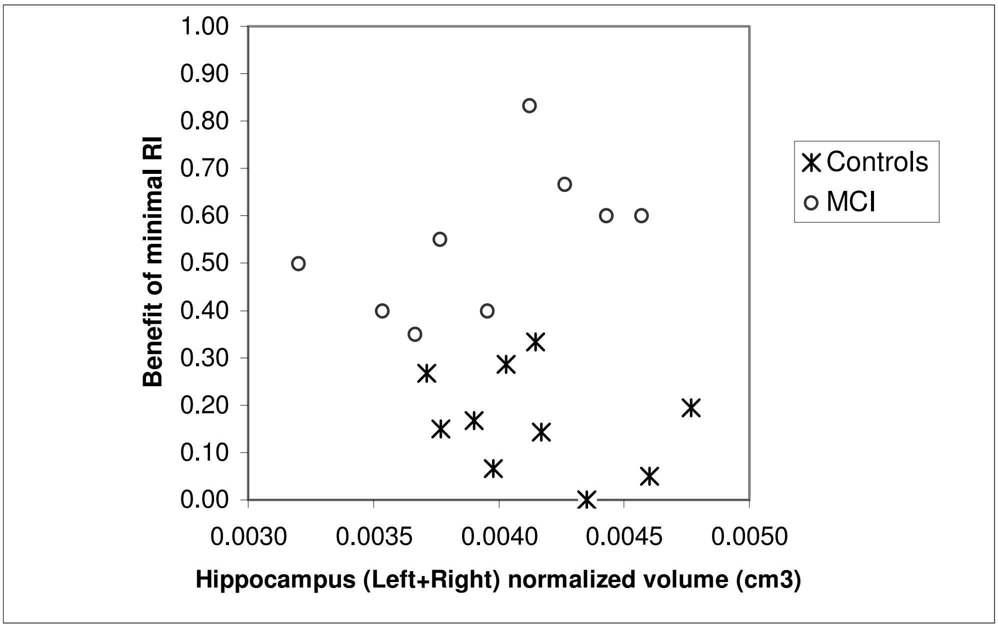


Figure 8.18. Degree of benefit from Minimal RI plotted against normalized volume of the left+right hippocampus for the aMCI patients and the controls.

In order to examine whether hippocampal volume was associated with proportion retention following RI in the aMCI sample and/or the controls, further correlations were run between normalized volume of the left, right and left+right hippocampus and proportion retention following RI (the First RI Condition of Experiment 5).

No significant correlations were obtained in the aMCI sample, while a significant positive correlation was revealed in the controls between normalized volume of the Left Hippocampus and proportion retention, $r = .723$, $p < 0.05$. Figure 8.19 depicts this significant correlation as well as the patient data. Furthermore left+right normalized hippocampus data is plotted against proportion retention following RI in Figure 8.20.

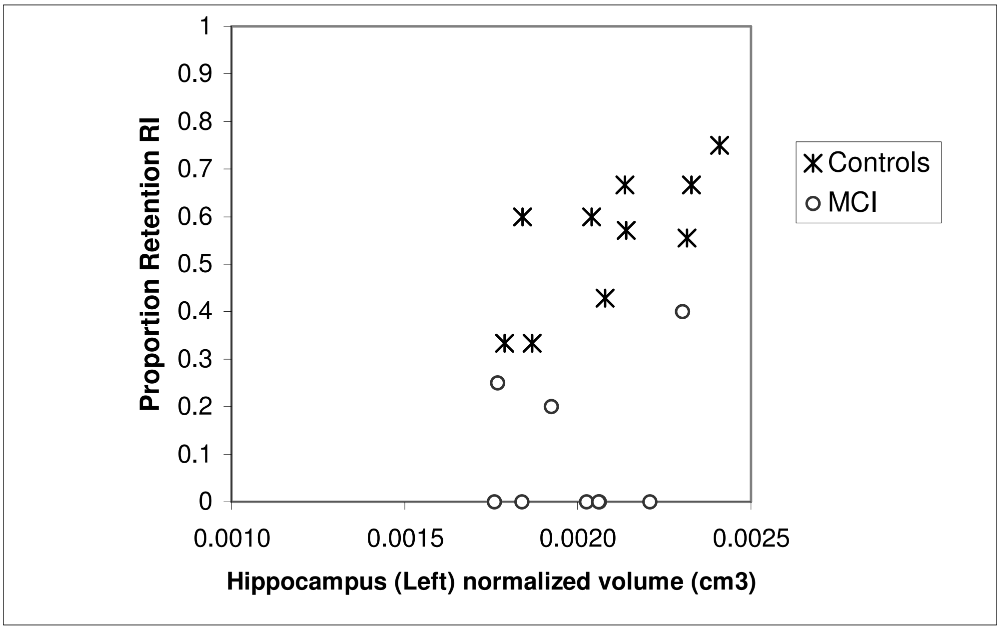


Figure 8.19. Proportion retention following RI plotted against normalized volume of the left hippocampus for the aMCI patients and the controls.

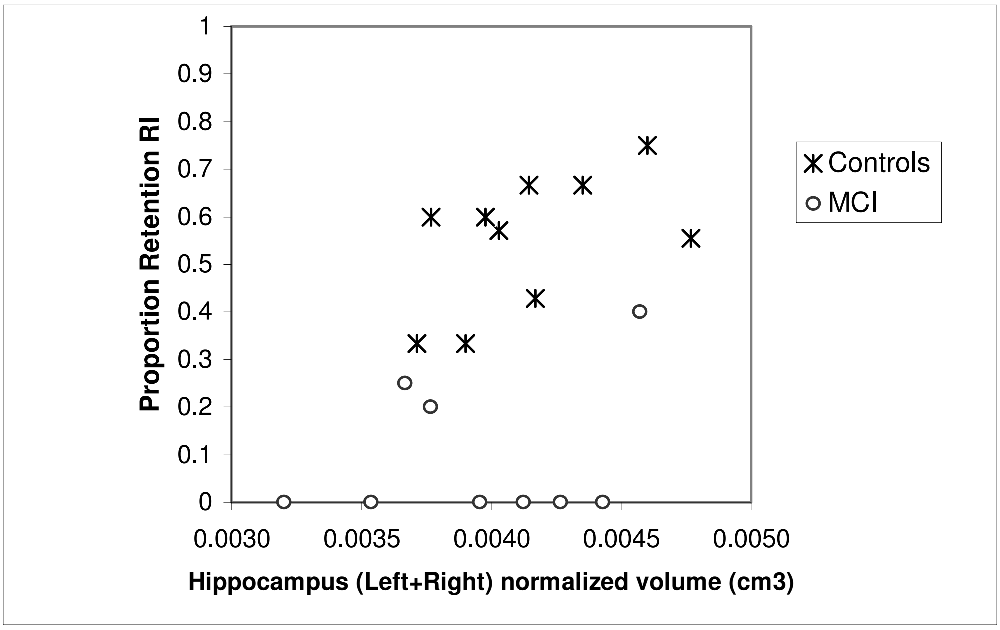


Figure 8.20. Proportion retention following RI plotted against normalized volume of the left+right hippocampus for the aMCI patients and the controls.

In order to examine whether or not an association was present between normalized hippocampus volume and proportion retention following Minimal RI in the aMCI patients and/or the controls, two further Pearson correlations were run. These correlations showed that there was no significant correlation between normalized hippocampus volume (Left, Right nor Left+Right) in the control sample nor the aMCI sample. However, a trend towards a significant positive correlation was obtained in the aMCI sample between the normalized volume of the Left+Right hippocampus and proportion retention following Minimal RI, r = .619, p = 0.076 and between the normalized volume of the Left hippocampus and proportion retention following Minimal RI, r = .608, p = 0.082. Proportion retention following Minimal RI is plotted against normalized volume of the left and the left+right hippocampus in Figures 8.21 and 8.22 for both the aMCI sample and the controls.

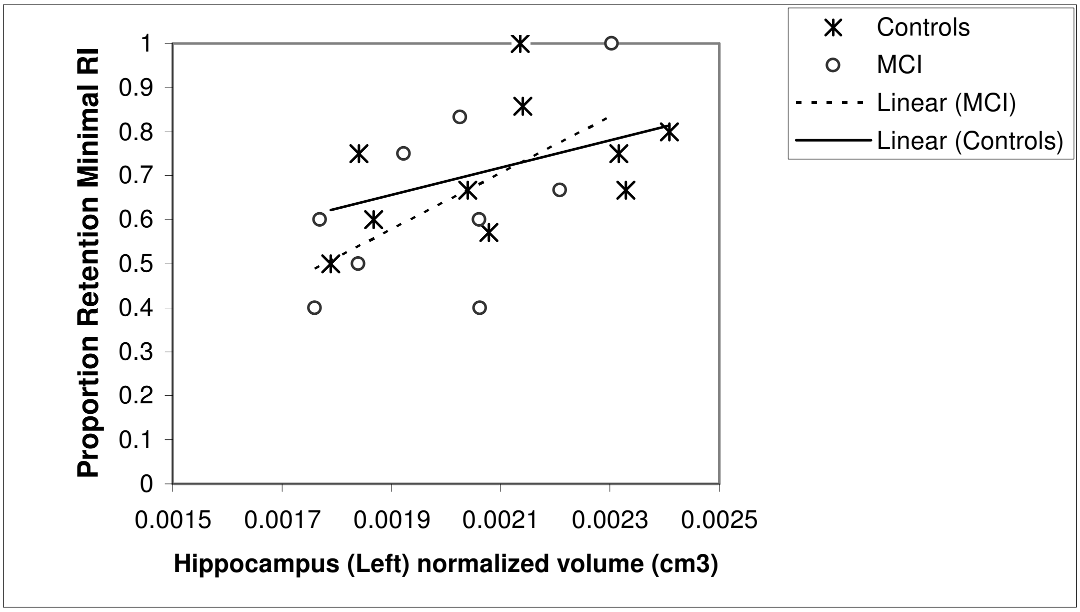


Figure 8.21. Proportion retention following Minimal RI plotted against normalized volume of the left hippocampus for the aMCI patients and the controls.

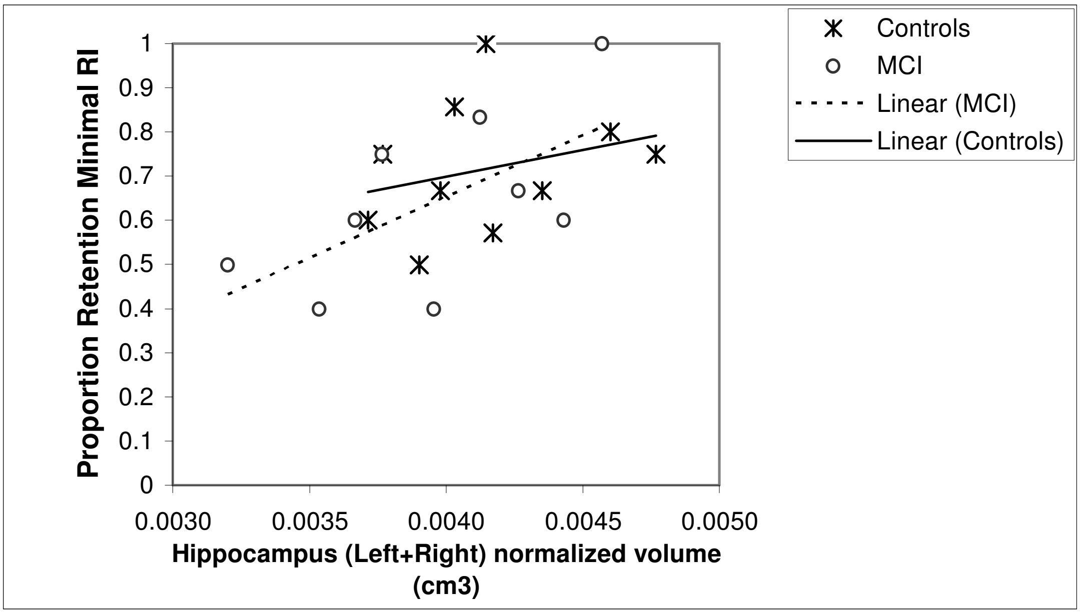


Figure 8.22. Proportion retention following Minimal RI plotted against normalized volume of the left+right hippocampus for the aMCI patients and the controls.

Given the aforementioned correlation between the degree of benefit of Minimal RI and the left inferior orbital frontal region in the patient group yet *not* in the control group, it was of further interest to inspect whether or not the controls showed a correlation between left inferior orbital frontal region volume and proportion retention following RI (i.e. as was found for the hippocampal data).
For such reason a Pearson correlation was run for the control group between proportion retention following RI and the normalized volume of the left inferior orbital Frontal region. No significant correlation was obtained.

Given such finding it was of interest to examine whether or not and to what extent bilateral hippocampal volume was correlated with left inferior orbital volume. Thus it could be possible that the apparent correlation between the benefit and left inferior orbital frontal volume is in fact the product of a relationship between hippocampal volume (which is associated with the benefit) and left inferior orbital volume. A Pearson correlation, including both the patient and control sample, between bilateral hippocampus volume and left inferior orbital frontal region indicated a significant positive relationship, $r = .468$, $p < 0.05$.

Having established significant differences between normalized hippocampus volume in the High and Low benefitters, it was of final interest to compare the controls to the Low and the High benefitters in terms of normalized hippocampus volume. A one-way ANOVA was run on the normalized volume of the Left, the Right and the Left+Right hippocampus, the between subject factor being Group (controls vs. MCI High benefitters vs. MCI Low benefitters). The assumptions for such ANOVAs were not violated as indicated by insignificant Levene's tests of Homogeneity. The ANOVAs showed a significant difference between the groups in the normalized volume of the right hippocampus, $F(2, 18) = 6.987$, $p < 0.01$, as well as the left+right hippocampus, $F(2, 18) = 7.171$, $p < 0.01$. Moreover a trend towards a significant group effect was found for the normalized volume of the left hippocampus, $F(2, 18) = 3.319$, $p = 0.062$. Newman-Keuls post-hoc tests (alpha level = 0.05) revealed that the significant Group differences in right hippocampus normalized volume as well as in left+right hippocampus volume were the result of significantly smaller normalized volumes in the low benefitter than the high benefitter and control groups. Figure 8.23 depicts group means and SEMs for the normalized volume of the left+right hippocampus.

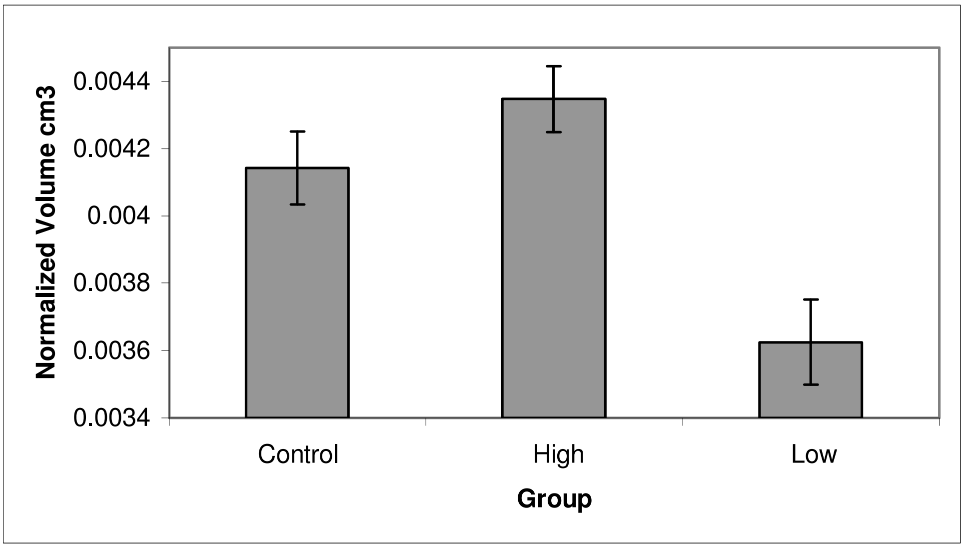


Figure 8.23. Group means and SEMs for the normalized volumetric data of the left+right hippocampus.

8.3.4 Discussion

The main aim of the present study was to examine whether hippocampal volume was associated with the degree of benefit of Minimal RI in patients diagnosed with aMCI.

The results of the present study reveal that indeed there was an association between the volume of the hippocampus and the degree of benefit in the present sample of aMCI patients: aMCI patients who benefited largely from Minimal RI (high benefitters) had significantly larger hippocampi than those aMCI patients who benefited to a lesser extent from Minimal RI (low benefitters).

Interestingly however, the two groups did not differ significantly on any of the neuropsychological test scores, proportion retention following RI or Minimal RI or any of the demographic variables apart from age. And even though such age difference was evident, the ANOVA with covariate age showed that the group difference in hippocampal volume was still present even after age differences had been controlled for.

Such findings are of great interest with respect to the tentative hypothesis of an association between the hippocampus and the benefit of Minimal RI (Cowan et al. 2005), more precisely, with respect to the aforementioned hypothesis of a relationship between *hippocampal volume* and the *degree of benefit of Minimal RI*.

Interestingly, while the patient sample as a whole appeared to show significantly smaller temporal lobe volume bilaterally within the superior temporal pole than the controls, no significant group difference was found in hippocampal volume.

Such lack of apparent mild hippocampal atrophy is not too surprising per se. Indeed others, for example Dickerson et al. (2005), have also revealed such lack of significant structural differences in hippocampal volume between patients with aMCI and matched neurologically intact controls. It is plausible that the current patients were in the early stages of aMCI and that no apparent structural changes were yet present. What *is* of particular interest with respect to such lack of significant group difference in hippocampal volume in the present study, is the fact that the patients nevertheless performed significantly poorer than the controls at delayed word recall following a (usual) RI-filled delay, yet not after Minimal RI. Thus it would appear that the heightened susceptibility to RI and thus much of the memory impairment observed in the present sample of patients cannot be attributed to reductions in hippocampal volume.

Moreover, while an association between hippocampal volume and degree of benefit was revealed within the patient sample, no such association was found in the control sample, thus strongly suggesting that such benefit – hippocampal volume relationship is particular to the patients, at least within this sample[8].

Such apparent group difference raises the question how hippocampal volume can have an effect on degree of benefit in one group, yet not in the other, even when there exists no overall difference between such groups in hippocampal volume.

This question is further complicated by the finding that in the controls left hippocampal size was strongly correlated with proportion retention following RI (a finding that replicates previous research findings, though see Van Petten, 2004 for a review), while in the MCI patients, most of whom performed at floor, such correlation was non-existent. Hence, patients with larger (left) hippocampi did *not* show better performance than those with smaller (left) hippocampi.

Thus, there are two somewhat contrasting findings in the present study:

One of an apparent association between hippocampal volume and the degree of benefit, yet no association between hippocampal volume and proportion retention following RI in the aMCI patients; the other of an apparent association between left hippocampal volume and proportion retention following RI, yet not between hippocampal volume and degree of benefit in the controls. While these two findings appear to conflict somewhat, it is possible that they can in fact be reconciled.

---

[8] It should be noted however that the presence of a ceiling effect in proportion retention following RI in the controls, especially those with large hippocampal volumes, could have occluded a potential benefit – hippocampal volume relationship in the controls. Future research, in which such ceiling effect in the controls is reduced via manipulation of the test stimuli and delay interval, is thus required to fully rule out the presence of a potential benefit – hippocampal volume relationship in the controls.

Indeed, the finding of no significant difference in proportion retention in the patients and controls following Minimal RI, as well as the trend towards a positive correlation between left+right hippocampal volume and proportion retention following Minimal RI in the patients tentatively suggests that when RI is removed, patients with aMCI not only perform as well as education and age matched normals, but also appear to show the same association between hippocampal size and proportion retention as normals: Thus, as in normals, patients with larger hippocampi appear to show greater proportion retention than do those with smaller hippocampi when there is no RI. For the purpose of this experiment it shall be assumed that such hippocampus-proportion retention association would have also be shown in the present patients had they not developed aMCI, and thus prior to disease onset. Assuming such, it could be argued that patients with larger hippocampi 'benefit' more from Minimal RI than patients with smaller hippocampi, not because the patients with larger hippocampi respond better to Minimal RI per se and perhaps in turn, because they are more susceptible to RI than those with small hippocampi, but because those patients with larger hippocampi would have also shown larger 'premorbid' proportion retention following RI and Minimal RI. Minimal RI may hence 'simply' reveal such premorbid individual differences in proportion retention associated with hippocampal volume. Nonetheless, future research is required in order to examine such hypothesis in further detail, especially given that the correlation between left+right hippocampal volume and proportion retention following Minimal RI in the patients did not reach significance.

In short then, it appears plausible that *both* the elucidated association between hippocampal volume and proportion retention following RI in controls, as well as that between hippocampal volume and the degree of benefit in the patients, may in fact be explained by an association between hippocampal volume and proportion retention.

Nonetheless, and irrespective of such potential underlying cause, the study strongly suggests that the extent to which a patient with aMCI can benefit from minimization of RI is at least partially dependent on the volume of his/her hippocampus, thus providing further evidence for a hippocampus hypothesis of the benefit of Minimal RI.

Of course the lack of a significant overall difference in hippocampal volume between the patients and controls limits such interpretation to those patients who do not (yet) show reductions in hippocampal volume. However, the results following the split of High and Low benefiting patients did reveal that the low benefitters had significantly smaller hippocampi than did the normal controls. Figure 8.18 further indicates that two of the low benefitters showed bilateral hippocampal volumes that were lower than that of any of the controls. Interestingly the Figure tentatively suggests that such two patients showed benefits of Minimal RI that were approximately in line with the general trend line of the patients whose hippocampal volumes did not differ from those of the controls. Thus, it may be tentatively hypothesized that the linear trend line for hippocampal volume and proportion retention following Minimal RI is approximately followed even when hippocampal volume is no longer normal. Indeed, the pilot findings by Della Sala et al. (2005) of no benefit of Minimal RI in AD may depict a point in the disease progress, in which hippocampal volume is too small to allow for any retention of material irrespective of whether RI is present or absent. Such very tentative hypothesis is illustrated in Figure 8.24 below.

Nonetheless, the finding of such pattern in two patients cannot be generalized and thus it is necessary to test such hypothesis via further research. Such future research will require inclusion of a larger number of aMCI patients whose hippocampal volumes are and are not significantly smaller than those of controls. In addition such future study would also benefit from the inclusion of patients with AD who show largely atrophied hippocampi.

If indeed a linear function is obtained it will be of great interest to identify the hippocampal volume at which the line intercepts hippocampal volume axis and to investigate to what extent such point may match classification of a patient as AD (see Figure 8.24). Such would also be of interest if the correlation between hippocampal volume and proportion retention following Minimal RI were to follow a different gradient or shape following structural changes in the hippocampus.

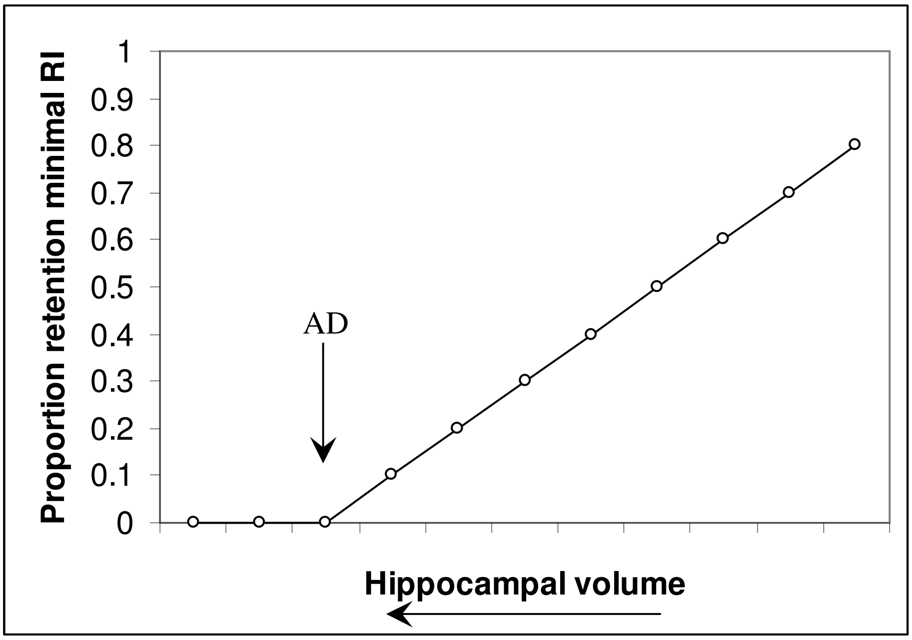


Figure 8.24. AD may depict a point in the disease progress, in which hippocampal volume is too small to allow for any retention of material irrespective of whether RI is present or absent, meaning that no benefit of Minimal RI is observed.

While the focus of the study was on the *hippocampus* and any potential relationship between its volume and the degree of benefit of Minimal RI, it is important to also examine the elucidated positive relationship between the benefit of Minimal RI and the volume of the *inferior orbital frontal region* in the patient sample.

Such finding is interesting given the frequent association of the frontal lobe with inhibitory responses (c.f. Baldo and Shimamura, 2002) including those required to overcome interference in memory, i.e. PI (c.f. Shimamura et al., 1995; Baldo and Shimamura, 2002).

However, while a significant correlation between the left inferior orbital frontal region and the degree of benefit of Minimal RI was obtained, it appears unlikely that the left inferior orbital frontal region volume actually has a direct effect on the degree of the benefit of Minimal RI: Firstly, the patients did not differ from the controls with respect to the volume of this region though showed a substantially higher benefit of Minimal RI. Secondly, no such correlation was shown for the control sample. It could of course be argued that in normals a larger left inferior orbital frontal region may be associated with a larger proportion retention in general, i.e. also after RI, i.e. as is argued with respect to hippocampal volume above. If such were the case the apparent positive correlation between this region and the benefit of Minimal RI may thus underlie 'premorbid' proportion retention. Such in turn could imply that this region is indeed of importance for the benefit of Minimal RI. However, in contrast to the hippocampal data, there was no association between the volume of the left inferior orbital frontal region and proportion retention following RI or Minimal RI in the controls.

Given such finding in the controls as well as the significant positive correlation between the volume of the hippocampus and the right inferior orbital frontal region overall, it appears likely that the apparent correlation in the patient sample could in fact underlie the association between *hippocampal* volume and the degree of benefit of Minimal RI. In other words, a correlation between left inferior orbital frontal region volume and the benefit of Minimal RI may arise because volume of such region is strongly related with that of the hippocampus, which again is associated with the degree of the benefit of Minimal RI. If such is the case a reduction in the volume of the left inferior orbital frontal region alone would not be predicted to affect the degree of benefit of Minimal RI in a patient sample such as the present one.

Nonetheless, it is important to underline that even though there appears to be little evidence for a direct effect of the volume of the left inferior orbital frontal region on the benefit of Minimal RI, such possibility cannot be excluded entirely and must therefore be addressed in future research, perhaps including patients with isolated and focal lesions to such region.

8.3.4.1 Neural correlates of the increased susceptibility to RI in aMCI

While the current study strongly suggests then that in aMCI the degree of benefit of Minimal RI is dependent on hippocampal volume, the neural correlates of the *RI susceptibility* seen in such patients remain to be established. Two possibilities are proposed:

(1) Temporal pole volume loss

Given the lack of a significant difference in hippocampal volume between the present aMCI sample and the control sample, one possibility is that the susceptibility to RI underlies structural damage to a non-hippocampal system.

As such damage would have to only be present in the patients with aMCI as opposed to in both the patients and controls, a first step to locating a potential neural correlate, is to consider the structural differences between the present aMCI sample and control sample. The main structural difference between the two groups was the significantly smaller normalized volume of the *superior temporal pole* in the aMCI sample. It may thus be questioned whether or not volume loss of the superior temporal pole may be the key to the apparent susceptibility to RI in the present aMCI sample. The temporal pole has strong connections with the hippocampus (Chabardès et al., 2002), and could thus potentially be associated with the consolidation process, either directly, or perhaps with a pre-consolidation stage (see discussion of Experiment 7). However, unfortunately very little is known about the possible cognitive function associated with this structure, or the more specifically about that of the *superior* temporal pole, thus rendering any potential temporal pole hypothesis of the susceptibility to RI somewhat speculative. Some research suggests that the temporal pole is involved in the *retrieval* of semantic (c.f. Griffith et al. 2006) and retrograde memory (Markowitch, 1985), two functions that would not appear to be closely related to memory consolidation or pre-consolidation processing. Nonetheless, more research, including fMRI research, is required in order to provide a more thorough understanding of the cognitive function of this structure before a temporal pole theory of RI can be rejected or indeed further advanced.

<u>(2) A functional deficit within the hippocampus</u>

A further possibility could be that the RI susceptibility observed in aMCI is the product of an impairment in the *functioning*, as opposed to the volume of the hippocampus: For example, there is the possibility that aMCI could be associated with a reduction in hippocampal resources required for the simultaneous processing of new incoming information. Thus, when RI follows to-be-retained material within a short time interval, i.e. when to-be-retained material is still highly fragile and in need of strengthening, the hippocampus may not have sufficient resources to process both stimuli with the consequence that the information is not strengthened.

While the present structural and behavioral data do not allow for the testing of such very tentative hypothesis, some potential evidence for such a hypothesis may be gleaned from research findings in other, yet related disciplines: (a) Firstly recent investigations into the level of activation of the hippocampus during learning in MCI and normal elderly and secondly (b) neuroscience research on early neuropathological changes in AD at the molecular level affecting long term potentiation (LTP, see Chapter 1).

(a) Differences in the level of hippocampal activation during learning in aMCI and normal elderly

A small number of studies have been run to examine potential differences between patients with aMCI and normal elderly in the activation of memory related areas, i.e. the medial temporal lobe (e.g. Machulda et al. 2003) and more specifically the hippocampus (e.g. Dickerson et al., 2005; Mondadori et al., 2006) during learning of stimuli. Interestingly these studies have shown significantly different levels of activation in such areas between patients with aMCI and normal elderly. However, such findings have differed regarding the direction of such difference. Dickerson et al. (2005) for example visually presented their participants with to-be-learned face-name pairs and measured hippocampal activity during the learning of such stimuli via fMRI. It was revealed that while the aMCI sample and the normal elderly sample did not differ significantly in hippocampal volume, the aMCI sample showed significantly greater hippocampal activation than the normal elderly sample. On the other hand Machulda et al. (2003) reported significantly lower activation in the medial temporal lobes (including the hippocampus) in patients with aMCI than normal elderly during the learning of visual scenes.

It is possible that the inconsistent findings in these two studies may have been the result of differing inclusion criteria: While Machulda et al.'s (2003) patients were selected via the full criteria by Petersen et al. (1999), i.e. such as the patients in the present study, Dickerson et al.'s (2005) patients did not have to present with objective memory impairment and so appeared to have milder degrees of MCI. Thus it is possible that hippocampal activation changes from increased to reduced activation as MCI progresses. Indeed, a recent fMRI study by Celone et al. (2006) revealed such findings exactly.

Nonetheless, for the purpose of the present study the important finding of such fMRI studies is that patients with aMCI and normal elderly appear to show significant differences in the *functioning* of the hippocampus during learning of new material. Indeed, the study by Dickerson et al. (2005) in particular highlights that the very early stages of aMCI, in which no objective memory impairment may yet be apparent, could be associated with changes in hippocampal *functioning* as opposed to structural changes. Such finding in turn suggests that the earliest neural correlates of memory impairment and thus perhaps the susceptibility to RI in aMCI could lie in the *functioning* as opposed to the *volume* of the hippocampus.

(b) Neuroscience research on early neuropathological changes in AD at the molecular level affecting LTP

The second potential evidence for a hippocampal hypothesis of RI comes from neuroscience research on AD at a molecular level. In short, it is strongly argued that the earliest changes in the brain of a patient with AD are likely to be *functional* as opposed to *structural* (Selkoe, 2002, Rowan et al., 2003, Rowan et al. 2006). More specifically, research in such field suggests that the earliest signs of memory impairment in AD, and hence those apparent during aMCI, may well underlie interruption of synapses required for the formation of new declarative memories (Selkoe, 2002). Indeed, research on mice suggests that the earliest stages of AD, and thus aMCI, could be associated with a deficit in LTP within the hippocampus (Selkoe, 2002; Rowan, 2006; Chen et al., 2000).

A deficit in LTP within the hippocampus prior to structural changes in the earliest stages of AD and thus MCI could be a potential 'neural correlate' candidate for the susceptibility to RI observed in patients with aMCI. Indeed, given the apparent association between synaptic consolidation (see Chapter 1) and LTP (Wixted, 2004), there could certainly be some scope in such very tentative hypothesis. For example, and as argued above, RI susceptibility may underlie an impairment in such synaptic consolidation and thus LTP.

8.3.5 Conclusion

The present study was set up to investigate whether or not there was an association between the degree of benefit from Minimal RI and hippocampal volume in patients with aMCI.

The results revealed that indeed there was such association: aMCI patients who showed larger benefits of Minimal RI were found to have significantly larger hippocampi than those patients who showed smaller benefits of Minimal RI.
Interestingly however, it appears that the apparent association between hippocampal volume and the degree of benefit from Minimal RI in the aMCI patients can be explained by a positive relationship between hippocampal volume and proportion retention in the elderly overall. Thus, an aMCI patient who is *susceptible to RI* and has a relatively *large* hippocampus will show *higher* retention when there is *no* RI than a patient who is *susceptible to RI* and has a relatively *small* hippocampus.

Given the lack of a significant difference in hippocampal size between the two groups it remains unknown whether or not the association between degree of benefit and hippocampal volume holds in aMCI patients with hippocampal atrophy and indeed patients with AD. Moreover, while no neural correlates of the increased RI susceptibility in aMCI was elucidated in the present experiment, it is suggested that the search for such neural correlate may need to take place at the *functional* as opposed to *structural* level, a hypothesis that shall be tested via functional imaging research in the future.

8.4 Experiment 9: Pilot study - Delayed verbal recall following modality specific and modality unspecific RI in a left temporal lobectomy patient

8.4.1 Introduction

The findings of Experiments 1 (see also Dewar et al., in press) and 2(a) demonstrate that all RI had to be removed during the delay interval for both neurologically intact individuals and patients with anterograde amnesia to show improved delayed verbal recall.

Such findings thus strongly suggest that RI need not be similar in material or modality to the to-be-retained material in order for it to have a detrimental effect on verbal memory processing in either neurologically intact individuals or patients with anterograde amnesia. Moreover, given the evidence for an effect of RI on *consolidation* (see Chapters 5,6 and 7; see also Wixted, 2004 and Dudai, 2004), it would appear that *any* newly encoded information has a detrimental effect on the *consolidation* of previously encoded to-be-retained verbal material, to some extent in neurologically intact individuals, and to an apparent substantial extent in some patients with anterograde amnesia.

Such findings are of interest with respect to the hypothesized lateralized processing of verbal and nonverbal memory in the healthy human brain (see for example Milner, 1972; Cohen et al., 1999; Lee et al., 2002).

Initial evidence for a specialization of the left medial temporal lobe for verbal memory processing and a specialization of the right medial temporal lobe for nonverbal memory processing came from patients who had undergone a unilateral temporal lobectomy for the surgical treatment of intractable medial temporal lobe epilepsy (see for example Milner, 1972), a syndrome which is most commonly caused by underlying hippocampal sclerosis (c.f. Janszky et al., 2005). While, as discovered in the famous patient HM, *bilateral* temporal lobectomy leads to a profound global and non-material-or modality specific amnesia (Scoville and Milner, 1957), the consequences of a *unilateral* temporal lobectomy are much less severe *modality specific* memory deficits (see for example Cohen et al., 1999; Lee et al., 2002): Resection from the language-dominant left temporal lobe frequently results in some reduction of *verbal memory* function (e.g. memory for words and prose) with sparing of non-verbal function, while resection from the right temporal lobe frequently results in a decrease in nonverbal memory function, with sparing of verbal memory function (e.g. memory for objects and the spatial location of stimuli) (see for example Smith and Milner, 1981; Smith and Milner, 1989; Frisk and Milner, 1990; Abrahams et al., 1997, Jones-Gotman et al., 1997, Pillon et al., 1999; Cohen et al., 1999; see also Lee et al., 2002 for a meta analysis).

Such findings of an apparent lateralization of memory processing have been further supported via functional imaging research (c.f. Kelley et al., 1998; Martin et al., 1997, Golby et al., 2001). Kelley et al. (1998) for example presented their participants with words, namable objects and unfamiliar faces while in the MRI scanner. It was found that the three types of stimuli led to significantly higher hippocampal activation than did a fixation point. Moreover, and most importantly, such hippocampal activation varied for the two hemispheres as a function of modality type: Words were mainly associated with left hippocampal activation, unfamiliar faces with right hippocampal activation and namable objects with bilateral hippocampal activation.

Given such evidence for a lateralization of verbal and nonverbal memory processing within the medial temporal lobe, and more specifically within the hippocampus, one would predict the consolidation of verbal material to be less affected by non-verbal RI than by verbal RI. Thus, it would be predicted that when there is verbal RI, the left hippocampus should have to process to-be-retained information *as well* as the new verbal material (RI). On the other hand, when there is nonverbal RI, the left hippocampus should only have to process the to-be-retained material as the right hippocampus would process the new nonverbal material. If such were the case one would not only predict a benefit of minimal diversion RI, but also a benefit of minimization of modality specific RI only. However, both Experiment 1 and Experiment 2(a) demonstrate that such was not the case in either neurologically intact individuals or patients with anterograde amnesia. Such indicates an apparent conflict between the diversion RI findings reported in Chapters 3 and 4 and the findings of a laterality of memory function.

However, it is important to highlight that while the left and right medial temporal lobes and hippocampi do indeed appear to be specialized for the processing of verbal and nonverbal information respectively, it is highly unlikely that they are functionally independent.

Indeed, while the functional imaging studies have revealed *greater* activation in the left medial temporal lobe/hippocampus than the right medial/temporal lobe during presentation of verbal material, some, albeit less activation is also found in the right medial temporal lobe/hippocampus. Similarly, while nonverbal material leads to greater activation of the right medial temporal lobe/hippocampus than of the left medial temporal lobe/hippocampus, some, yet less activation is also found in the left medial temporal lobe/hippocampus (Kelley et al., 1998; Martin et al., 1997; Golby et al., 2001). Golby et al., (2001) for example state that *'The encoding activations are better characterized as <u>asymmetrical</u> than unilateral, because even the most lateralized activation and patterns included activation in the contralateral hemisphere'* (p. 1850).

Further evidence against a full lateralization of verbal and nonverbal memory in the normal brain comes from the finding of memory impairment in a word list recall study in commissurotomy patients (i.e. patients whose corpus callosum has been surgically severed for treatment of intractable epilepsy) (Dobbins et al., 1998). Indeed, such research suggests that verbal memory processing requires communication between the left and right hippocampi.

Moreover, while patients who have had a unilateral temporal lobectomy do frequently show a modality specific memory deficit, such deficit is generally not severe, i.e. such patients are not amnesic (c.f. Helmstaedter and Kurthen, 2001) which suggests that the spared medial temporal lobe/hippocampus is likely to be able to process some of the material for which the contralateral medial temporal lobe/hippocampus is specialized in the normal brain (c.f. Pillon et al., 1999). In fact, recent fMRI work by Richardson et al. (2003) demonstrated a *reorganization* of verbal function to the right medial temporal lobe in patients with left hippocampal sclerosis, suggesting that in some left temporal lobectomy patients with hippocampal sclerosis the right hippocampus may indeed be very capable of processing verbal information (see also Herman, 2004).

With respect to a non-modality specific effect of RI on verbal memory processing, it is also important to consider that while an experiment on retention of verbal material and RI 'only' requires the processing of such to-be-retained verbal material as well as the RI stimuli, the intact hippocampus is likely to automatically process many other aspects of such a testing session. Indeed, as Martin (1999) highlights, the fact that any neurologically intact participant taking part in a memory experiment will, at a later time, remember (a) having participated in such experiment and (b) various contextual aspects of the testing session, demonstrates that the hippocampus is likely to automatically process much more information than is 'required' by the experiment per se. Indeed, Martin (1999) and Martin et al. (1997) argue that the hippocampus is likely to be active *whenever* any event is experienced. This means that even though an RI task may be solely nonverbal and a nonverbal memory task, the left hippocampus may nevertheless be active due to processing the experience associated with engaging in the task itself.

It may thus be possible to reconcile the findings of a *modality specific* specialization of the right and left hippocampi and the reported findings of a *non-modality specific* RI effect in neurologically intact population in the following way: While processing of to-be-retained verbal material may be primarily undertaken by the left hippocampus in neurologically intact individuals, any RI, whether verbal or nonverbal as well as any other automatic processing, should to some extent also activate the left hippocampus and thus lead to some slight interference. Thus, memory improvement could only be derived via removal of all RI. The story could be the same for patients with anterograde amnesia who benefit from Minimal RI. However, given their very poor retention of verbal material following diversion RI, one would predict any RI to have a much more profound effect on the processing of verbal material within the left hippocampus of such patients than in the neurologically intact.

Given such potential hypothesis as well as the modality specific memory impairment and potential reorganisation of memory functioning in unilateral temporal lobectomy patients, an interesting question is how *Minimal RI* as well as *modality* and *non-modality specific RI* may affect *verbal retention* in a patient whose *left hippocampus*, and thus the site specialized for verbal memory processing, has been resected via a left temporal lobectomy.

Thus, seeing as new verbal LTM can still be formed, albeit to a much lesser extent in a patient whose left hippocampus has either been partially or fully resected, it is of interest to examine whether such verbal LTM formation can be improved via Minimal RI, and thus whether such a patient shows a benefit of Minimal RI. Moreover, seeing as (a) such patients present with an isolated verbal memory deficit, i.e. a modality-specific memory deficit and (b) that the right non-specialized hippocampus may take over a great extent of verbal memory processing, it is of further interest to investigate whether or not modality-specific and non-modality specific RI may differentially affect verbal retention in such a patient.

8.4.2 Aims of Experiment 9

The aim of this pilot study was thus to investigate (a) whether or not a benefit of Minimal RI would emerge for the retention of verbal memory in a left temporal lobectomy patient and (b) whether or not there was an effect of modality of RI on verbal memory retention in such a patient.

8.4.3 Case Description

NM, a 31 year old University educated (BSc in Mechanical Engineering) male presented with a history of simple partial seizures, which were treated via two left temporal lobectomies, firstly a left amygdalo hippocampectomy in 1998, followed by a standard left temporal lobectomy in 2005, since when he has been completely seizure free. NM showed a left speech pass on the presurgical WADA test.

8.4.4 Neuropsychology

NM's initial post surgical neuropsychological evaluation conducted at Ninewells Hospital, Dundee in 1999, revealed a Verbal Memory Index of 56, a Visual Memory Index of 86 and a Delayed Recall Index of 59 (WMS-R). A recent second assessment at Ninewells Hospital, Dundee, following his surgery in 2005 showed substantial improvement in all above measures: 79, 119 and 91 in the Verbal Memory Index, The Visual Memory Index and Delayed Recall Index respectively. According to his Consultant Neurologist (Dr Richard Robert) such improvement is likely to be related to the absence of subclinical epileptic activity persistently involving the temporal lobes.

Prior to experimental testing NM underwent further neuropsychological assessment. The assessment revealed normal immediate verbal memory, as indicated by above cut off performance on the WMS Logical Memory I, the WMS digit span and a word span task, normal delayed verbal LTM as evinced by the WMS Logical Memory II. However, it should be noted that his WMS Logical Memory II score was in the low average range, which was lower than would be predicted for a person of his education level. Nonetheless, he showed normal Immediate and Delayed Visuospatial Memory (both 75th percentile) as shown by an above cut off performance on the AMIPB Figure recall, normal language functioning, as revealed by an above cut off performance of the Frenchay Aphasia Screening Test, normal visuospatial ability as evinced by the AMIPB Figure Copy, normal information processing, as indicated by a below cut off trail making A performance and normal executive functioning as indicated by a below cut off trail making B performance. The test scores and cut off values are provided in Table 8.5 below.

Measure	Raw	t-score/scaled score	Cut-off
WASI similarities	40	57	/
WASI vocabulary	55	47	/
Frenchay Aphasia Screening Test	29	/	27
AMIPB Figure Copy	80	75^{th} percentile	/
Trail Making A	19	/	>40
Trail Making B	41.7	/	>67
WMS-III Logical Memory I	33	9	4
WMS-III Logical Memory I - Thematic Total score	16	9	4
WMS-III Logical Memory I 1st Recall Total score	18	7	4
WAIS-III Digit span (forward)	9	/	/
Word span	5	/ *	/
AMIBP Figure Immediate recall	78	75^{th} percentile	/
WMS-III Logical Memory II	15	7	4
WMS-III Logical Memory II - Thematic Total score	9	8	4
WMS-III Logical Memory Learning slope	5	10	4
WMS-III Logical Memory % Retention	65	9	4
AMIBP Figure Delayed Recall recall	78	75^{th} percentile	/

Table 8.5. NM's Neuropsychological Test data.

WASI (Wechsler, 1999); WAIS-III (Wechsler, 1997); WMS-III (Wechsler, 1997); AMIBP (Coughlan and Hollows, 1985); Trail Making (Tombaugh, 2004), cut-of based on 10^{th} percentile. *Word span test designed by Michaela Dewar and Sergio Della Sala, pilot version, no norms are available yet.

8.4.5 Pre-and post surgical neuropathology

NM's first pre-surgical scan revealed mesial temporal sclerosis as well as abnormal development of the left temporal lobe.

NM's most recent MRI (February 2006) (see Figure 8.25) shows complete resection of the left hippocampus. According to his neurologist some medial amygdala remains and the lateral cortex was removed to about 4.5cm from the temporal pole.

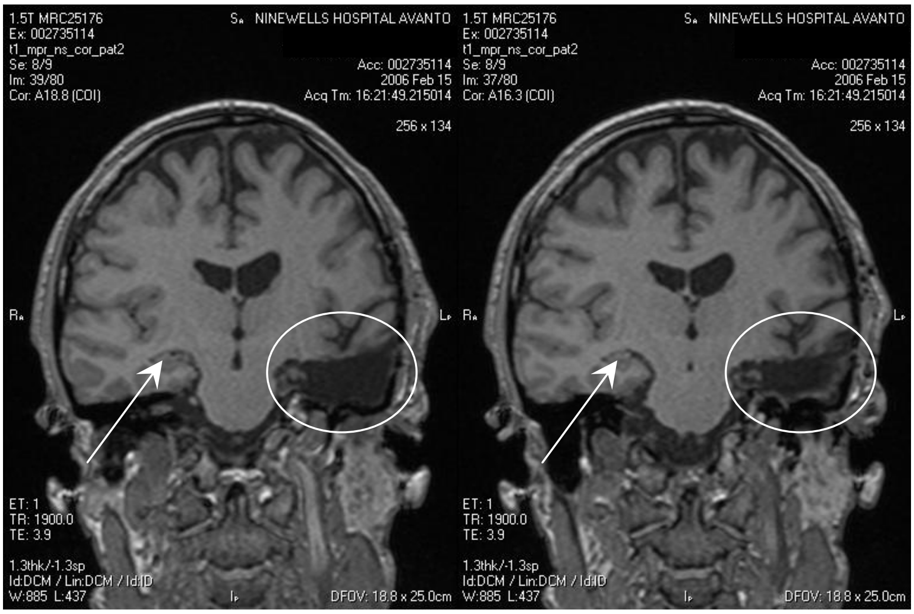


Figure 8.25. T1 coronal MRI scan of NM's brain (left and right reversed). The circle indicates the surgical excision from the left temporal lobe including the left hippocampus. The intact right hippocampus is indicated via the arrow.

8.4.6 Materials and Methods

The main memory stimuli in the present study were five to-be-retained word lists (see Appendix F). Each word list contained 15 words, which were compiled from the MRC Psycholinguistic Database and matched for familiarity, imaginability and concreteness (300 – 700) (Kucera and Francis, 1967). Word frequency (1000 – 5000) was taken from the British National Corpus as this provides more recent frequency measures than that by Kucera and Francis (1967). Care was taken to ensure that each word list contained a balanced set of words ranging from a BNC frequency of around 1000 to 5000. Moreover even though all words selected were in the range of 300 – 700 for familiarity, imaginability and concreteness and had 2-4 syllables, and thus were already highly matched, care was taken that the words in each lists also showed a very similar range in the number of letters, syllables, familiarity, concreteness and imaginability. I.e. each list contained some words that were in the lower, medium and high range of each of these variables. Furthermore, great care was taken to ensure that none of the words were semantically or phonologically similar, especially within each list. Moreover, while words in each list were randomly ordered, care was taken to ensure no two words starting with the same letter were ever placed next to each other. All word lists were highly similar in *total* BNC frequency, Imaginability, Contreteness, familiarity and letters. All lists had a total syllable count of 40 to ensure articulation time was equal across the lists.

8.4.6.1 Word lists – Pilot study

While the five lists were carefully balanced it was nevertheless decided to run a pilot immediate recall experiment on a sample of 10 healthy participants (4m/6f, Age range = 22 to 31 years, Education range = 18 to 26 years) in order to assure that none of the lists were more or less difficult to remember than the others. Participants were presented with each of the five word lists and asked to immediately recall as many of the words as they could following each list. The lists were either presented in order 1-2-3-4-5 or 5-4-3-2-1. The pilot study revealed no significant difference between the five lists in immediate word list recall nor did the participants' feedback reveal any common subjective differences in difficulty, thus indicating that the five lists were indeed equally balanced.

8.4.6.2 Case study

NM was verbally presented with one of the five word lists at a rate of one word every two seconds in each of the five trials, and asked to remember as many of the words as he could for subsequent immediate recall. In each trial word list presentation was followed by free immediate recall. The end of immediate recall marked the beginning of a five minute delay interval, which contained Minimal RI in the first and fifth trial and RI in the second, third and fourth trials. Following the delay interval, NM was requested to recall once more as many of the words from the prior word list as possible.

During the Minimal RI delays NM was simply requested to rest in the darkened room while the experimenter was preparing the next test in the other room.

The critical manipulation in the three RI delay intervals was the *type* of RI:

Verbal

Reading

In order to examine NM's delayed word list recall following modality specific (i.e. verbal) RI, NM was asked to read aloud a passage of text (on facts about nature, see Appendix G) for the duration of the delay interval. Care was taken to ensure that none of the to-be-retained words featured in this passage of text.
The aim was to examine whether the encoding of new verbal material per se, as opposed to the *intentional learning* of such verbal material, would have an effect on NM's delayed word list recall. For such reason NM was explicitly informed that he would *not* be required to recall any of the information provided in the passage of text at a later point.

Spatial

Map search

In this RI delay NM was presented with a sheet of A3 paper containing an abstract and visually busy gray scale map (see Figure 8.26a as well as Appendix H). The map contained various large shapes and lines of varying gray shades and sizes, as well as 100 of each of six random symbols In order to minimize any verbal interference, the shapes and symbols were designed to be difficult to verbalize.

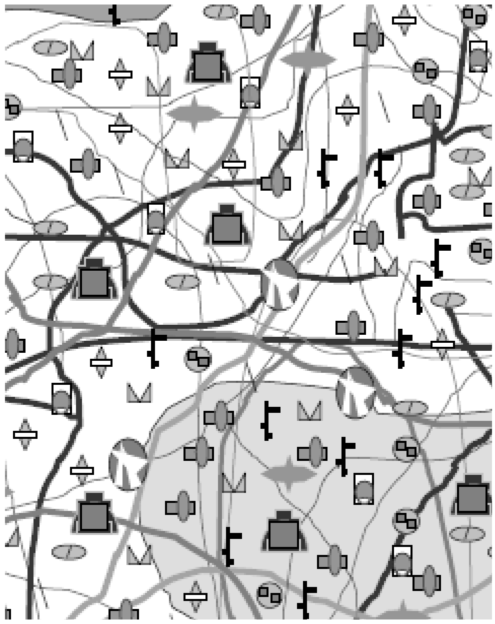


Figure 8.26a. Small section of the gray-scale map

Moreover, NM was presented with a A4 sheet containing one of the six symbols featuring on the map (see Figure 8.26b for an example of the first 3 symbols). He was instructed to search for all copies of the particular symbol on the map as quick and thoroughly as possible and circle these with a pen. He was further informed that he should tap the table on finishing his search to request a new copy of the map and a new symbol to search. Such nonverbal signal was required in order to minimize any verbal interference during this non-verbal RI delay period.

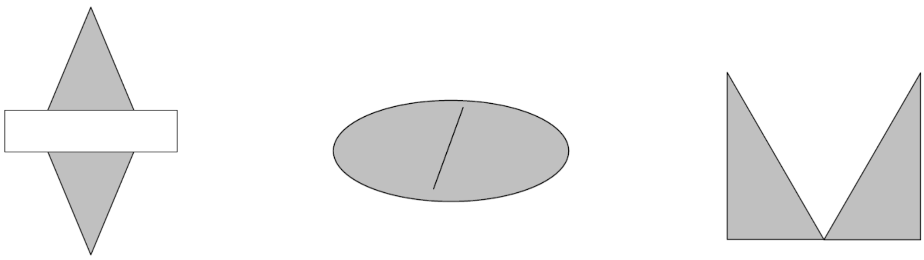


Figure 8.26b. An example of the symbols (NM was presented with the first two from the left)

Minimal RI with rehearsal blocker

Articulatory Suppression

In order to examine NM's delayed recall following a period of Minimal RI during which the use of any subvocal rehearsal could be greatly minimized, it was decided to include an articulatory suppression (Baddeley et al., 1975) delay interval. Given that the duration of the delay period was five minutes, the patient could not be requested to engage in articulatory suppression *throughout* the delay interval. For such reason a task was designed which required articulatory suppression only during the initial 20 seconds of each of the five minutes of the delay interval, while the remaining 40 seconds of each of the 5 minutes would remain unfilled.

The task consisted of NM being presented with a recording of a person saying aloud 'da' at a rate of one 'da' every second during the first 20 seconds of each of the five minutes. NM was instructed to shadow the person saying 'da' aloud whenever she said 'da', and to be silent and rest when she was silent. NM was further informed that during the unfilled periods he should not listen out for the first 'da' of the subsequent shadowing period, but to simply rest and begin shadowing after hearing the first 'da'. Such was done in order to minimize mental effort during this Delay Condition.

In order to minimize any additional interference following immediate recall, all RI instructions as well as a practice trial were provided prior to word list presentation in each of these three Delay Conditions. Following immediate recall NM was thus only ever given a very brief reminder.

Following the Experiment NM was asked for feedback concerning various aspects of the experiment.

8.4.7 Results

Firstly it is important to highlight that the data for the first Minimal RI trial could not be utilized as 'Minimal RI' data, as unaware to the Experimenter (who was in a different room) NM turned on his mp3 player and spent the duration of the delay interval listening to a recorded conversation he had had with his neurologist. It was thus decided to rename this trial ‘verbal listening’ for the purpose of this pilot study.

NM’s proportion retention of the presented word lists was initially computed for immediate recall of each of the five Delay Conditions.

In order to examine whether NM’s immediate word list recall deviated from that of neurologically intact individuals of similar age and education, NM’s mean immediate recall proportion retention was compared to that of 9 age and education matched controls (who had previously taken part in a pilot study on this experiment[9]) (Mean Age = 29, SD = 5.89; Mean Education = 17.58, SD = 1.24). NM’s mean immediate proportion word list retention as well as that of the controls is shown in Figure 8.27. Figure 8.27 shows that while NM’s mean immediate proportion word list retention (0.32) was lower than that of the controls (0.48), it was within 2 standard deviations from the control mean.

[9] It should be noted that the word lists utilised in the pilot work on neurologically intact participants deviated slightly from those used in the present study. The pilot work very tentatively indicated that some of the word lists may have not been perfectly matched with respect to how well they could be initially retained by neurologically intact individuals. They were thus reshuffled for the purpose of the present experiment and tested via the aforementioned immediate recall pilot study. Subsequent analysis however revealed no significant differences between immediate recall of the previous word lists (Mean = 0.48, SD = 0.031) and the reshuffled word lists used in the present experiment on NM (Mean = 0.472, SD = 0.035). Thus NM’s mean immediate recall was also within 2SDs from that of the 10 controls taking part in the aforementioned immediate recall pilot experiment on identical word lists.

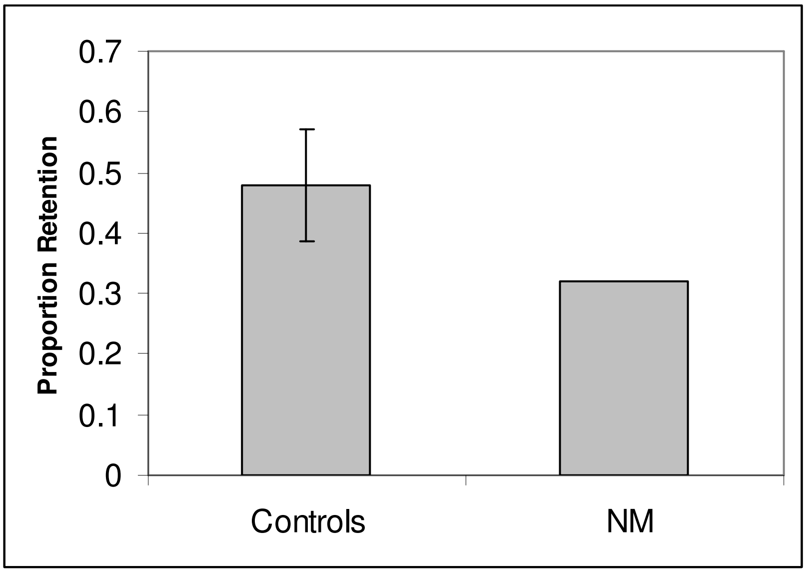


Figure 8.27. Mean number of words recalled at Immediate by NM and 9 age and education matched controls. Error bar = 1SD.

NM's proportion retention of the presented word lists was subsequently computed for delayed recall of each of the Delay Conditions. Figure 8.28 depicts this data as well as the data for proportion retention of the presented word lists at immediate recall of each of the five Delay Conditions. The Figure shows that while NM showed some retention of to-be-retained word list stimuli at immediate recall of each of the five Delay Conditions, he only showed retention at delayed recall of the second Minimal RI, the map search and the articulatory suppression RI delay intervals.

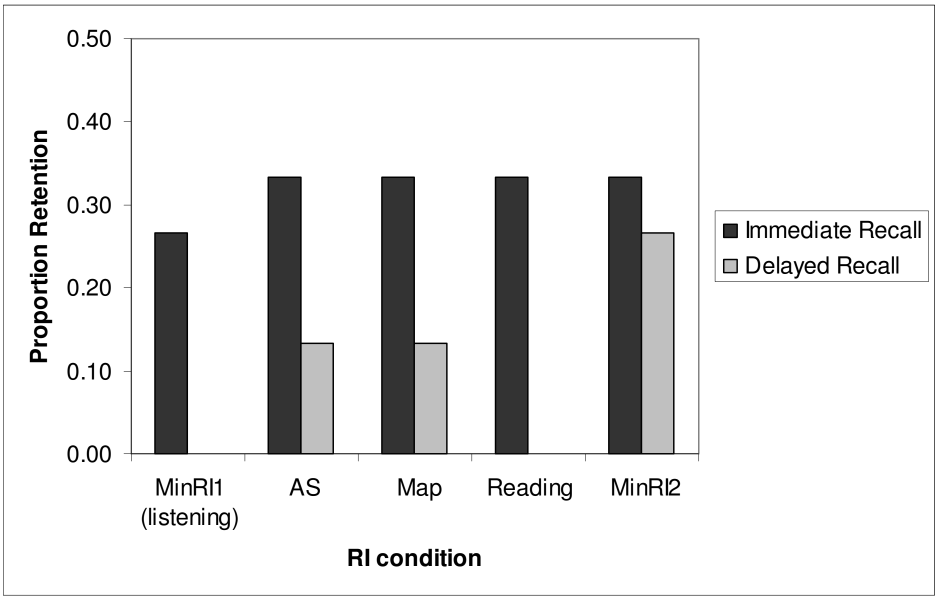


Figure 8.28.

As in the previous RI studies by Cowan et al. (2004) and Della Sala et al. (2005) as well as the previous experiment reported in this thesis, NM's proportion retention at delayed recall was measured as the number of correct words recalled at delayed recall divided by the number of correct words recalled at Immediate recall (i.e. DR/IR). NM's proportion retention (DR/IR) data for each of the five Delay Conditions is depicted in Figure 8.29, which also shows mean proportion retention data and SEMs for the sample of the 9 neurologically intact individuals. Moreover, Table 8.6 provides both NM's proportion retention as well as normal cut-offs (2SD cut-off based on data of the 9 controls) for proportion retention for the Minimal RI, the reading, the map search as well as the articulatory suppression Delay Conditions. Note that no proportion retention cut-off is available for NM's 'listening' (first Minimal RI) data.

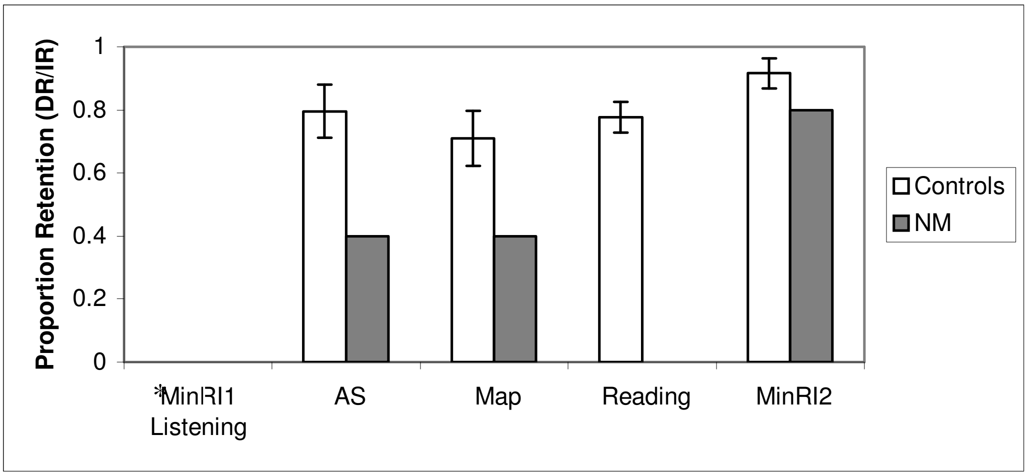


Figure 8.29. NM's proportion retention in the Listening, the articulatory suppression, the map search, the reading and the second Minimal RI Delay Conditions as well as the controls' mean proportion retention and SEMs for these conditions. *Note that no data was available for the control group for the 'Listening' Delay Condition.

	NM	Normal cut-off
AS	0.4	0.4
Map	0.4	0.32
Reading	**0**	**0.45**
Listening	**0**	/
MI2	0.8	0.66

Table 8.6. NM's proportion retention following AS, Map, Reading, Listening and MinRI2 and normal cut-off (2SD cut off based on proportion of 9 age and education matched controls, Mean Age = 29, SD = 5.89; Mean Education = 17.58, SD = 1.24). Note that no Listening data was available for the controls.

8.4.8 Discussion

The present pilot study revealed that NM, a left temporal lobectomy patient, whose left hippocampus has been fully surgically removed, performed better at delayed word list recall following a delay period of Minimal RI than RI, thus indicating that this patient *benefited* from Minimal RI.

Moreover, as depicted in Table 8.6, while NM's proportion retention was within 2SDs from the mean of the age and education matched controls for the second Minimal RI, it was at cut-off for the map search and close to cut-off for the articulatory suppression Delay Condition. Moreover, his proportion retention for the reading condition was substantially below the normal cut-off. While no listening data was available for the controls, NM's proportion retention in this condition was at floor and it appears likely that such proportion retention would have also been below the normal cut-off.

Such difference between NM's proportion retention and the mean control proportion retention following RI overall thus suggests that patient NM showed a benefit of Minimal RI that was over and above that expected for a neurologically intact person of similar age and education.

Furthermore, while NM showed 0 retention following the two verbal RI delay intervals, he did show some retention following both the map search as well as the articulatory suppression delay periods. Such finding thus tentatively suggests a larger susceptibility to (meaningful) verbal than nonverbal RI in retention of verbal material in this particular patient. While the articulatory suppression task was designed to be minimally interfering yet to impede rehearsal, it cannot be told whether NM's lower performance following such condition than the second Minimal RI Condition was the product of a blocking of subvocal rehearsal or the presence of some new albeit non-meaningful verbal material. Indeed, as reported above, Martin (1999) and Martin et al. (1997) strongly argue that the hippocampus is active whenever any event is experienced. Thus there is the possibility that the presence of the non-meaningful verbal material may have led to some interference also. In fact, Martin et al. (1997) report in their fMRI study that in a sample of neurologically intact participants meaningful material led to greater hippocampal activation than did non-meaningful material, a finding that could explain why repeating of a nonsense word ('da') may have led to less interference than reading of a meaningful passage of text.

Nonetheless, it should be noted that post experimental feedback revealed that NM did attempt to rehearse some material during the second Minimal RI delay, yet not *throughout* the delay ('I repeated it a couple of times'), but that he did not rehearse any material during any of the other conditions. Given the lack of surprise delayed recall data from the first Minimal RI Condition (i.e. the ‘listening’), in which rehearsal would have been minimal, it can thus not be excluded that some of the benefit of Minimal RI may have been augmented via some subvocal rehearsal during the second Minimal RI delay interval.

Nonetheless, the finding of an apparent *higher* susceptibility to *verbal* than *nonverbal* RI during retention of verbal material in the present patient is highly interesting given the lack of such a modality specific RI effect in both neurologically intact individuals and global amnesiacs.

At this stage it is not known whether the findings of a modality specific RI effect can be generalized to the left temporal lobectomy patient population or whether such finding is particular to patient NM. Indeed, further planned research on a larger sample of left temporal lobectomy patients will shed light on this outstanding question. Nevertheless, the current pilot study does provide some speculative hypotheses, which may or may not hold following the testing of further left temporal lobectomy patients.

<u>*Some preliminary speculations:*</u>

As postulated above, it may be hypothesized that in neurologically intact individuals as well as those anterograde amnesiacs who are able to benefit from Minimal RI any to-be-retained material as well as any type of RI, i.e. diversion RI, will lead to some processing in both hippocampi, thus leading to non-modality specific RI effects.

The story is likely to be different in a patient whose entire left hippocampus has been resected as is the case in patient NM. Given the findings of some activation in the right hippocampus during verbal material presentation in normals ((Kelley et al., 1998; Martin et al., 1997; Golby et al., 2001). Golby et al., (2001), as well as some spared verbal memory function left temporal lobectomy patients (c.f. Pillon et al., 1999), it appears likely that the right hippocampus can process verbal material in such patients, too, at least to some extent. Indeed, the recent demonstration by Richardson et al. (2003) of a *reorganization* of verbal function to the right medial temporal lobe in patients with left hippocampal sclerosis, suggests that the right hippocampus in some left temporal lobectomy patients may be somewhat capable of processing verbal information (see also Herman, 2004). Nonetheless, and assuming for a moment that in the case of NM the right hippocampus has indeed taken over some verbal memory function, there is still the possibility that the right hippocampus alone, may not be able to process verbal information as easily as it can process nonverbal material.

Thus the processing of verbal material may be more effortful than that of nonverbal material for the right hippocampus, which is alleged to be specialized for the processing of *nonverbal* information in the normal brain.

It may hence be speculatively hypothesized that in a word list memory paradigm such as the present one, patients such as NM may benefit from Minimal RI because the right hippocampus only has to process the-to-be retained verbal material. In fact, given that NM's proportion retention following the second Minimal RI Condition was well within the normal range (as indicated by the control data), it appears that NM's right hippocampus may be able to process verbal material remarkably well (though as argued above it cannot be excluded at this point that NM's performance may have been improved by some subvocal rehearsal during the second Minimal RI delay).

When there is RI, the processing of verbal to-be-retained material may become somewhat more demanding for the right hippocampus as it has to deal with further incoming material, a task that in the normal brain is likely to be shared by the two hippocampi. Indeed, the finding that NM's delayed recall following RI was substantially lower than the control mean suggests that NM may be more susceptible to RI than are neurologically intact individuals of similar age and education. Nonetheless, given the fact that individuals with an intact right and left hippocampus (i.e. neurologically intact individuals) show some susceptibility to RI, it would not be surprising to find that only one hippocampus, that is not specifically designed for the processing of verbal material to begin with, should be detrimentally affected by RI.

Furthermore, given the right hippocampus' specialization for nonverbal material processing, it could be argued that the right hippocampus is more able to deal with nonverbal than verbal RI because the additional processing required by the nonverbal RI may be less effortful than that required by verbal RI. Hence, when RI is nonverbal, the processing of verbal to-be-retained material may still take place, albeit to a lesser extent than when there is no RI, thus resulting in lower yet not severely impaired delayed recall. In contrast, when there is verbal RI, the processing of the to-be-retained verbal material as well as the new verbal material may become too effortful for the right hippocampus, resulting in very poor or even no delayed recall of the to-be-retained material, as observed in patient NM.

As stated above, such hypothesis is speculative only at this point. Indeed, in order for such hypothesis to be sustained, the current pattern of results would have to be obtained in a larger sample of left temporal lobectomy patients [10]. If such is the case, one could further consider a correlational analysis between (a) the magnitude of the benefit of Minimal RI and the volume of the remaining left hippocampus (if some hippocampus remains, unlike in NM) as well as between (b) the difference in delayed recall following verbal RI and nonverbal RI and the volume of the remaining left hippocampus. Based on the present findings, the underlying predictions could be that the more spared and intact left hippocampus there is, the better verbal retention may be after RI. Such in turn would lead to the prediction of a negative correlation between the benefit of Minimal RI and the degree of spared left hippocampus in such patient group.

With respect to the difference between delayed recall following verbal and nonverbal RI, a possible prediction could be that there may be a negative correlation between the volume of spared and intact left hippocampus and the difference in delayed recall following verbal and nonverbal RI. Thus, a patient with a largely spared left hippocampus may show no or only a slight effect of modality of RI

[10] Such experiment is currently being set up.

because the verbal to-be-retained material and the verbal RI could be processed partially by the spared left hippocampus. On the other hand, a patient with very little spared or no left hippocampus (such as NM) may show a relatively large effect of modality of RI because as speculated above, the right hippocampus, which is not specialized for verbal material, may have to process both the to-be-retained verbal material and the verbal RI.

It would also be interesting to study the effects of verbal and nonverbal RI on to-be-retained *nonverbal* material in left temporal lobectomy patients in order to examine whether such patients show (a) a benefit of Minimal RI and (b) a modality specific effect of RI during retention of their spared nonverbal memory function. Thus, while the right hippocampus is fully intact in left temporal lobectomy patients, and while they show normal nonverbal memory, there is the possibility that any reorganization of verbal function in the right hippocampus may lead to greater interference effects during the processing of nonverbal material also. Indeed, in a commentary on the aforementioned fMRI findings by Richardson et al.' (2003), Herman (2004) questions whether '*if the right hippocampus becomes a mediator of verbal information, is there a "crowding out" of its presumed ability to mediate retention of nonverbal material?*' (p. 139).

Moreover, it may prove interesting to study the effects of verbal and non-verbal RI on both verbal and non-verbal to-be-retained material in both a left temporal lobectomy and a right lobectomy sample.

Furthermore it may also be interesting to run an fMRI version of such study to examine activation patters in the left and right hippocampi in both patient groups as well as neurologically intact individuals.

One further finding specific to patient NM should be pointed out:

Given NM's normal performance on neuropsychological tests of verbal memory, including verbal memory following a filled delay interval, as well as his apparent normal day-to-day verbal memory, the present finding of poor delayed word recall following RI, in particular, verbal RI, was rather conflicting.

However, it is possible that the present study revealed a particular deficit in NM that may not be very apparent in the day-to-day life and standard neuropsychological assessment. First of all, it is possible that NM has a greater difficulty with the retention of unrelated words than a prose passage, for which he showed normal delayed recall in the pre-experimental assessment, or the retention of day-to-day verbal material. Secondly, it should be pointed out that during in the pre-experimental assessment immediate prose memory was followed by a nonverbal task (abstract figure and copy). Thus, unlike in the present experiment to-be-retained material was not immediately followed by material of the same modality which could have given the memory system some chance to process the material in the absence of modality specific interference, i.e. akin to the findings of a benefit of delayed RI reported in Chapters 5 and 6. Such may also explain the normal delayed verbal memory index revealed during NM's most recent neuropsychological assessment. Indeed, tests of verbal learning in the WMS-III are never followed directly by a further verbal test.

8.4.9 Conclusion

The present pilot study provides some tentative evidence for a benefit of Minimal RI as well as a modality specific susceptibility to RI in a word list learning paradigm in a left temporal lobectomy patient. The modality specific effect of RI was interesting given the lack of such effect in the neurologically intact population and anterograde amnesiacs. Nonetheless, such findings do not necessarily conflict. Indeed it is very tentatively suggested that the apparent larger effect of verbal than nonverbal RI revealed in the present study may be the product of an excess in cognitive load within an already overloaded right hippocampus. However such hypothesis is speculative only at present and awaits the findings of a larger scale experiment on a sample of left temporal lobectomy patients.

Chapter 9: General Discussion

9.1 Thesis aims

Chapters 2 to 8 of this thesis document and discuss a series of experiments designed to further examine and test the *retroactive interference* hypothesis of forgetting in anterograde amnesia that tentatively emerged from RI research by Cowan et al. (2004) and Della Sala et al. (2005). Each of these experiments was designed and run to tackle at least one of four main aims/questions of this thesis:

1.) Which precise conditions are required for a benefit of Minimal RI to arise in anterograde amnesiacs? And thus how modality/material specific is RI.
2.) Which cognitive processes underlie the benefit of Minimal RI in anterograde amnesiacs?
3.) What are the effects of RI and Minimal RI on memory in neurologically intact individuals, both young and elderly? (as questions 1 and 2)
4.) What are the neural correlates of the benefit of Minimal RI?

This final chapter will be organized in the following way:

Firstly each of the aims/questions will be addressed individually: The main experimental findings relating to each aim will be summarized (please see experiment discussions in Chapters 2-8 for details) and discussed with respect to the question asked (note that question/aim 3 will be mainly discussed alongside questions 1 and 2).

Subsequently, the experimental work and its findings will be discussed and integrated within the broader context of the thesis in order to provide a *diversion RI hypothesis of forgetting*.

The chapter will be concluded via a discussion of the implications of the present thesis research as well as future directions.

9.2 Summary of the results and discussion of the main aims

9.2.1 The nature of RI – Similarity or Diversion RI – Patients and normals Chapter 2 (review of early RI research and findings), Experiment 1, Experiment 2(a) and Experiment 2(b)

As discussed in **Chapter 2** Müller and Pilzecker (1900) coined the term Retroactive Interference and defined it as interference by general mental effort, more latterly defined as 'diversion RI' in this thesis and by Dewar et al. (in press). Nonetheless, a glance at a modern psychology textbook or even modern research article in the field provides a somewhat different definition of RI. Indeed, RI is nowadays defined as the interference of to-be-retained material by highly similar subsequent material. Nonetheless, Müller and Pilzecker's (1900) RI chapters (see Chapter 2) reveal somewhat impressive and fascinating early experimental designs and findings, which cannot be ignored in contemporary psychology. Indeed, while their findings and hypotheses were to some extent based on experimental manipulations that could not exclude all possible alternative hypotheses (e.g. modality specificity), **Experiment 1 (Chapter 3)**, set up to minimise such alternative hypotheses, strongly suggests that, in neurologically intact individuals RI need not be material or even modality specific to have a detrimental effect on retention of to-be-retained material. Thus, all diversion RI had to be minimised in order for neurologically intact individuals to benefit from Minimal RI.

Given the strong evidence for an effect of diversion RI on retention of to-be-retained material in neurologically intact individuals, the question of whether or not such may also be the case in anterograde amnesia, albeit to a greatly increased extent, was of great interest.

Interestingly, the results of **Experiment 2(a)** strongly suggest that *diversion* RI is also likely to play a role, albeit a more substantial role, in the severe forgetting of at least some patients with anterograde amnesia due to focal brain injury: Indeed, not only modality or material specific RI but all *diversion RI* had to be minimized in order for the majority of patients to show improvements at delayed recall. Interestingly the findings of 0 proportion retention following the ignore tones delay interval in the majority of patients in **Experiment 2(b)** further suggest that *any* subsequent material or task, even if not mentally effortful, may need to be minimised for patients with anterograde amnesia to show memory improvement. Thus, the definition of diversion RI may need to be modified to encompass not only subsequent mental effort, as defined by Müller and Pilzecker (1900), but any subsequent material, whether mentally effortful or not. However as discussed in Chapter 4 (see discussion of Experiment 2(b)) such finding may have been the result of some flaws in the Experiment meaning that further research on both amnesia patients and neurologically intact individuals is required before changes to the definition of diversion RI should occur.

Irrespective of whether or not such redefinition will be required, the findings of Experiment 2(a) are very interesting with respect to previous interference research on patients with amnesia, i.e. PI (c.f. Shimamura et al., 1995; Baldo and Shimamura, 2002), in which *similarity* of to-be-retained and interfering material has been assumed to be the key player in forgetting.

As argued with respect to the findings of both similarity RI and diversion RI in normals, such differing findings and interpretations within the amnesia literature are not necessarily irreconcilable. Indeed, as discussed in Chapter 4 and will be discussed in more detail later in the discussion, it is likely that both types of RI susceptibility can emerge in patients with anterograde amnesia; which one emerges depending most probably on the lesion site and specific cognitive damage of the individual patient.

Overall then, the research on the modality/material specificity of RI reported in this thesis strongly highlights that all RI must be minimised in order for patients with anterograde amnesia and neurologically intact individuals to show facilitated proportion retention at delayed verbal recall. Such finding thus strongly suggests that *diversion* RI plays a substantial role in both normal as well as pathological forgetting.

9.2.2 The role of RI – Cognitive processes underlying the benefit of Minimal RI (Experiment 3, Experiment 4(a), Experiment 4(b), Experiment 5, Experiment 6)

In order to examine the potential cognitive process(s) underlying the benefit of Minimal RI in patients with anterograde amnesia as well as neurologically intact individuals, a series of experiments were run (Experiment 3a, Experiment 4(a), Experiment 4(b), Experiment 5, Experiment 6).

The results of **Experiments 3 – 4(b)** indicated that some patients with anterograde amnesia due to focal brain injury were able to benefit from Minimal RI even if such was followed by RI. Given that STM maintenance would have been very difficult during such post Minimal RI interference (see Chapter 5), the finding of such 'extended' retention following Minimal RI tentatively suggests that the cognitive process underlying the benefit of Minimal RI may be some uninterrupted LTM *consolidation*, at least in some patients with anterograde amnesia. Such tentative finding and interpretation is somewhat interesting as it suggests that some patients with anterograde amnesia are in fact able to *consolidate* new information, at least to some extent, under conditions of Minimal RI.

However, the results emerging from Experiments 3 – 4(b) were based on a small number of trials and on post Minimal RI interference that was not always entirely consistent across all participants and trials (see Chapter 5), meaning that such findings and the resulting consolidation hypothesis had to be treated as tentative.

Nonetheless, the more tightly controlled **Experiment 5** strongly supported the tentative consolidation hypothesis of the benefit of Minimal RI: Indeed this experiment revealed that patients with aMCI were able to retain word list material even in the presence of RI *if* the temporal onset of such RI was delayed.

As argued in Chapter 6, if the benefit of Minimal RI in these patients had underlain STM maintenance of some kind, temporal onset of RI should not have had an effect on later retention of to-be-retained material because RI should have interrupted such maintenance irrespective of whether it occurred at the start or the end of the delay interval.

Moreover, the specific finding of an effect of temporal onset of RI, i.e. the elucidated *temporal gradient of RI*, in the patients with aMCI as well as the neurologically intact elderly and young participants in **Experiment 5** and **Experiment 6** greatly augments the evidence for a consolidation hypothesis of the benefit of Minimal RI in both normals and patients, at least those with aMCI: Indeed, the elucidated 'behavioural' temporal gradient is in close accordance with the theories and findings by both Müller and Pilzecker (1900) and contemporary neuroscience (c.f. Dudai, 2004) of a time based consolidation process (in the normal brain), in which information is increasingly strengthened and rendered resistant to RI as a function of time. Thus, the later the RI, the less susceptible the to-be-retained material and hence the higher the probability that such to-be-retained material will be retained.

Overall then, it appears from Experiments 3 – 6 that 'uninterrupted' consolidation is a highly likely candidate regarding the cognitive process(es) underlying the benefit of Minimal RI in both neurologically intact individuals as well as at least some patients with anterograde amnesia.

However it is important to underline that such 'uninterrupted' consolidation hypothesis of the benefit of Minimal RI may be too general. Indeed, the findings of initial apparent consolidation yet a lack of retention following longer delay intervals in the focal brain injury patient PB as well as some of the anterograde amnesiacs participating in Experiment 4(b) indicates that Minimal RI may not allow for sufficient consolidation for the to-be-retained material to become lasting LTM. Given the fractionation of synaptic (fast) and systems (slow) consolidation within neuroscience models of LTM formation (c.f. Dudai, 2004), it is possible that in such patients both types of consolidation are greatly impaired and that only synaptic consolidation is ameliorated under conditions of Minimal RI. However given the hypothesised short lasting nature of synaptic consolidation (Dudai, 2004) the memories, temporarily strengthened during Minimal RI and possibly also thereafter, may be displaced or lost, possibly akin to in patients presenting with accelerated forgetting or Long Term Amnesia (Kapur et al., 1997; O'Connor et al., 1997; Zeman et al., 1998; Blake et al., 2000; Mayes, 2003).

It may thus be necessary to change 'uninterrupted' consolidation hypothesis of the benefit of Minimal RI to 'uninterrupted' *synaptic* consolidation hypothesis of the benefit of Minimal RI in the future. However, more research containing various delayed recall as well as assessments of recent premorbid retrograde memory, postulated to underlie systems consolidation is necessary to test such specific hypothesis. It will also be necessary to run such study on normals in order to examine whether or not Minimal RI has a long lasting beneficial effect on memory in individuals in whom both types of consolidation are intact.

In conclusion, the aforementioned experiments and their results suggest that the benefit of Minimal RI is very likely to underlie uninterrupted consolidation in at least some patients with anterograde amnesia as well as neurologically intact individuals. However, Minimal RI may not lead to lasting LTM benefit. Thus it is very tentatively suggested that Minimal RI may allow for improved synaptic (i.e. short term) consolidation but not for improved systems consolidation. However, future research is required to test such tentative prediction.

9.2.3 The role of RI in ageing (Experiment 6 and Experiment 5)

Experiment 6 was set up to examine whether or not elderly people differed from young people with respect to the benefit of Minimal RI as well as with respect to the temporal gradient of RI. Such was primarily done in order to elucidate whether or not the increased susceptibility to RI observed in the elderly with aMCI was an exaggerated degree of potentially normal age-related increases in diversion RI susceptibility, or whether it was qualitatively distinct from normal age-related memory decline. While overall Experiment 6 did reveal lower memory performance in the elderly than the young, no specific significant differences between the elderly and young sample were obtained for the benefit of Minimal RI or the temporal gradient of RI. Such results suggest that normal age-related memory decline is unlikely to be the cause of an increased susceptibility to RI. Cognitively then, normal age-related 'anterograde amnesia' appears to be qualitatively different from that shown in patients with aMCI, a finding that could prove interesting both theoretically and practically (see later part of this discussion on implications of this research).

9.2.4 Neural correlates of the benefit of Minimal RI and the susceptibility to RI (Experiment 7, 8 & 9)

The original studies by Della Sala et al. (2005) and Cowan et al. (2005) very tentatively suggested that an intact temporal lobe/hippocampus may be required for a benefit of Minimal RI to emerge in patients with anterograde amnesia. Given the strong and more recent behavioural evidence for a *consolidation* hypothesis of RI (Experiments 3 – 5), and the strong postulated link between consolidation and the temporal lobe, in particular the hippocampus (c.f. Squire, 1992; Squire and Alvarez, 1995; Alvarez and Squire, 1994; Squire et al., 2004), such tentative hypothesis in fact appeared somewhat apt.

The first aim was to examine whether or not Cowan et al.'s (2004) finding of no benefit of Minimal RI in temporal/hippocampal patients would hold in a larger sample. **Experiment 7** showed clearly that such initial finding did not hold. Indeed all four patients with structural temporal/hippocampal lesions were able to benefit from Minimal RI. Nonetheless there was potential evidence that hippocampal lesions may lead to a reduced benefit. The aim of **Experiment 8** was hence to further explore the possible role of the hippocampus and its volume in the benefit, and degree of benefit, of Minimal RI in a sample of patients with aMCI. The study revealed an association between hippocampal volume and the degree of benefit from Minimal RI in the patient sample, with patients with larger hippocampi benefiting more from Minimal RI than patients with smaller hippocampi.

However, no such association was observed in the control group. Moreover and importantly, no difference emerged in hippocampal volume between the patient and the control sample despite the marked difference in the degree of the benefit.

Given the findings of a significant positive correlation between hippocampal volume and proportion retention following RI in the controls, it is thus tentatively suggested that the apparent hippocampal volume – benefit of Minimal RI association in the aMCI group may have underlain 'pre-morbid' differences in proportion retention (see Chapter 6 discussion for details). Thus, hippocampal volume may determine capacity, but not RI susceptibility meaning that a patient who is susceptible to RI and has a relatively large hippocampus will show higher retention when there is no RI than a patient who is susceptible to RI and has a relatively small hippocampus. Whether or not such hypothesis may extend to aMCI patients or indeed focal brain injury with hippocampal atrophy, i.e. the more atrophy the less retention capacity, cannot be inferred from these results. However, the speculative findings of a reduced benefit of Minimal RI in the two hippocampal patients in **Experiment 7** may provide some very tentative evidence for such possibility. If such were the case it could be argued that patients with AD who present with marked hippocampal atrophy and showed no benefit of Minimal RI in the pilot work by Della Sala et al. (2005), may no longer have sufficient capacity to process information even when there is no RI.

Experiment 9 was primarily run in order to examine whether a left temporal lobectomy patient whose entire left hippocampus had been surgically resected would benefit from Minimal RI. Secondly, given the modality specific memory deficits that can follow a temporal lobectomy (verbal following resection of the left hippocampus and nonverbal following that of the right hippocampus), yet the lack a of modality specific RI effects in both neurologically intact individuals and anterograde amnesiacs, it was also of interest to examine whether such patient may show a modality specific RI effect in a verbal memory paradigm.

The results suggest that the left temporal lobectomy patient was indeed able to benefit from Minimal RI. Secondly, the results suggest a modality-specific effect of RI, at least in the patient tested in Experiment 9: While verbal RI lead to 0 proportion retention, nonverbal RI did allow for some retention, even if not as much as Minimal RI. While based on a single case only, it was tentatively hypothesized that the apparent modality specific RI effect may be explained by differences in mental effort required for the processing of verbal and nonverbal RI by the right hippocampus (see discussion of Experiment 9). Nonetheless, a larger scale study is necessary in order to sustain such hypothesis. Within the general frame of Chapter 8, the study demonstrated that an entire hippocampus was not required for a benefit of Minimal RI to emerge for verbal retention.

Overall, it appears from the three Experiments that, as speculated by Della Sala et al. (2004) and Cowan et al. (2005), the *hippocampus* is a likely *neural correlate* of the *benefit of Minimal RI*. However, the findings of Experiments 7 and 9 clearly show that the emergence of a benefit of Minimal RI in patients with anterograde memory impairment does not require a structurally *fully* intact hippocampus. Nonetheless given the findings of an association between hippocampal volume and the degree of benefit of Minimal RI in Experiment 8, it is tentatively suggested that patients with substantial bilateral hippocampal atrophy may benefit less than patients without or less hippocampal atrophy.

9.3 The RI hypothesis of forgetting – a proposed model

The above summary and discussion of the findings relating to each of the main aims/questions indicates that all four main questions of this thesis were answered, at least to some extent - future research will undoubtedly provide further and even possibly new or different answers.

Nonetheless, while these four questions differed somewhat, they were all asked in order to shed more light onto a *single* RI hypothesis of forgetting, and thus each formed a piece of the same puzzle. It is thus of great importance to not only discuss the findings within the boundary of the four aims, but to integrate them in order to try to form a more complete picture of the puzzle.

By doing so an RI hypothesis of forgetting based on both the cognitive as well as the neural correlates findings will be proposed subsequently:

[11]Firstly, despite the common negligence of Müller and Pilzecker's (1900) original RI research and definition (i.e. diversion RI) in Psychology today, it is highly evident from the review of their work (Chapter 2) and present research (Chapters 3 and 4) that such factor does play a considerable role in human memory. While such 'rediscovery' of RI does not signify the demise of similarity RI, it does call for a revision of the current RI theory.

A potential revision that integrates both diversion as well as similarity RI in neurologically intact people as well as anterograde amnesiacs is proposed by us (Dewar et al., in press). It is suggested that *both* diversion and similarity RI exist (as proposed by Skaggs in 1925) but that they differ (a) in terms of the cognitive processes they affect (as proposed by Skaggs in 1933) as well as (b) potentially in terms of the neural substrates they have an effect on (see Figure 9.1).

It is proposed on the basis of the old (see Chapter 2) and new research (Chapter 7) reported within this thesis, that in neurologically intact people diversion RI affects the consolidation stage of memory. Given the frequent association of consolidation and the hippocampus it is further suggested that such interference occurs within the hippocampus.

Similarity RI, on the other hand is likely to affect retrieval processes. Due to its close resemblance to PI and the association between PI and frontal lobe activity, it is tentatively proposed that similarity RI affects frontal lobe processes, though this warrants further research. Furthermore, while diversion RI can occur independently of similarity RI, the reverse does not seem plausible. Hence, any interpolated material/task, including similar material, causes diversion RI and will therefore affect consolidation. The memory decrement induced by interpolation of similar material is thus likely to be the cause of an additive effect of diversion RI and similarity RI, and hence the cause of interference at the consolidation and retrieval stage. Therefore, while minimising similarity RI should only allow for uninterrupted retrieval, minimising all RI should allow for both uninterrupted consolidation and retrieval.

[11] Part of this text features in Dewar et al. (in press)

Further similarity RI studies based on Müller and Pilzecker's (1900) delayed RI paradigm may allow for a teasing apart of the similarity and diversion RI effects caused by similar interpolated material (i.e. due to a reduced susceptibility to diversion RI when interpolation of subsequent material is delayed) and hence an elucidation of the true magnitude of the actual similarity RI effect.

It is further proposed that the memory deficits in at least some amnesiacs may be the result of a severely heightened susceptibility to the diversion and/or similarity RI (and PI) experienced to a mild extent by all neurologically intact people. Patients with specific damage to the retrieval system (as may be the case in patients with lesions to the frontal lobes) may thus present with a severely heightened susceptibility to similarity RI and PI (c.f. Shimamura et al., 1995; Baldo and Shimamura, 2002) and 'normal' susceptibility to diversion RI. On the other hand, patients with specific damage to the consolidation processes or to the mechanisms that feed into such processes may present with severely heightened susceptibility to diversion RI.

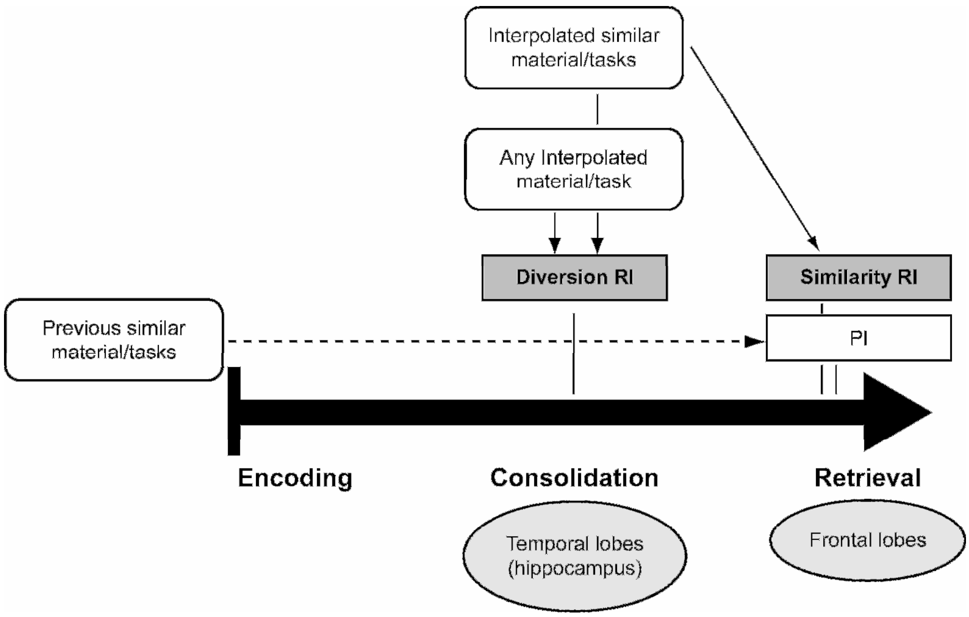


Figure 9.1. Long-term memory processes affected by interference. The above diagram is an illustration of the potential effects of diversion RI and similarity RI on the normal memory process. The horizontal thick arrow depicts the cognitive processing of a to-be-retained stimulus from its initial encoding to its storage and last to its retrieval. Material/activity interpolated between the encoding and retrieval of

the stimulus has a detrimental effect at delayed recall of this stimulus caused by interference at its storage and/or retrieval stage. Any interpolated material/activity (diversion RI) affects the consolidation stage (predicted to underlie temporal lobe processes) of the to-be-retained stimulus by interfering with its consolidation process. Interpolated material highly similar to the to-be-retained stimuli further leads to similarity RI and hence also affects retrieval (predicted to underlie frontal lobe processes) of the to-be-retained material (as does PI, caused by similar material occurring prior to encoding of the to-be-retained material). Figure and caption modified from Dewar et al. (in press).

9.4 The *diversion* RI hypothesis of forgetting – a proposed model

Given that the emphasis of this thesis has been on *diversion* RI, it is important to home in on the part of the model depicting diversion RI as well as the cognitive process(es) and neural substrate it is proposed to affect.

9.4.1 A consolidation hypothesis for the susceptibility to diversion RI and the benefit of Minimal RI

Assuming that the benefit of Minimal RI does underlie some uninterrupted consolidation in both normals and patients, it is of great interest and importance to try to understand within both a cognitive and neuroanatomical framework *how* such consolidation is interrupted when there *is* RI, and thus how such consolidation is enhanced when there is no or Minimal RI.

Two hypotheses may be postulated, one implicating the consolidation system (the hippocampus) itself, the other a system linked with and required by the consolidation system (non-hippocampal structure):

9.4.1.1 Hypothesis implicating consolidation system itself

Patients

Firstly it seems somewhat possible that damage to the consolidation system itself, could lead to a heightened susceptibility to RI. For example, some impairment to this system could render the system unable to simultaneously process as much information, or as many units of information as an intact system, perhaps due to a decrease in necessary resources. Thus, when RI immediately follows presentation of to-be-retained material, resources being used for consolidation of the to-be-retained material may have to be divided for or concentrated on concurrent consolidation of RI material.

If resources are scarce due to impairment to the system such sharing or transfer of resources may lead to none of the material being consolidated and hence very poor delayed recall. However, if RI is delayed, the system may have sufficient time and resources to strengthen the to-be-retained material adequately for it to be stable enough to persist even when resources are divided or transferred to consolidation of the subsequent RI material. Such may explain the results of some extended retention in some of the patients reported in Chapter 5.

Given the notion that memories increase in strength as a function of time in the intact brain (Müller and Pilzecker, 1900; Dudai, 2004; Wixted, 2004), one would predict to-be-retained material to gain in stability and thus in probability of being retained as the delay in RI increases, i.e. as was found in Experiment 5.

While such hypothesis appears to explain and predict the heightened susceptibility to diversion RI as well as the benefit of Minimal RI rather well, it is not directly apparent how such hypothesis may be reconciled with the neuroanatomical data reported in this thesis: Thus while two patients within the focal brain injury research had structural damage to the hippocampus, the residual patients who showed apparent susceptibility to diversion RI had somewhat diverse lesion sites (parietal, thalamic, temporal, hippocampal, frontal) (See Experiment 2(a) and Experiment 7). Moreover, the aMCI sample in Experiment 5 did not show any reduction in hippocampal volume when compared to an age and education matched control group, yet presented with significantly greater susceptibility to RI than the latter.

Nonetheless, as discussed in Chapter 8 (Experiment 8), functional imaging as well as molecular research suggests that the earliest changes within the brain, and more precisely the hippocampus and related structures, of AD and aMCI patients are likely to be of the *functional* as opposed to *structural* type. While such findings cannot be utilised directly to support the here-proposed consolidation hypothesis of diversion RI, they do suggest that such consolidation hypothesis may not be implausible. The changes in hippocampal activation during learning in aMCI in particular (e.g. Dickerson et al., 2005; Mondadori et al., 2006; Machulda et al., 2003; Celone et al., 2006) provide very tentative evidence that there may be a functional impairment in consolidation, perhaps due to a reduction in resources, that could be related to a heightened susceptibility to diversion RI. However, such argument is very tentative at this stage and will need to be examined thoroughly via an fMRI RI study, in which hippocampal activity should be compared between patients with aMCI and controls under both Minimal RI and RI.

Nonetheless, even if the RI susceptibility (and the benefit of Minimal RI) in aMCI could be explained via a functional impairment within the hippocampus, and thus within the consolidation system, the question of how such susceptibility could arise in the focal brain patients without hippocampal impairment would still be left unanswered.

While unlikely it could be postulated that perhaps such patients did have some hippocampal impairment.

Firstly, it could be questioned whether at least some of the patients entering Experiment 7 could have also had very subtle undetected lesions to other regions of the brain, perhaps including the hippocampus. Indeed the majority of the patients with non-temporal/hippocampal damage had suffered closed head injuries, which frequently result in focal damage as well as *further diffuse* damage caused by the brain moving back and forth inside the skull during the impact. Secondly, even in the absence of any structural damage to the hippocampus, hippocampal impairment may have still been present albeit of the functional type. Evidence for such latter possibility can be gleaned from recent fMRI research by Caulo et al. (2005) on a patient with Wernicke-Korsakoff syndrome with no evident structural damage to the medial temporal lobe. The study showed that in contrast to controls, no hippocampal activation was present in this patient during a task requiring the memorization of presented faces. In line with such finding the patient also performed poorly on a subsequent recognition task. Nonetheless, behavioural as well as other brain activation provided evidence that the patient attended to the stimuli meaning that the findings of hippocampal inactivation could not be simply explained by a failure to attend to the faces. Thus, such study provides evidence that functional hippocampal impairment can be present in a patient showing no apparent structural damage to the hippocampus. This in turn highlights the apparent necessity to implement fMRI in the future RI research on focal brain injury patients as well. Indeed, Maguire et al. (2001; 2005) highlight that the use of both MRI and fMRI is also of great importance in research on amnesic patients with structural hippocampal damage. They underline the fact that MRI alone cannot provide any information about potential spared functional ability of the structurally damaged hippocampus by reporting hippocampal activation during a memory retrieval paradigm in one patient with bilateral hippocampal structural damage but not in another patient with similar structural damage.

While there is little concrete neuroanatomical evidence at present for a diversion RI hypothesis based on the consolidation system/the hippocampus itself, it is possible that future functional research may provide the evidence required to sustain such specific diversion RI hypothesis of forgetting in anterograde amnesia.

Neurologically intact

A diversion RI hypothesis may also be postulated for forgetting in the neurologically intact population. While no reduction in available resources would be assumed in the intact consolidation system, it is nevertheless possible that such resources are limited and hence that the input of RI immediately following input of to-be-retained material would lead to less resources being available for the consolidation of the to-be-retained material (see also Wixted, 2004 for a discussion). Of course the presence, and *immediate* presence, of RI is the norm in everyday life meaning that the intact consolidation system must be highly capable of processing various units of information concurrently. Nonetheless, even a capable system with sufficient, yet not unlimited, resources may still perform better if it can focus its efforts on only a limited amount of information. Thus, Minimal RI in neurologically intact individuals may lead to higher retention of to-be-retained material because the consolidation system is able to focus on such material only. Moreover, the longer time the system has for such focused consolidation, the stronger and thus less susceptible to later resource sharing by RI such memory is likely to become. Such consolidation hypothesis could thus not only explain the finding of a significant benefit of Minimal RI in neurologically intact individuals (i.e. Experiment 1 & Experiment 6 as well as in the controls of several of the here-reported studies, and Müller and Pilzecker's (1900) experiments), but also the finding of a temporal gradient of RI (Experiment 6 and Müller and Pilzecker's (1900) and Skaggs' experiments).

While the cognitive support for such specific diversion RI hypothesis appears strong, functional imaging support is necessary in order to provide evidence for the neural correlates predictions of such specific hypothesis. A possible paradigm could be one akin to Experiment 6, in which hippocampus activation could be compared for RI and no RI as well as for different RI temporal onset times, the underlying prediction being that Minimal RI and delayed RI may be less effortful for the hippocampus thus, possibly resulting in less activation.

9.4.1.2 Hypothesis implicating a system linked to consolidation system

Patients

There is also the possibility that the consolidation system itself is (largely) spared in amnesic patients who benefit from Minimal RI and that the RI susceptibility is the product of damage to a system linked to the consolidation system. For example it could be argued that a system required for the filtered and organised input of incoming information into the consolidation system may be impaired. Such impairment could mean that too much material is entered into the consolidation system at the same time with the potential consequence that the system is overloaded and so cannot successfully consolidate to-be-retained material. Note, that as in the above hypothesis any, i.e. diversion RI would be predicted to lead to such effect.

In the absence of RI, or if RI is delayed such impairment of a filter system may not greatly matter as only the to-be-retained material would be entered into the consolidation system, which could then proceed with its task of strengthening the to-be-retained material. With respect to the neural correlates of such damage it could be argued that all of the somewhat wide raging lesioned brain structures reported in the patients in Experiment 8 may play a role in such pre-consolidation processing. Thus damage to any of these structures may lead to a heightened susceptibility to RI. With particular respect to the patients with aMCI in Chapter 6 it could be argued that the reduction in superior temporal pole volume may be a neural correlate of such pre-consolidation system (though see discussion of Experiment 8).

While such hypothesis could certainly account for the benefit of Minimal RI per se, it may not provide a very good account for the findings of a steep temporal gradient in the patients with aMCI (Experiment 5): Unless in the normal memory system such temporary storage and filter system maintained RI for a long period of time prior to feeding it into the consolidation system, one would assume that a delay in RI onset of a few minutes should be more than sufficient for the patients' consolidation system to strengthen to-be-retained material to the same extent as in normals. One would thus also predict the temporal gradient of RI to parallel that of the neurologically intact group. However, Experiment 5 showed that while retention was improved following a three and a six minute delay in RI onset (the Mid RI Condition), there nevertheless was a large difference in proportion retention as well as the temporal gradients between the aMCI patients and controls.

However, such argument does not necessarily make the 'filter system' consolidation system hypothesis of RI redundant. Indeed, it is not known, as yet, whether such a steep temporal gradient of RI is also observed in other, perhaps focal brain injury, patients who benefit from Minimal RI. Experiments 3 – 4(b), for example, indicated that some patients could consolidate some to-be-retained material when RI did not occur until after 10 minutes. However, as no shorter delays in RI onset time were applied it is not known whether or not their retention would have been substantially lower following an RI onset time of say three minutes.

It will thus be of great interest to run Experiment 5 on other, perhaps focal brain injury patients, as well in order to possibly shed more light on the underlying cognitive causes of the apparent RI consolidation hypothesis.

Normals

If there indeed exists a filter system that temporarily holds information and feeds this into the consolidation system in processable units, then one would assume that such system should be intact in neurologically intact individuals and thus not overload the consolidation system with RI. It thus appears somewhat difficult to account for the RI susceptibility and the benefit of Minimal RI in normals via such a filter hypothesis.

Future research, in particularly that involving functional imaging as well as the investigation of a temporal gradient in focal brain injury patients is necessary to provide sound evidence for either or these two hypotheses.

9.4.1.3 Synaptic and systems consolidation

When homing in on the diversion RI aspect of the overall RI model proposed above it also appears somewhat important to consider the two types of consolidation that feature within models of memory within neuroscience: synaptic consolidation, the fast type of consolidation postulated to take place in the hippocampus, and systems consolidation, the slower type of consolidation, hypothesised to take place in between the hippocampus and the neocortex (c.f. Dudai, 2004).

Indeed, as discussed in Chapter 1, RI-unrelated research on accelerated forgetting in patients (Kapur et al., 1997; O'Connor et al., 1997; Zeman et al., 1998; Blake et al., 2000; Mayes, 2003) has already provided some initial *neuropsychological* evidence for the existence of such two types of consolidation, thus indicating that their inclusion in cognitive/neuopsychological models of memory is somewhat feasible.

As discussed in Chapters 5 and 6, it appears that while Minimal RI does indeed appear to allow for some consolidation, the retained material may not be available after a longer period, as was for example found in the single case PB. In order to account for such finding, the fractionation of consolidation into synaptic and systems consolidation within neuroscience is thus adopted within the proposed model of diversion RI. Such is depicted in Figure 9.2.

It is tentatively proposed that synaptic and systems consolidation are both impaired in patients with anterograde amnesia (i.e. unlike in accelerated forgetting where only systems consolidation appears to be impaired). While synaptic consolidation may still be able to function to some extent when there is no RI, systems consolidation may either not be facilitated by Minimal RI or may no longer function, irrespective of whether there is diversion RI or Minimal RI. In fact, the presence of temporally graded RA in most patients with anterograde amnesia suggests that the latter possibility may be more likely.

It thus cannot be inferred whether or not diversion RI may affect both types of consolidation in the normal brain, and hence whether or not Minimal RI may allow both for a benefit after a short delay of a few minutes and a benefit after a longer delay of say a few days or weeks. It will thus be of great interest to investigate proportion retention of material presented prior to RI and Minimal RI at multiple instances, ranging from minutes to days and possible months in neurologically intact individuals.

It will also be very interesting to run such study on patients with anterograde amnesia in order to examine whether indeed all patients who benefit from Minimal RI only do so for a limited amount of time, or whether perhaps some patients may show longer lasting benefits. It would appear unlikely that the latter could occur in focal brain injury patients presenting with both anterograde amnesia *and* a temporally graded RA. However, it may possible to find such pattern in a focal patient presenting with an isolated anterograde amnesia or indeed patients in the earliest stages of aMCI in which systems consolidation may still function to some extent.

Such predictions depend greatly on whether or not synaptic and systems consolidation are parallel or sequential processes, a question that has not been answered as yet in neuroscience (note that Figure 9.2 depicts these consolidation types as parallel lines for simplicity). For example, if systems consolidation occurs following synaptic consolidation has been initiated and possible completed, the diversion RI that is likely to affect synaptic consolidation is unlikely to also affect systems consolidation. However, if both take place in parallel it is possible that both may be affected by the same diversion RI.

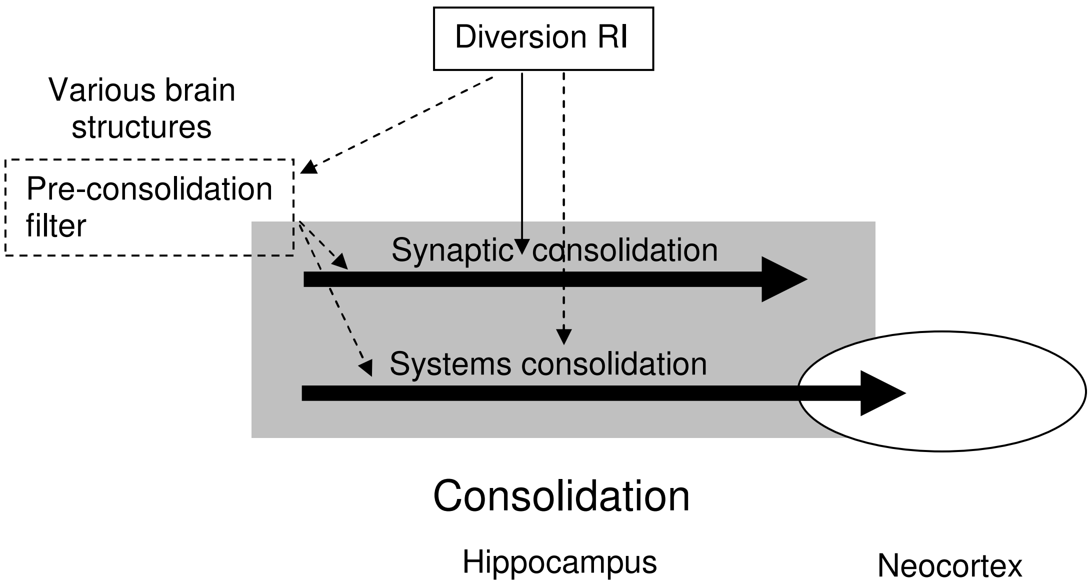


Figure 9.2. A model of diversion RI. In the normal brain it is hypothesised that diversion RI may require hippocampal resources that are also necessary for the processing of to-be-retained material, thus leading to a slight reduction in proportion retention of to-be retained material. When RI is minimal all resources can be focused on the to-be-retained material, leading to a benefit of Minimal RI.

In patients with anterograde amnesia there may be a fault in a pre-consolidation filter meaning that the hippocampus is overloaded when there is RI; or there has been a reduction in hippocampal resources meaning that the hippocampus cannot process to-be-retained material when such limited resources have to be shared. Both would be predicted to lead to very poor retention of to-be-retained material. When there is Minimal RI however, the hippocampus only has to deal with the to-be-retained material, meaning that some consolidation can take place, leading to a benefit of Minimal RI.

In order to account for the apparent LTM retention following a short delay but not a long delay in patient PB and some of the anterograde amnesiacs tested in Experiment 4(b), consolidation has been fractionated into synaptic and systems consolidation, as documented in neuroscience. It is tentatively hypothesised that in such patients both types of consolidation may be impaired but that the synaptic type can still function to some extent when there is no RI, indicating that such process may be vulnerable to diversion RI. Given the temporally graded RA in the majority of anterograde amnesia patients it is hypothesised that systems consolidation may be impaired entirely irrespective of whether RI is present or absent. Nonetheless it is possible that in the normal brain diversion RI affects both types of consolidation (arrows have thus been added from diversion RI to both synaptic and systems consolidation for now) and thus that Minimal RI may lead to both short and long lasting benefits.

9.5 Implications of the present thesis findings and research

Besides offering and examining a new hypothesis of forgetting in anterograde amnesiacs as well as the neurologically intact population, the present research also has some more general implications, both theoretical and applied:

9.5.1 Implications of the present research and proposed model for the standard cognitive model of memory

So far the findings of this thesis have been largely interpreted within a theoretical framework based upon current *neuroscience* models of memory. The main reason for turning to neuroscience for such interpretations is the lack of a psychological/cognitive model that can account for the present findings, in particular the findings of a consolidation deficit. Indeed, as discussed in Chapter 1, current cognitive models of memory are simply based upon a STM and a LTM, with no apparent *intermediate* stage. In line with such 'modal model' of memory, anterograde amnesia is rather simply hypothesized to underlie damage to LTM storage while STM is spared. It is posited that information can thus only be retained for as long as attention keeps it in STM.

The research on anterograde amnesia reported in this thesis (in particularly Experiments 3 to 5) however clearly indicates that such argument cannot be sustained for all patients with anterograde amnesia. Indeed, the majority of patients within the present research were able to retain material even *following* attention diverting RI, *if* the onset of such was delayed, i.e. if it followed a period of Minimal RI. Such findings coupled with the elucidation of a temporal gradient of RI strongly suggests that in at least some patients with anterograde amnesia attention diversion affects not simply STM maintenance, but a *consolidation* process. Moreover, the findings of a temporal gradient of RI in neurologically intact young and elderly further indicate that attention diversion is also likely to affect such consolidation process in neurologically intact individuals, albeit to a much lesser extent.

Such in turn clearly highlights the need to integrate a *consolidation stage* into the current cognitive model of memory.

Moreover, given neuroscience's further fractionisation of such consolidation stage into a synaptic and systems type as well as the tentative evidence for such a split from Experiment 3 and 4(b) and the research on accelerated forgetting, it may be necessary to consider such two types in the future cognitive modeling of human memory as well.

9.5.2 Practical implications of the present research and proposed model

In addition to such apparent theoretical implications the present thesis research also has some potential practical implications.

Firstly, given the remarkable memory improvement observed in some anterograde amnesiacs following Minimal RI in the lab, there may be some potential for future implementation of training techniques based on Minimal RI (i.e. giving patients a period of minimal interference following encoding to allow them the time for thorough consolidation). Indeed family members and carers of some of the patients tested in the here-reported studies as well as in the study reported by Cowan et al. (2004) were greatly surprised by the apparent beneficial effects of Minimal RI, and were very eager to try such 'technique' at home. For example, both PB and his wife commented immediately after his improved retention in Experiment 3 that such findings were 'very encouraging' and that they would try to implement such 'technique' at home also. Moreover, Experiment 2(a)'s very amnesic Patient PG who, much to the amazement of his parents, recalled that there had been a 'blond doctor' whom he 'spoke English to' further tentatively suggests that Minimal RI may not only allow for beneficial effects in laboratory based verbal memory tests, but also possibly in more everyday memory. However, it cannot be told for sure whether such particular recall was the cause of Minimal RI or not. Further research on Minimal RI – related training techniques is thus necessary.

Secondly, the tentative findings of a qualitative RI-related cognitive difference between 'normal' age related decline in memory and the memory decline associated with aMCI (i.e. no apparent effect of ageing on RI susceptibility while such is the case for aMCI) could have some interesting future practical implications. Indeed, given the difficulty in distinguishing the mild changes of very early AD from those associated with early ageing, a technique such as a simple RI/Minimal RI test, which may separate the groups may be very welcome (Morris, 2006). Detection of such very mild changes of very early AD is of course of utmost importance regarding early interventions. However, future research on a larger sample is firstly required in order to examine whether the tentative findings hold and thus whether future resources should be directed at the design of such possible classification tool (see future directions).

Thirdly, given that not all patients with aMCI progress to AD, there is the possibility that the benefit of Minimal RI and/or its degree could be a predictor of progression to AD. Again, future research will be required to indicate whether or not such may be the case (see future directions).

9.6 Future directions

The research reported in this thesis has shed more light on both the role and nature of RI in anterograde amnesia and forgetting in neurologically intact individuals and in doing so has led to the proposal of a diversion RI hypothesis of forgetting. Nonetheless, the research has also led to a wealth of *new* and *unanswered* questions, which will be tackled in the future.

Most of these new and unanswered questions have been highlighted within the individual chapters, as have been potential future studies that could tackle such questions. These are summarised broadly in the subsequent outline of future directions:

- **Functional MRI:** Chapter 8 as well as the above discussion on neural correlates highlights the necessity to implement fMRI in future RI research in order to examine whether or not hippocampal activation during RI and Minimal RI in anterograde amnesiacs may differ from that in neurologically intact individuals even in the absence of any structural damage to the hippocampus in such patients. Such study will help to clarify whether or not the high diversion RI susceptibility seen in some patients with anterograde amnesia with focal brain injury and aMCI can be attributed to (possibly functional) hippocampal impairment or whether the search for neural correlates of such susceptibility must be focused on other structures.

- **Multiple delayed recall sessions:** Chapter 5 as well as the above discussion highlight that in anterograde amnesiacs the apparent LTM benefits of Minimal RI may not be long lived. In order to explain such pattern synaptic and systems consolidation have been implemented within the proposed model of diversion RI. However at present little predictions can be made regarding the specific effects of RI and Minimal RI on such two types of consolidation in either the intact or the damaged brain. In order to do so further research containing both a larger sample of patients as well as neurologically intact individuals and a larger quantity of structured delayed recall sessions is required.

- **Longitudinal study on neurologically intact elderly and aMCI patients:** As discussed in the above practical implications there may be the possibility that an RI-based test could allow for the early detection of the very mild stages of early AD/aMCI as well as potentially differentiate between those aMCI patients who progress to AD and those who do not. In order to examine such possibilities a longitudinal RI/Minimal RI study on a large sample of both patients with aMCI and controls will be necessary.

- **Minimal RI: Minimisation of all new material or attention diverting new material?** As discussed in Experiment 2(b) and in the present chapter it is unclear as yet whether or not all new material or only attention diverting new material has to be minimised in order for anterograde amnesia patients as well as neurologically intact individuals to show any memory improvement. Such question is of theoretical importance: If indeed all material has to be minimised, the original definition of RI as 'mental effort' will need to be redefined as 'any new material/task'. Future research, in which the potential flaws pointed out in Experiment 2(b) are considered and abolished, is thus necessary.

- **Temporal gradient of RI in focal brain injury patients**

As discussed above, it will be of interest to run a delayed RI study such as Experiment 5 on patients with focal brain injury in order to examine whether their temporal gradient differs from that of patients with aMCI. The findings of such research may shed further light of the as yet unresolved question of whether the RI susceptibility in such patients is related to an impairment of the consolidation process itself (in which case the temporal gradient may be akin to that of the aMCI group), or whether it is related to a different system, e.g. a pre-consolidation filter (in which case performance at First RI may be very low but increase sharply after, so that the remaining temporal gradient may be more akin to that of normals).

- **Non-verbal memory**

So far all the research on diversion RI has been conducted on to-be-retained verbal memory only (i.e. word lists or prose passages). However, in order to gain a more comprehensive understanding of the effects of diversion RI on memory in both anterograde amnesiacs and neurologically intact people, it will also be important to examine the effect of diversion RI on nonverbal to-be-retained material. Moreover and in line with the aforementioned practical implications, it will be of further interest to examine the effects of diversion RI on everyday memory (e.g. names of people, recent autobiographical memory) as well as prospective memory.

- **The effects of *Degree* of mental effort of RI on retention:**

On various occasions within this thesis it has been hypothesised that the detrimental effects of diversion RI may be associated with a limit in (hippocampal) consolidation resources: In normals such limit may reflect a ‘normal’ limitation in resources (see also Wixted, 2004) while in patients such limit may reflect a substantial depletion in consolidation resources. It is very tentatively suggested that diversion RI may require resources that would have otherwise been available (in the case of normals) or necessary (in the case of patients) for processing of the to-be-retained material. Furthermore Experiment 9 very tentatively suggests that the amount of consolidation resources required by subsequent information may be related to the mental effort imposed by such information (in this particular case verbal information processing was hypothesised to be more effortful for the spared right hippocampus, thus requiring more resources than nonverbal information processing). It will be of interest to examine whether or not the mental effort of RI may indeed play a role in the proportion retention of to-be-retained material, both in patients and neurologically intact individuals. Depending on the outcome of behavioural research on degree of mental effort such research may also open the door to an fMRI study of this effect.

9.7 Conclusion

The present thesis research ***on the role and nature of retroactive interference in anterograde amnesia*** has provided some very interesting new insight into the recent finding of a substantial memory *improvement* in some patients with anterograde amnesia following *Minimal RI*:

The research demonstrates that in order for a patient with anterograde amnesia to show such memory improvement, *all RI* must most likely be removed.

Moreover and crucially, the reported studies strongly suggest that the demonstrated memory improvement following Minimal RI underlies some *uninterrupted consolidation*. Thus, it strongly appears that at least some anterograde amnesiacs are in actual fact (still) able to *consolidate new information*, but that a *high susceptibility to diversion RI* impairs such process substantially.

Interestingly the research further suggests that a consolidation process is also disrupted to some extent by diversion RI in neurologically intact people, albeit to a much lesser extent.

Last but not least, it is tentatively postulated that some spared, yet not an *entirely* spared hippocampus may be necessary for anterograde amnesia patients to benefit from Minimal RI.

These main findings are of interest for several reasons:

On a practical note, the findings indicate strongly that some patients with anterograde amnesia may be more capable of forming new LTM than previously assumed. Future research on Minimal RI could thus lead to fruitful memory training techniques.

With respect to theoretical implications, the present findings demonstrate that, in striking contrast to the modern psychology definition of RI, yet in line with its original definition, RI need not be similar to the to-be-retained material in order for it to have a detrimental effect.

Moreover and importantly, the present thesis research clearly highlights the necessity for modern psychology to follow in the footsteps of both Müller and Pilzecker (1900) and contemporary neuroscience and (re-)incorporate an intermediate *consolidation stage* into its standard two-stage model of memory,…

…indeed,

'There must be time for nature to do her part. Without appealing to any mystical form of mental or cerebral activity it is clear that a night's sleep may be more effective in fixing a lesson in the memory than continued repetition. Hurry defeats its own end.'

Burnham, 1903, p. 131

References

Abrahams, S., Pickering, A., Polkey, C.E. & Morris, R.G. (1997). Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. *Neuropsychologia, 35*, 11-24.

Aggleton, J.P. & Shaw, C. (1996). Amnesia and recognition memory: A re-analysis of psychometric data. *Neuropsychologia, 34*, 51-62.

Akhtar, S., Moulin, C. J.A. & Bowie P.C.W. (2006). Are people with mild cognitive impairment aware of the benefits of errorless learning? *Neuropsychological Rehabilitation, 16*, 329-346.

Alvarez, P. & Squire, L.R. (1994). Memory consolidation and the medial temporal lobe: A simple network model. *Proceedings of the National Academy of Sciences, USA, 91*, 7041-7045.

Anderson, M.C. & Bjork, R.A. (1994). Mechanisms of inhibition in long-term memory: A new taxonomy. In D. Dagenbach and T.Carr (Eds), *Inhibitory processes in attention, memory and language*. Academic Press , pp. 265-326.

Anderson, M.C. (2003). Rethinking interference theory: Executive control and the mechanisms of forgetting. *Journal of Memory and Language, 49*, 415-445.

Baddeley, A. (1986). *Working memory*. Oxford, Claredon Press, 1986.

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences, 4*, 417-423.

Baddeley, A. (2001). Is working memory still working? *European Psychologist, 7,* 85-97.

Baddeley A. & Hitch, G.J. (1974). Working memory. In GA Bower (Ed.), *The Psychology of Learning and Motivation*. Academic Press, pp. 47-89.

Baddeley, A., Thompson, N. & Buchanan, M. (1975). Word length and the structure of short-term memory. *Journal of Verbal Learning and Verbal Behaviour, 14*, 575-589.

Baddeley, A. & Vargha-Khadem, F. & Mishkin, M. (2001). Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *Journal of Cognitive Neuroscience, 13*, 357-369.

Baddeley, A. & Wilson, B.A. (2002). Prose recall and amnesia: implications for the structure of working memory. *Neuropsychologia, 40*, 1737-1743.

Baldo, J.V. & Shimamura, A.P. Frontal lobes and memory (2002). In A. Baddeley, M.D. Kopelman & B.A Wilson (Eds.), *The handbook of memory disorders*. 2nd ed. Chichester (UK): John Wiley, pp. 363-379.

Bigham, J. (1894). Memory. *The Psychological Review, 1*: 453-461.

Blake, R.V., Wroe, S.J., Breen, E.K. & McCarthy, R.A. (2000). Accelerated forgetting in patients with epilepsy. Evidence for an impairment in memory consolidation. *Brain, 123*, 472-483.

Blank, H. (2002). The role of horizontal categorization in retroactive and proactive interference. *Experimental Psychology, 49*, 196-207.

Bliss, T.V.P. & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology, 232*, 331-356.

Bosshardt S, Schmidt CF, Jaermann t, Degonda N, Boesiger P, Nitsch RN, Hock C and Henke K (2005). Effects of memory consolidation on human hippocampal activity during retrieval. *Cortex, 41*, 486-498.

Bowles, R.P. & T.A. Salthouse (2003). Assessing the age-related effects of proactive interference on working memory tasks using the rasch model. *Psychology and Aging, 18*, 608-615.

Box, G.E.P. (1953). Non-normality and tests on variances. Biometrika, 40, 318-335.

Burnham, W.H. (1903). Retroactive amnesia: Illustractive cases and tentative explanation. *The American Journal of Psychology, 14*, 118-132.

Brazzelli M, Della Sala S, Laiacona M (1993). Taratura della versione Italiana del Rivermead Behavioural Memory Test: un test di valutazione ecologica della memoria. *Supplemento al Manuale del TMCR*. Florence: Organizzazioni Speciali.

Brazzelli M., Capitani E., Della Sala S., Spinnler H. & Zuffi M.A. (1994) Neuropsychological instrument adding to the description of patients with suspected cortical dementia: the Milan Overall Dementia Assessment. *Journal of Neurology Neurosurgery & Psychiatry, 57*, 1510-1517.

Buschke, H. Buschke Selective Reminding Test (BSRT). In: O. Spreen & E. Strauss (1991). *A compendium of neuropsychological tests*: *Administration, norms, and commentary.* NY: Oxford University Press, pp.125-138.

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F. & Venneri., A. (2002). Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurological Sciences, 22*, 443-447.

Carlesimo, G.A., Caltagirone, C., Gainotti, G. (1996). The Mental Deterioation Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioation Battery. *European Neurology, 36*, 378-384.

Carlson, N.R., Martin, G.N. & Buskist, G.N. (2004). *Psychology* (2nd ed.). Harlow, UK: Pearson Education.

Caulo, M., Van Hecke, J., Toma, L., Ferretti, A., Tartaro, A., Colosimo, C. et al. (2005). Functional MRI study of diencephalic amnesia in Wernicke-Korsakoff syndrome. *Brain, 128*, 1584-1594.

Celone, K.A., Calhoun, V.D., Dickerson, B.C., Atri, A., Chua, E.F., Miller, S.L. et al. (2006). Alterations in memory networks in Mild Cognitive Impairment and Alzheimer's Disease: and independent component analysis. *The Journal of Neuroscience, 26*, 10222-10231.

Chabardes, S., Kahane, P., Minotti, L., Hoffman, D. & Benabid, A.L. (2002). Anatomy of the temporal pole region. *Epileptic Disorders, 4*, 9-16.

Chen, Q.S., Kagan, B.L., Hirakura, Y. & Xie, C.W. (2000). Impairment of hippocampal long-term potentiation by Alzheimer's amyloid b-peptides. *Journal of Neuroscience Research, 60*, 65-72.

Claparede, E. (1911). Recognition et moite. *Archives de Psychologie, 11*, 79-90.

Cohen, N.J., Ryan, J., Hunt, C., Romine, L., Wszalek, R. & Nash, C. (1999). Hipppcampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. *Hippocampus, 9*, 83-98.

Collins, D.L., Holmes, C.J., Peters, T.M. & Evans, A.C. (1995). Automatic 3-D model-based neuroanatomical segmentation. *Human Brain Mapping, 3*, 190-208.

Collins, D.L., Zijdenbos, A.P., Baare, W.F.C. & Evans, A.C. (1999). ANIMAL+INSECT: Improved cortical structure segmentation. In *Proceedings of the 16th International Conference on Information Processing in Medical Imaging, IPMI*, 210 –223.

Coughlan, A.K. & Hollows, S.E. (1985). The Adult Memory and Information Processing Battery (AMIBP). AK Coughlan, StJames's University Hospital, Leeds.

Cowan, N. (2001). The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and Brain Sciences, 24*, 87-185.

Cowan, N., Beschin, N. & Della Sala S. (2004). Verbal recall in amnesiacs under conditions of diminished retroactive interference. *Brain, 127*, 825-834.

Curran, T. & Schacter, D.L. (2000). Amnesia II: Cognitive neuropsychological issues. In M.J. Farah and T.E. Feinberg (Eds.), *Patient-Based Approaches to Cognitive Neuroscience*. The MIT Press. 291-299.

Davis, H.P., Small, S.A., Stern, Y. & Mayeux, R, Feldstein, S.N., Keller, F.R. (2003). Acquisition, recall, and forgetting of verbal information in long-term memory by young, middle-aged, and elderly individuals. *Cortex, 39*, 1063-1091

De Renzi, E. & Faglioni, P.(1978). Normative data and screening power of a shortened version of the Token Test. *Cortex, 14*, 41-19.

Della Sala S., Cowan, N., Beschin, N. & Perini M. (2005). Just lying there, remembering: Improving Recall of Prose in Amnesic Patients with Mild Cognitive Impairment by Minimizing Interference. *Memory, 13*, 435-440.

Dewar, M.T., Della Sala, S. & Cowan, N. (2006). Forgetting due to retroactive interference: A fuse of Müller and Pilzecker's (1900) early insights into forgetting and recent research on anterograde amnesia. Abstract of paper presented at the 16th annual meeting of Theoretical & Experimental Neuropsychology (TENNET 16). Symposium IV – History of memory. *Brain and Cognition, 60*, 333-334.

Dewar, M.T., Cowan, N. & Della Sala, S. (in press). Forgetting due to retroactive interference: A fusion of Muller and Pilzecker's (1900) early insights into forgetting and recent research on anterograde amnesia. *Cortex*.

Dey, M.K. (1969). Retroactive inhibition as a function of similarity of meaning in free-recall learning. *Psychologische Forschung, 33*, 79-84.

Dickerson, B.C., Goncharova, I., Sullivan, M.P., Forchetti, C., Wilson, R.S. Bennet, D.A. (2001). MRI-derived enorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiological Aging, 22*, 747-754.

Dickerson, B.C., Salat., D.H., Greve., D.N., Chua, E.F., Rand-Giovannetti, E., Rentz, D.M. et al. (2005). Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology, 65*, 404-411.

Dobbins, I.G., Kroll, N.E.A., Tulving, E., Knight, R.T. & Gazzaniga, M.S. (1998). Unilateral medial temporal lobe memory impairment: type deficit, function deficit, or both? *Neuropsychologia, 36*, 115-127.

Dudai, Y. (2004). The neurobiology of consolidation, or, how stable is the engram? *Annual Review of Psychology, 55*, 51-86.

Dudai, Y. & Morris, R.G.M. (2000). To consolidate or not to consolidate: what are the questions? In J.J. Bolhuis (Ed.) *Brain, Perception, Memory. Advances in Cognitive Sciences*. Oxford: Oxford University Press, pp. 149-162.

Dunlosky, J. & Salthouse, T.A. (1996). A decomposition of age-related differences in multitrial free recall. *Aging, Neuropsychology, and Cognition, 3*, 2-14.

Ebbinghaus, H. (1985). *Über das Gedächtnis*. Leipzig, Germany: Duncker & Humbolt.

Enderby, P.,Wood, V. & Wade, D. (1987). *Frenchay Aphasia Screening Test (FAST).*Windsor: UK: NFER-Nelson.

Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975). Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research, 12*, 189-198.

Frisk, V. & Milner, B. (1990). The relationship of working memory to the immediate recall of stories following unilateral temporal or frontal lobectomy *Neuropsychologia, 28*, 121-135.

Gazzaniga, M.S., Ivry, R.B. & Mangun, G.R. (1998). *Cognitive neuroscience. The biology of the mind*, Norton and Company, New York.

Giovagnoli, A.R., Del Pesce M., Mascheroni S., Simoncelli M., Laiacona M. & Capitani, E (1996). Trail making test: normative values from 287 normal adult controls. *Italian Journal of Neurological Science, 17*, 305-309.

Gleitman, H., Fridlund, A.J. & Reisberg, D. (1999). *Psychology* (5th edition). New York: Norton.

Golby, A.J., Poldrack, R.A., Brewer, J.B., Spencer, D., Desmond, J.E., Aron, A.P. et al. (2001). Material-specific lateralization in the medial temporal and prefrontal cortex during memory encoding. *Brain, 124*, 1841-1854.

Gonzalez, H.M., Mungas, D. & Haan, M.N. (2002). A verbal learning and memory test for English-and Spanish-speaking older Mexican-American adults. *The Clinical Neuropsychologist, 16*, 439-451.

Gonzalez, H.M., Mungas, D., Reed, B.R., Marshall, S. & Haan, M.N. (2001). A new verbal learning and memory test for English-and Spanish-speaking older people. *Journal of the International Neuropsychological Society, 7*, 544-555.

Gooding, P.A., Isaac, C.L. & Mayes, A.R. (2005). Prose recall and amnesia: more implications for the episodic buffer. *Neuropsychologia, 43*, 583-587.

Graf, P., Squire, L.R. & Mandler, G. (1984). The information that amnesic patients do not forget. *Journal of Experimental Psychology: Learning, Memory and Cognition, 10*, 164-178.

Griffifth, H.R., Richardson, E., Pyzalski, R.W., Bell, B., Dow, C., Herman, B.P. et al. (2006). Memory for famous faces and the temporal pole: functional imaging in temporal lobe epilepsy. *Epilepsy & Behavior, 9*, 173-180.

Haist, F., Shimamura, A.P. & Squire, L.R. (1992). On the relationship between recall and recognition memory. *Journal of Experimental Psychology: Learning, Memory and Cognition, 18*, 691-702.

Hasher, L., Chung, C., May, C.P. & Foong, N. (2002). Age, Time of Testing, and Proactive Interference. *Canadian Journal of Experimental Psychology, 563*, 200-207.

Hedden, T. & Park, D. (2001). Aging and Interference in Verbal Working Memory. *Psychology and Aging,16*, 666-681.

Hedden, T., & Park, D. C. (2003). Contributions of source and inhibitory mechanisms to age-related retroactive interference in verbal. *Journal of Experimental Psychology: General, 132*, 93-112.

Helmstaedter C. & Kurthen M. (2001). Memory and epilepsy: characteristics, course, and influence of drugs and surgery. *Current Opinion in Neurology, 14*, 211-216.

Herman, B. (2004). Memory and its reorganization in temporal lobe epilepsy. *Epilepsy Currents, 4*, 139-140.

Hirst, W., Johnson, M.K., Kim, J.K, Phelps, E.A., Risse, G. & Volpe, B.T. (1986). Recognition and recall in amnesics. *Journal of Experimental Psychology: Learning, Memory and Cognition, 12*, 445-451.

Hirst, W. & Volpe, B.T. (1984). Encoding of spatial relations with amnesia. *Neuropsychologia, 22*, 631-634.

Hughes, C.P., Berg. L.. Danziger, W.L., Coben, L.A. & Martin, R.L. (1982). A new clinical scale for the staging dementia. *Bristish Journal of Psychiatry, 140*, 566-572.

Huppert, F.A. & Kopelman, M.D. (1989). Rates of forgetting in normal ageing: a comparison with dementia. *Neuropsychologia, 27*, 849-860.

Huppert, F.A. & Piercy, M. (1977). Recognition memory in amnesic patients: A deficit of acquisition? *Neuropsychologia, 15*, 643-652.

Huppert, F.A. & Piercy, M. (1978). Dissociation between learning and remembering in organic amnesia. *Nature, 275*, 317-318.

Huppert, F.A. & Piercy, M. (1979). Normal and abnormal forgetting in oreganic amnesia: effects of locus of lesion. *Cortex, 15*, 385-390.

Jack, Jr., C.R., Petersen, R.C., Xu, Y.C., O'Brien, P.C., Smith, G.E., Ivnik, J. et al. (1999). Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology, 52*, 1397-1404.

Janszky, J., Jamszky, I., Schulz, R., Hoppe, M., Behne, F., Pannek, H.W. et al. (2005). Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. *Brain, 128*, 395-404.

Jones-Gotman, M., Zatorre, R.J., Olivier, A., Andermann, F., Cendes, F., Staunton, H. et al. (1997). Learning and retention of words and designs following excision from medial or lateral temporal lobe structures. *Neuropsychologia, 35*, 963-973.

Kane, M. J., & Hasher, L. (1995). Interference. In G. Maddox (Ed.), *Encyclopedia of Aging*, 2nd Edition. New York, NY.: Springer Publishing Co., pp. 514-516.

Kaplan, E., Goodglass, H. & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia: Lea & Febiger.

Kapur, N., Millar, J., Colburn, C., Abbot, P., Kennedy, P. & Docherty, T. (1997). Very Long-term amnesia in association with temporal lobe epilepsy: evidence for multiple-stage consolidation processes. *Brain and Cognition, 35*, 58-70.

Kelley, W.M., Miezin, F.M., McDermott, K.B., Buckner, R.L., Raichle, M.E., Cohen, N.J. et al. (1998). Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal encoding. *Neuron, 20*, 927-936.

Kopelman, M.D. (2002). Disorders of memory. *Brain, 125*, 2152-2190.

Kosslyn, S.M. & Rosenberg, R.S. (2004). *Fundamentals of Psychology: The Brain, the person, the world* (2nd ed.) New York, NY: Allyn & Bacon Publishers.

Lee, T.M.C., Yip, J.T.H. & Jones-Gotman, M. (2002). Memory deficits after resection from left or right anterior temporal lobe in humans: a meta-analytic review. *Epilepsia, 43*, 283-291.

Logie, R.H. & D'Esposito M. (2007). Working memory and the brain. *Cortex, 43*, 1-4.

Lynch, M.A. (2004). Long-Term potentiation and memory. *Physiological Reviews, 84*, 87-136.

Machulda, M.M., Ward, H.A., Borowski, B., Gunter, J.L., Cha, R.H., O'Brien, P.C.O. et al. (2003). Comparison of memory fMRI responses among normal, MCI, and Alzheimer's patients. *Neurology, 61*, 500-506.

Maguire, E.A., Frith, C.D., Rudge, P. & Cipolotti, E. (2005). The effect of adult-acquired hippocampal damage on memory retrieval: and fMRI study. *NeuroImage, 27*, 146-152.

Maguire, E.A., Vargha-Khadem, F. & Mishkin, M. (2001). The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval. *Brain, 124*, 1156-1170.

Manes, F., Graham, K.S., Zeman, A., de Lujan Calcagno, M. & Hodges, J.R. (2005). Autobiographical amnesia and accelerated forgetting in transient epileptic amnesia. *Journal of Neurology, Neurosurgery & Psychiatry, 76*, 1387-1391.

Manzano, M., Pineiro, A. & Reigosa, V. (1997). Estudio de las caracteristicas de un conjunto de 260 figuras en sujetos adultos de habla hispana. *Cognitiva, 9,* 29-65.

Markowitsch, H.J. (1995). Which brain regions are critically involved in the retrieval of old episodic memory? *Brain Research Reviews, 21*, 117-127.

Marslen-Wilson, W.D. & Teuber, H.L. (1975). Memory for remote events in anterograde amnesia: recognition of public figures from newsphotographs. *Neuropsychologia, 13*, 353-364.

Martin, A. (1999). Automatic activation of the medial temporal lobe during encoding: lateralized influences of meaning and novelty. *Hippocampus, 9*, 62-70.

Martin, A., Wiggs, C.L. & Weisberg, J. (1997). Modulation of human medial temporal lobe activity by form, meaning and experience. *Hippocampus, 7*, 587-593.

Mayes, A.R., Downes, J.J., Symons, V. & Shoqeirat M. (1994). Do amnesics forget faces pathologically fast? *Cortex, 30*, 543-563.

Mayes, A.R. & Downes, J.J. (1997). What do theories of functional deficit(s) underlying amnesia have to explain? *Memory, 5*, 3-36.

Mayes, A.R., Downes, J.J., Shoqeirat, M., Hall, C. & Sagart, H.J. (1993). Encoding ability is preserved in amnesia: Evidence from a direct test of encoding. *Neuropsychologia, 31*, 745-759.

Mayes, A.R., Isaac, C.L., Holdstock, J.S., Cariga, P., Gummer, A. & Roberts, N. (2003). Long-term amnesia: A review and detailed illustrative case study. *Cortex, 39*, 567-603.

McClelland, J.L., Naughton, B.L. & O'Reilly, R.C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the success and failures of connectionist models of learning and memory. *Psychological Reviews, 102*, 419-457.

McGaugh, J.L. (2000). Memory-a century of consolidation. *Science, 287*, 248-251.

McGaugh, J.L. (1999). The perseveration-consolidation hypothesis: Mueller and Pilzecker, 1900. *Brain Research Bulletin, 50*, 445-446.

McGeoch, J.A. & McDonald, W.T. (1931). Meaningful relation and retroactive inhibition. *American Journal of Psychology, 43*, 579-588.

McGeoch, J.A. & Nolen, M.E. (1933). Studies in retroactive inhibition IV. Temporal point of interpolation and degree of retroactive inhibition. *The Journal of Comparative Psychology, 15*, 407-417.

McGeoch, J.A. (1932). Forgetting and the law of disuse. *Psychological Review, 39*, 352-370.

Meeter, M. & Murre, J.M.J. (2005). Tracelink: A model of consolidation and amnesia. Cognitive *Neuropsychology, 22*, 559-587.

Mensink, G.J. & Raaijmakers, J.G.W. (1988). A model for interference and forgetting. *Psychological Review, 95*, 434-455.

Milner, B. (1968). Disorders of memory after brain lesions in man. *Neuropsychologia, 6*, 175-179.

Milner, B. (1966). Amnesia following operations on the medial temporal lobes. In C.W.M.Whitty and O.L. Zangwill (Eds.), *Amnesia*. London: Butterworths, pp. 109-133.

Milner, B. (1972). Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin, 27*, 272-277.

Mondadori, C.R.A., Buchman, A., Mustovic, H., Schmidt, C., Boesiger, P., Nitsch, R.M. et al. (2006). Enhanced brain activity may precede the diagnosis of Alzheimer's disease by 30 years. *Brain, 129*, 2908-2922.

Morris, J.C. (2006). Mild Cognitive Impairment is early-stage Alzheimer Disease. *Archives of Neurology, 63*, 15-16.

Morris, R.G.M. (2003). Long-term potentiation and memory. *Philosophical Transactions of the Royal Society of London, B, 358*, 643-647.

Mottron, L., Belleville, S., Stip., E. & Morasse, K. (1998). Atypical memory performance in an autistic savant. *Memory, 6*, 593-607.

Moulin, C.J.A., James, N., Freeman, J.E. & Jones, R.W. (2004). Deficient acquisition and consolidation: intertrial free recall and performance in Alzheimers's Disease and Mild Cognitive Impairment. Journal of Clinical and Experimental *Neuropsychology, 26*, 1-10.

Müller, G.E. & Pilzecker, A. (1900). Experimentelle Beiträge zur Lehre vom Gedächtniss. *Zeitschrift für Psychologie. Ergänzungsband 1*: 1–300.

Novelli, G., Papagno, C., Capitani, E., Laiacano, M., Cappa, S.F. & Vallar, G. (1986). Tre test clinici di memoria verbale a lungo termine. Taratura su soggetti normali. *Archivo di psicolgia, neurologia e psichiatria, 47*, 278-96.

O'Connor, M., Sieggreen, M.A., Ahern, G., Schomer, D. & Mesulam, M. (1997). Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. *Brain and Cognition, 35*, 71-84.

Odgen, J. (1996). Marooned in the moment. In J Odgen (Ed.), *Fractured minds. A case-study approach to clinical neuropsychology*. New York: Oxford University Press, pp. 41-58.

Pallar, A.P. (1997). Consolidating dispersed neocortical memories: the missing link in amnesia. *Memory, 5,* 73-88.

Petersen, R.C., Smith, G.E., Waring, S.C. Ivnik, R.J., Tangalos, E.G. & Kokmen, E. (1999). Mild Cognitive Impairment. Clinical characterization and outcome. *Archives of Neurology, 56*, 303-308.

Pillon, B., Bazin, B., Deweer, B., Ehrle, N., Baulac, M. & Dubois, B. (1999). Specificity of memory deficits after right or left temporal lobectomy. *Cortex, 35*, 561-571.

Pucket, J.M. & Stockburger, D.W. (1988). Absence of age-related proneness to short-term retroactive interference in the absence of rehearsal. *Psychology and Aging, 3*, 342-347.

Raven, J.C. (1965). The *Coloured Progressive Matrices: Sets A, Ab, B*. London: H.K.Lewis.

Reitman JS. (1974). Without surreptitious rehearsal, information in short-term memory decays. *Journal of Verbal Learning & Verbal Behavior, 13*, 365-377.

Ribot, T.A. (1892). *Diseases of memory*. Washington.DC:Univ.Publ.Am.

Richardson, M.P., Strange, B.A., Duncan, J.S. & Dolan R.J. (2003). Preserved verbal memory function in left medial temporal pathology involves reorganisation of function to right medial temporal lobe. *NeuroImage, 20*, S112-S119.

Ritchie, K. & Touchen, J. (2000). Mild cognitive impairment: conceptual basis and current nosological status. *The Lancet, 355*, 225-228.

Robinson, E.S. (1920). Studies from the psychological laboratory of the University of Chicago: Some factors determining the degree of retroactive inhibition. *Psychological Monographs, 28*,1-57.

Rowan, M.J., Klyubin, I., Cullen, W.K. & Anwyl, R. (2003). Synaptic plasticity in animal models of early Alzheimer's disease. *Philosophical Transactions of the Royal Society of London, B, 358*, 821-828.

Rowan, M.J., Klyubin, I., Wang, Q. & Anwyl, R. (2006). Synaptic plasticity disruption by amyloid b protein: modulation by potential Alzheimer's disease modifying therapies. *Biochemical Society Transactions, 33,* 563-567.

Scoville, W.B. & Milner, B (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry. 20*, 11-21.

Selkoe, D.J. (2002). Alzheimer's disease is a synaptic failure. *Science, 298*, 789-791.

Shimamura, A.P., Jurica, P.J., Mangles, J.A., Gershberg, F.B. & Knight, R.T.(1995). Susceptibility to memory interference effects following frontal lobe damage: findings from tests of paired-associate learning. *Journal of Cognitive Neuroscience, 7*, 144-152.

Silverstein, A.B. (1982). Two-and four-Subtest Short Forms of the Wechsler Adult Intelligence Scale-Revised. *Journal of Consulting and Clinical Psychology, 50*, 415-418.

Simons, J.S. & Spiers, H.J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience, 4*, 637-648.

Skaggs, E.B. (1933). A discussion on the temporal point of interpolation and degree of retroactive inhibition. *The Journal of Comparative Psychology, 16*, 411-414.

Skaggs, E.B. (1925). Further studies in retroactive inhibition. *Psychological Monographs, Whole No. 161*, 1-60.

Smith, M.L. & Milner, B. (1981). The role of the right hippocampus in the recall of spatial location. *Neuropsychologia, 19*, 781-795.

Smith, M.L. & Milner, B. (1989). Right hippocampal impairment in the recall of spatial location: encoding deficit or rapid forgetting? *Neuropsychologia, 27*, 71-81.

Snodgrass, J.G. & Vanderwart, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology. Human learning and memory, 6*, 174-215.

Spinnler, H. & Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *The Italian Journal of Neurological Sciences Suppl. 8 to No. 6*, 1-120.

Squire, L.R. (1980). Specifying the defect in human amnesia: storage, retrieval and semantics. *Neuropsycholgia, 18*, 368-372.

Squire, L.R. (1982). The neuropsychology of human memory. *Annual Review of Neuroscience, 5*, 241-273.

Squire, L.R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review, 99*, 195-231.

Squire, L.R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiology of Learning and Memory, 82*, 171-177.

Squire, L.R. (2006). Lost forever or temporarily misplaced? The long debate about the nature of memory impairment. *Learning & Memory, 13*, 522-529.

Squire, L.R. & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Current Opinion in Neurobiology, 5*, 169-177.

Squire, L.R., Stark, C.E.L. & Clark, R.E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*, 279-306.

Tendolkar, I., Doyle, M.C. & Rugg, M.D. (1997). An event-related potential study of retroactive interference in memory. *Neuroreport, 8*, 501-506.

Tombaugh, T.N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology, 19*, 203-214.

Tombaugh, T.N. & Hubley, A.M. (2001). Rates of forgetting on three measures of verbal learning using retention intervals ranging from 20min to 62 days. *Journal of the International Neuropsychological Society, 7*, 79-91.

Trahan, D.E. & Larrabee, G.J. (1992). Effect of normal aging on rate of forgetting. *Neuropsychology, 6*, 115-122.

Tulving, E. & Schacter, D.L. (1990). Priming and Human Memory Systems. *Science, 247*, 301-303.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta analysis. *Neuropsychologia, 42*, 1394-1413.

Warrington, E. & McKenna, P. (1983). *The graded naming test*. London: NFER

Warrington, E.K. & Weiskrantz, L. (1968). New method of testing long-term retention with special reference to amnesic patients. *Nature, 217*, 972-974.

Warrington, E.K. & Weiskrantz, L. (1970). Amnesic Syndrome: Consolidation or retrieval? *Nature, 288*, 628-630.

Warrington, E.K. & Weiskrantz, L. (1974). The effect of prior learning on subsequent retention in amnesic patients. *Neuropsychologia, 12*, 419-428.

Warrington, E.K. & Weiskrantz, L. (1978). Further analysis of the prior learning effect in amnesic patients. *Neuropsychologia, 1978*, 169-177.

Watkins, M.J., Watkins, O.C., Craik, F.I.M., & Mazuryk, G. (1973). Effect of nonverbal distraction of short-term storage. *Journal of Experimental Psychology, 101*, 296-300.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale-Revised*. San Antonio: Psychological Corporation.

Wechsler D. (1997). *The Wechsler Memory Scale-III*. Psychological Corporation.

Wechsler D. (1998). *The Wechsler Adult Intelligence Scale*. 3rd ed. London: Psychological Corporation.

Wechsler D. (1999). The *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation.

Wegner, D.M., Schneider, D.J., Carter III, S.R. & White, T.L. (1987). Paradoxical effects of thought suppression. *Journal of Personality and Social Psychology, 53*, 5-13.

Weiskrantz, L. (1982). Comparative aspects of studies of amnesia. *Philosophical Transactions of the Royal Society of London, 298*, 97-109.

Welch, B.L. (1951). On the comparison of several mean values: and alternative approach. *Biometrika, 38*, 330-336.

Wetzel, D.C. & Squire, L.R. (1980). Encoding in anterograde amnesia. *Neuropychologia, 18*, 177-184.

Wilson, B.A. (1987). *Rehabilitation of memory*. New York: The Guilford Press.

Wilson, B., Cockburn, J. & Baddeley, A.D. (1985). *The Rivermead Behavioural Memory Test. Reading*: Thames Valley Test Group.

Wixted, J.T. (2004). The Psychology and neuroscience of forgetting. *Annual Review of Psychology, 55*, 235-269.

Wixted, J.T. (2005). A theory about why we forget what we once knew. *Current Directions in Psychological Science, 14*, 6-9.

Wolf, H., Hensel, A., Kruggel, F., Riedel-Heller, S.G., Arendt, T., Wahlund, L.O. et al. (2004). Structural correlates of mild cognitive impairment. *Neurobiology of Aging, 25*, 913-924.

Woodard, J.L., Dunlosky, J. & Salthouse, T.A. (1999). Task decomposition analysis of intertrial free recall performance on the Rey Auditory Verbal Learning Test in normal aging and Alzheimer's Disease. *Journal of Clinical and Experimental Neuropsycholoy, 21*, 666-676.

Zeman, A.Z.J., Boniface, S. & Hodges, R. (1998). Transient epileptic amnesia: a description of the clinical and neuropsychological features in 10 cases and a review of the literature. *Journal of Neurology, Neurosurgery & Psychiatry, 64*, 435-443.

Appendix A: Word Lists – Experiment 1

Word	Let	Syl	K&F freq	Fam	Con	Imag	BNC freq
List 1							
ROMANCE	7	2	13	517	313	551	1033
OUTBREAK	8	2	2	471	358	359	1192
EMERGENCE	9	3	3	459	346	387	1242
COMPOSER	8	3	31	448	487	467	1470
PRINCIPAL	9	3	92	491	381	402	1599
ORCHESTRA	9	3	60	533	578	619	1686
WHISKEY	7	2	17	574	604	592	1935
CATHEDRAL	9	3	8	440	553	599	2072
DIVIDEND	8	3	6	387	366	313	2300
COMFORT	7	2	43	566	402	421	2792
OPPONENT	8	3	15	495	440	408	2993
DISASTER	8	3	26	548	405	505	3318
POLLUTION	9	3	6	555	463	509	3789
CHAMPION	8	2	23	507	459	508	4318
CONVENTION	10	3	28	466	488	502	4673
		40					2427.47
List 2							
BIOLOGY	7	4	7	526	400	441	1029
CARAVAN	7	3	8	304	539	562	1281
WOODLAND	8	2	2	423	585	608	1247
ENCOUNTER	9	3	28	463	316	370	1471
DISMISSAL	9	3	7	447	300	362	1603
AMBULANCE	9	3	6	499	595	627	1690
CLOTHING	8	2	20	614	570	588	1892
HARDWARE	8	2	11	496	560	576	2076
FRIENDSHIP	10	2	27	567	335	535	2353
PROFILE	7	2	15	445	510	572	2792
MEDICINE	8	2	30	547	517	551	3040
PERSONNEL	9	3	74	482	429	375	3325
RESISTANCE	10	3	48	540	358	416	3799
INQUIRY	7	4	17	485	358	321	4377
CHANNEL	7	2	16	482	527	508	4676
		40					2443.4

Word	Let	Syl	K&F freq	Fam	Con	Imag	BNC freq
List 3							
DAYLIGHT	8	2	15	547	492	575	1033
GRAVITY	7	3	7	493	302	388	1189
AMBASSADOR	10	4	22	477	546	545	1264
WELCOME	7	2	50	529	350	470	1484
SERGEANT	8	2	28	480	511	549	1621
WORKING	7	2	151	609	383	458	1701
HIERARCHY	9	4	9	409	333	435	1952
NURSERY	7	2	13	461	528	542	2103
TRAVELLER	9	2	3	494	492	491	2396
CORRIDOR	8	3	17	579	568	553	2798
ALCOHOL	7	3	13	578	618	598	3066
PERMISSION	10	3	27	533	425	331	3343
PROTEST	7	2	23	530	339	472	3809
TERRITORY	9	4	31	465	459	445	4382
WRITING	7	2	117	630	467	540	4727
		40					2457.87

Let = number of letters, Syl = number of syllables, K&F frequ = frequency measure taken from Kucera and Francis (1967), Fam = familiarity, Con = concreteness, Imag = Imaginability, BNC freq = British National Corpus (BNC) frequency measure

Appendix B: Prose Passages – Experiments 2(a) and 4(a)

Prose passages (taken from the Rivermead Behavioural Memory Test):

Scottish sample:

Prose A

Mr Brian / Kelly / a Security Express employee / was shot dead / on Monday / during a bank raid / in Brighton. / The four raiders / all wore masks / and one carried / a sawn-off / shotgun. / Police detectives / were sifting through / eye-witness accounts / last night. / A police spokesman said / ‘He was a very brave man. / He went for / the armed raider / and put up a hell of a fight’.

Prose B

Firemen / and volunteers / worked all day / yesterday / beating out / a moorland fire / six miles / south / of Keswick / in the Lake District. / Fire engines / were unable to reach the area / so fire-fighting equipment / was brought in by helicopter. / Livestock / was evacuated / from the neighbouring / Highlands Farm / as it was engulfed / in clouds / of dense white smoke.

Prose C

Two hundred men / at a shipyard / on Tyneside / went on strike / this morning. / The men walked out / over a dispute / concerning fifty / redundancies. / The shop steward / Mr. Thomas / Lindsay / told reporters / ‘It is outrageous! / The Company has full order-books / for the next two years’. / A management spokesman said / ‘We are hoping to begin / fresh negotiations / at head-office / tomorrow’.

Prose D

A Dutch / oil tanker / sank / ten miles / off the Norfolk coast / last night. / The crew / were picked up / by a coast-guard patrol boat. / An oil slick / is already forming / and conservationists / are worried / about the effects / on wildlife. / Local enthusiasts / are mounting an operation / to save / any birds / found stranded / on the beaches.

Italian sample:

Prose A

Il signor Alberto / Fossati, / una guardia giurata, / e stato ucciso / lunedi / durante una rapina in banca / a Perugia. / I quattro rapinatori / portavano tutti un maschera / e uno di loro aveva / anche una pistola / con silenziatore. / Ieri notte / la polizia / he raccolto / le testimonianze oculari. / Un signore presente ha detto: / 'E stato davvero molto coraggioso. / Ha rincorso / I rapinatori armati / ed ha iniziato una furibonda sparatoria'.

Prose B

Vigili del fuoco / e volontari / hanno lavorato tutto il giorno / ieri / per domare / un tremendo incendio / in Toscana / 6 chilometri / a sud / di Siena. / La autopompe / non potevano arrivare sul posto / cosi le attrezzature per spegnere il fuoco / sono state portate in elicottero. / Il bestiame / e stato fatto evacuare / dalla vicina / fattoria del signore Mollica / che era avvolta / in una folta coltre / di fumo bianco.

Prose C

Duecento dipendenti / di un cantiere navale / die Savona / sono scesi in sciopero / questa mattina. / La loro protesta reguarda / il licenziamento / di cinquanta / operai. / Il rappresentante sindacale / signor Giovanni / Ornaghi / he dichiarato ai giornalisti presenti. / "E vergognoso! / La compagnia ha richieste di furniture / per i prossimi due anni". / Un dirigente della compagnia ha affermato: / "Speriamo di poter iniziare / domain / nuove trattative / con la sede centrale". /

Prose D

Una petroliera, / olandese / e affondata / la notte scorsa / a 10 miglia / dalla costa di Livorno. / Gli uomini dell equipaggio / sono stati tratti in salvo / da un'unita di pattuglia della guardia costiera. / Si sta gia formando / un'enorme macchia d'olio, / e gli ecologisti / sono preoccupati / per I danni / all'ambiente. / Alcuni volontari della zona / si stanno organizzando / per salvare / gli ucelli / arenati / sulle spiagge.

Appendix C: Prose Passages – Experiment 2(b)

Prose 1 (Novelli et al., 1986)

Anna / Pesenti / di Bergamo / che lavora / come donna delle pulizie / in una ditta / di costruzioni / riferi / al maresciallo / dei carabinieri / che la sera / precendente / mentre rincasava / era stata aggredita / e derubata / die 50.000 lire. / La poveretta / aveva Quattro / bambini / piccoli / che non mangiavano / da due / giorni / e doveva pagare / l'affitto. / I militari / commossi / fecero una colletta.

Prose 2 (Spinnler and Tognoni, 1987)

Ser / dicemore / La scorsa / settimana / un fiume straripo/ in una piccola / citta / situata / a 20 km / da Torino./ L'acgua ivase le strade / e le case. / Quattordici / persone / annegarono le seicento / si ammalarono / a causa dell umidita / e del freddo. / Nel tentative di salvare / un ragazzo / un uomo / si teri / le mani. /

Appendix D: Word Lists – Experiments 5(a) and 6

List 1	List 2	List 3	List 4
Arma	Barra	Bote	Cine
Balón	Cielo	Burro	Cordon
Cárcel	Colcha	Ceja	Tete
Cobre	Dado	Circo	Canon
Disco	Guerra	Dolar	Ciclon
Flecha	Kiosko	Golpe	Hijo
Goma	Letra	Hacha	Playa
Leche	Madre	Jugo	Peso
Lluvia	Plumon	Lirio	Pino
Plata	Puente	Metro	Cuadro
Punta	Queso	Pincel	Talco
Sopa	Risa	Potro	Dulce
Tapa	Sabor	Radio	Tela
Tinta	Tecla	Tiza	Laton
Viento	Yuca	Zunzun	Papel

Appendix E: Group ROI means – Experiment 8

** p < 0.05, ** p < 0.01; ROI volumes in cm3*	Controls		Patients		
ROI	Mean Vol	SEM	Mean Vol	SEM	
Frontal_Sup_L	0.005029	0.000228	0.005084	0.000227	
Frontal_Sup_R	0.005414	0.000266	0.005716	0.000191	
Frontal_Sup_Bilateral	0.010443	0.000476	0.0108	0.000411	
Frontal_Sup_Orb_L	0.001922	6.57E-05	0.002007	6.51E-05	
Frontal_Sup_Orb_R	0.001978	5.84E-05	0.00207	6.36E-05	
Frontal_Sup_Orb_Bilateral	0.0039	0.00012	0.004077	0.000115	
Frontal_Inf_Orb_L	0.003376	8.45E-05	0.003556	8.45E-05	
Frontal_Inf_Orb_R	0.003621	8.43E-05	0.003772	6.17E-05	
Frontal_Inf_Orb_Bilateral	0.006997	0.000151	0.007329	0.000135	
Occipital_Sup_L	0.002152	7.19E-05	0.002068	9.79E-05	
Occipital_Sup_R	0.002206	0.000106	0.002256	0.000109	
Occitipal_Sup_Bilateral	0.004358	0.000162	0.004324	0.000197	
Occipital_Inf_L	0.001641	5.3E-05	0.001545	6.95E-05	
Occipital_Inf_R	0.001674	6.36E-05	0.001732	7.94E-05	
Occitipal_Inf_Bilateral	0.003315	0.000107	0.003277	0.000131	
Thalamus_L	0.002055	7.68E-05	0.002225	6.47E-05	
Thalamus_R	0.0023	4.93E-05	0.002328	5.29E-05	
Thalamus_Bilateral	0.004356	0.000121	0.004554	8.89E-05	
Cerebelum_L	0.000196	1.26E-05	0.000206	2.37E-05	
Cerebelum_R	0.000306	1.65E-05	0.000279	2.37E-05	
Cerebelum_Bilateral	0.000502	2.76E-05	0.000485	4.49E-05	
Cingulum_Ant_L	0.002833	9.08E-05	0.002897	5.9E-05	
Cingulum_Ant_R	0.002592	9.26E-05	0.002622	6.5E-05	
Cingulum_ANT_Bilateral	0.005425	0.000179	0.005519	0.000111	
Hippocampus_L	0.002095	6.83E-05	0.001995	6.31E-05	
Hippocampus_R	0.002048	5.61E-05	0.001951	9.87E-05	
Hippocampus_Bilateral	0.004143	0.000109	0.003946	0.000149	
Amygdala_L	0.000648	7.02E-06	0.000676	2.23E-05	
Amygdala_R	0.000724	1.7E-05	0.000742	1.28E-05	
Amygdala_Bilateral	0.001372	1.83E-05	0.001419	3.33E-05	
ParaHippocampal_L	0.002173	4.89E-05	0.002259	0.000106	
ParaHippocampal_R	0.002758	6.35E-05	0.002679	8.28E-05	
Parahippocampus_Bilateral	0.004931	0.000101	0.004938	0.000184	
Temporal_Inf_L	0.00735	0.000168	0.007777	0.000205	
Temporal_Inf_R	0.008237	0.000164	0.008798	0.000254	
Temporal_Inf_Bilateral	0.015587	0.000311	0.016574	0.000442	
Temporal_Med_L	0.010259	0.000233	0.01087	0.000302	
Temporal_Med_R	0.00962	0.000198	0.009907	0.000285	
Temporal_Med_R+L_Bilateral	0.019879	0.00042	0.020776	0.000565	
Temporal_Pole_Med_L	0.00198	3.88E-05	0.002051	0.000118	
Temporal_Pole_Med_R	0.002789	9.49E-05	0.0031	0.00011	
Temporal_Pole_Med_Bilateral	0.004769	0.00011	0.005151	0.000206	
Temporal_Pole_Sup_L	0.002237	0.000106	0.001851	0.000126	*
Temporal_Pole_Sup_R	0.002231	8.5E-05	0.001889	0.000127	*
Temporal Pole_Sup_Bilateral	0.004467	0.000141	0.003741	0.000223	**
Temporal_Sup_L	0.004434	0.000131	0.004435	9.3E-05	
Temporal_Sup_R	0.005649	0.000135	0.005433	0.000218	
Temporal _Sup_Bilateral	0.010083	0.000252	0.009868	0.000292	

Appendix F: Word Lists – Experiment 9

	Let	Syl	K&F freq	Fam	Con	Imag	BNC freq
LIST 1							
JUNCTION	8	2	7	489	477	502	2037
OBSERVER	8	3	16	469	505	489	2624
AMBULANCE	9	3	6	499	595	627	1690
TERRITORY	9	4	31	465	459	445	4382
HARBOUR	7	2	0	512	603	597	1515
OPPONENT	8	3	15	495	440	408	2993
EPISODE	7	3	12	431	391	370	2012
TRIANGLE	8	3	4	512	523	597	1057
FRIENDSHIP	10	2	27	567	335	535	2353
DAYLIGHT	8	2	15	547	492	575	1033
WRITING	7	2	117	630	467	540	4727
PERSONNEL	9	3	74	482	429	375	3325
SEGMENT	7	2	10	451	485	480	1543
PROFESSOR	9	3	57	583	549	587	2168
CORRIDOR	8	3	17	579	568	553	2798
SUM	122	40	408	7711	7318	7680	36257
LIST 2							
APARTMENT	9	3	81	491	575	556	1901
LECTURE	7	2	16	624	451	564	2867
BISCUIT	7	2	2	521	574	571	1552
INQUIRY	7	4	17	485	358	321	4377
WOODLAND	8	2	2	423	585	608	1247
ORCHESTRA	9	3	60	533	578	619	1686
BIOLOGY	7	4	7	526	400	441	1029
ROMANCE	7	2	13	517	313	551	1033
CHANNEL	7	2	16	482	527	508	4676
GARMENT	7	2	6	440	552	507	1272
CATHEDRAL	9	3	8	440	553	599	2072
ENGINEER	8	3	42	514	531	495	4080
TOURIST	7	2	16	536	533	577	3306
EDITION	7	3	37	499	439	373	3166
COMMANDER	9	3	28	409	512	478	1977
SUM	115	40	351	7440	7481	7768	36241

LIST 3

	Let	Syl	K&F freq	Fam	Con	Imag	BNC freq
CONTINENT	9	3	17	459	459	478	1940
LAUGHTER	8	2	22	570	411	613	2190
PROSPERITY	10	4	14	477	301	436	1106
CEILING	7	2	31	531	606	557	2715
GRADUATE	8	3	30	520	455	516	1787
LIGHTNING	9	2	14	465	525	599	1515
PRISONER	8	3	7	485	548	565	4574
BACTERIA	8	3	8	460	560	505	1265
PLATFORM	8	2	72	498	547	529	3366
COSTUME	7	2	10	456	544	538	1042
ASSAULT	7	2	15	470	410	481	2395
FISHERMAN	9	3	5	471	567	610	1004
RELIGION	8	3	119	565	375	434	4798
ARRIVAL	7	3	23	548	328	419	3815
SPECIALIST	10	3	16	495	487	448	2728
SUM	123	40	403	7470	7123	7728	36240

LIST 4

	Let	Syl	K&F freq	Fam	Con	Imag	BNC freq
BUILDER	7	2	29	554	532	551	1795
MEDICINE	8	2	30	547	517	551	3040
OPENING	7	2	83	542	455	462	4504
CHILDHOOD	9	2	50	515	335	489	2853
REVOLUTION	10	4	70	477	378	513	4629
CARAVAN	7	3	8	304	539	562	1281
DIAMOND	7	3	8	512	610	623	1642
ACADEMY	7	4	24	509	499	504	1025
HIGHWAY	7	2	40	488	575	581	1084
PEASANT	7	2	7	422	550	540	3345
STADIUM	7	2	25	526	569	586	1062
DISCOVERY	9	4	45	513	332	401	3512
CLOTHING	8	2	20	614	570	588	1892
MONUMENT	8	3	21	455	558	543	1272
DISASTER	8	3	26	548	405	505	3318
SUM	116	40	486	7526	7424	7999	36254

	Let	Syl	K&F freq	Fam	Con	Imag	BNC freq
LIST 5							
UNIFORM	7	3	51	484	550	591	1893
JOURNAL	7	2	42	486	563	509	2818
SUNSHINE	8	2	8	627	527	655	1197
MINERAL	7	3	12	454	527	432	1453
PROTEST	7	2	23	530	339	472	3809
INVENTION	9	3	20	489	388	408	1218
EMERGENCY	9	4	39	558	334	487	3707
COMPOSER	8	3	31	448	487	467	1470
DETECTIVE	9	3	52	509	505	524	2700
HARVEST	7	2	12	466	535	562	1059
SERVANT	7	2	19	437	515	508	4762
RESISTANCE	10	3	48	540	358	416	3799
WHISKY	7	2	17	574	604	592	1935
EXPEDITION	10	4	15	435	403	472	1438
STOMACH	7	2	37	547	617	551	2985
SUM	119	40	426	7584	7252	7646	36243

Let = number of letters, Syl = number of syllables, K&F frequ = frequency measure taken from Kucera and Francis (1967), Fam = familiarity, Con = concreteness, Imag = Imaginability, BNC freq = British National Corpus (BNC) frequency measure

Appendix G: Passage of text – Experiment 9

Endurance

The amazing ability of some animals to endure extreme temperatures, survive great journeys or bear weights many times greater than their own is due to adaptations their predecessors have made. These physical modifications, which have developed over generations, equip animals perfectly to endure the difficult environments in which they have to live. Staying airborne for four years, for example, is a simple matter for the common swift, thanks to a physical makeup which enables it to eat, drink and sleep and mate on the wing. Camels and polar bears both have special means to cope with scorching heat and freezing cold.

Weightlifters
Some of the most remarkable load-bearers of the animal kingdom are some of its smaller members. Ants have two sets of jaws: one for chewing and one for carrying. Many species forage alone and have to carry prey over seven times their own body weight. One species, which measures only 3 mm long, has been observed dragging a prey 10mm in length, such as locusts, to its nest. This would be the equivalent to humans carrying a small car in their teeth over a distance of 8km.The trap door spiders of North America and Japan can endure weights up to 40 times their own while defending their burrows from intruders. But perhaps the strongest of all are the rhinoceros beetles, which can carry up to 100 times their own body weight.

Highs and lows
Jumping spiders have been found at altitudes of 6,5000m in Mount Everest, but it is birds that endure the highest altitude of any animal. In December 1967, a pilot spotted 30 whooper swans on their way from Iceland to Northern Ireland flying at an altitude, confirmed by radar, of over 8,230m. The highest flying bird on Earth, however, is the Ruppell's vulture which can soar at altitudes of 11,000m. In November 1973, one of these birds, identified from feathers retrieved afterwards, collided with an aircraft at 11,277m over the Ivory Coast. At the other extreme, tusk shells – marine mollusks with a tapering shell which houses a foot for digging – are found in ocean waters at depths of up to 24,000m, often buried in the sea bed. The deepest living fish, the brotulid, has been found in the Puerto Rican Trench in the Atlantic Ocean at depths of an incredible 8,300m.

Hot and hardy
Camels inhabit scorching desert regions in Africa and Asia where they can survive without water for up to 17 days. These phenomenally hardy animals can lose 25% of their body weight through dehydration without suffering any ill effects. The single hump of the Arabian camel, or dromedary, and the double hump of the Bactrian camel store fat which can keep the camel alive when the food is not available and can be converted to water. Their broad feet enable camels to walk easily on soft sand and double eyelashes and sealable nostrils protect their eyes and nose during sandstorms. They can survive on the thorny desert plants which other animals could not endure. These remarkable adaptations have made camels extremely useful as desert pack animals. When water is made available after long journeys, camels can drink 100 litres within a matter of minutes to replenish their body supply.

Cold and hungry

The polar bear survives in icy Artic conditions thanks to its remarkable coat and a 10-cm layer of insulating fat. Each of the coat's hairs is a clear hollow tube which directs heat from the sun to the skin. The coat is white to provide the polar bear with perfect camouflage on the drifting ice sheets of Canada, Greenland, Norway, Russia and Alaska. Underneath the fur, however, lies a thick black skin which absorbs the sun's rays. The bear's head is small to minimise heat loss, but the long snout contains large membranes that warm and moisten the freezing dry air before it reaches the lungs. The bear's large feet are covered in fur to stop it slipping on ice. After the ice has melted in the summer the polar bear lives for some eight months without food. Gorging on seals from April to July, the impregnated females can increase their body fat by 50% or more. They build up a thick layer of fat around the thighs and rump which will provide additional calories when food is scarce.The massive polar bear – weighing up to 750 kg and standing 1.5 m at the shoulder – is a strong swimmer, living up to its scientific name *Ursus maritimus* or 'sea bear'. It often swims over 150 km fro land or ice, searching for its main prey: seals.

Great journeys

Migrating bird travel long and difficult journeys, often in search of food not available in one region. Ducks, geese, swans and swifts migrate across Europe, while the golden plover flies the 3,900 km from Alaska to Canada each year.

Animals domesticated for their endurance

Since the first wolves were domesticated thousands of years ago, humans have used their dogs for their endurance as well as for companionship. Some of the hardiest breeds are the Alaskan Malamute and the Siberian Husky. Both are intelligent, making them easy to train, and have thick coats to protect them form the severe col. Malamutes have even been used in the Antarctic. Their large size and great strength make them ideal for pulling sledges over snow and ice.

Mules – the offspring of a male ass and a female horse – are also used for their strength. Standing about 150 cm tall, these animals have a thick head and sturdy muscular build. First used as beasts of burden in Asia Minor 3,000 years ago, mules are still valued today for their ability to cope with rough and steep terrain. The Arabian horse is valued for its carrying capacity, but for speed and stamina. It was first bred for these specific qualities in the 7th century AD and has formed the blueprint for horse-breeding to the present day.

High altitude

Plant life is scare at altitudes due to low temperatures and barren soil. In the northern Andes in Columbia and Ecuador, alpine meadows called *paramo* contain grass and herbaceous plants. Some of these plants, called frailefones, can grow 4-6 m. In the southern paramo, rough grasses, cushion and rosette plants, shrubs and cacti survive. The Alps support a range of hardy plants called pulsatillas. The key to the survival of these plants is their thick, long, woody rootstocks that penetrate deep into the sparse soil and gravel. The plants open their leaves for a short period of activity during the early spring thaw, producing enough food to see them through the winter. Once the flowers are pollinated, they produce fuzzy seeds with tufts of hair to carry them in the wind.

Hardy lichens

The Earth's polar regions are some of the most barren of all, where only 10 mm of rain falls each year and the soil is always frozen. Only in the six months of summer sunlight, when snow meltwater is available, can the flora of these regions emerge. In the Arctic, temperatures rise above freezing for only one month a year. But this is enough for 1,000 species of ferns and flowers, 950 species of fungi, 300 liverworts and around 2,000 algae to flourish. Perhaps the hardiest of all the Arctic's plants are the lichens. These tiny plants can survive on barren rocks, nourished by the occasional bird dropping. In the Antarctic, around 400 species of lichen survive, along with snow algae which colour the coastal landscape red, green and yellow.

Fertile deserts

Desert plants have to face scorching sun and lack of water. In the Arabian Desert plants spring into action at the first sight of rain – seeds, buried for months in the dry gravel soil, germinate and send up shots without hours. Mustard, pea, daisy, caper, iris and milkweed plants turn the normally barren plains green with their hastily produced shoots and blooms. Along with these seasonal plants, hardy shrubs survive, yielding fragrant frankincense and myrrh. The desert carrion flower of southern Africa has no leaves. Just spine-tipped stems which store rainwater and protect the plant from grazing animals. At the tips of these stems the plant produces odd star-shaped flowers. Patterned in yellow and red to imitate rotting flesh, the flowers give off a foul stench like carrion to attract flies which pollinate the flowers, enabling the plant to reproduce.

Spiky cacti

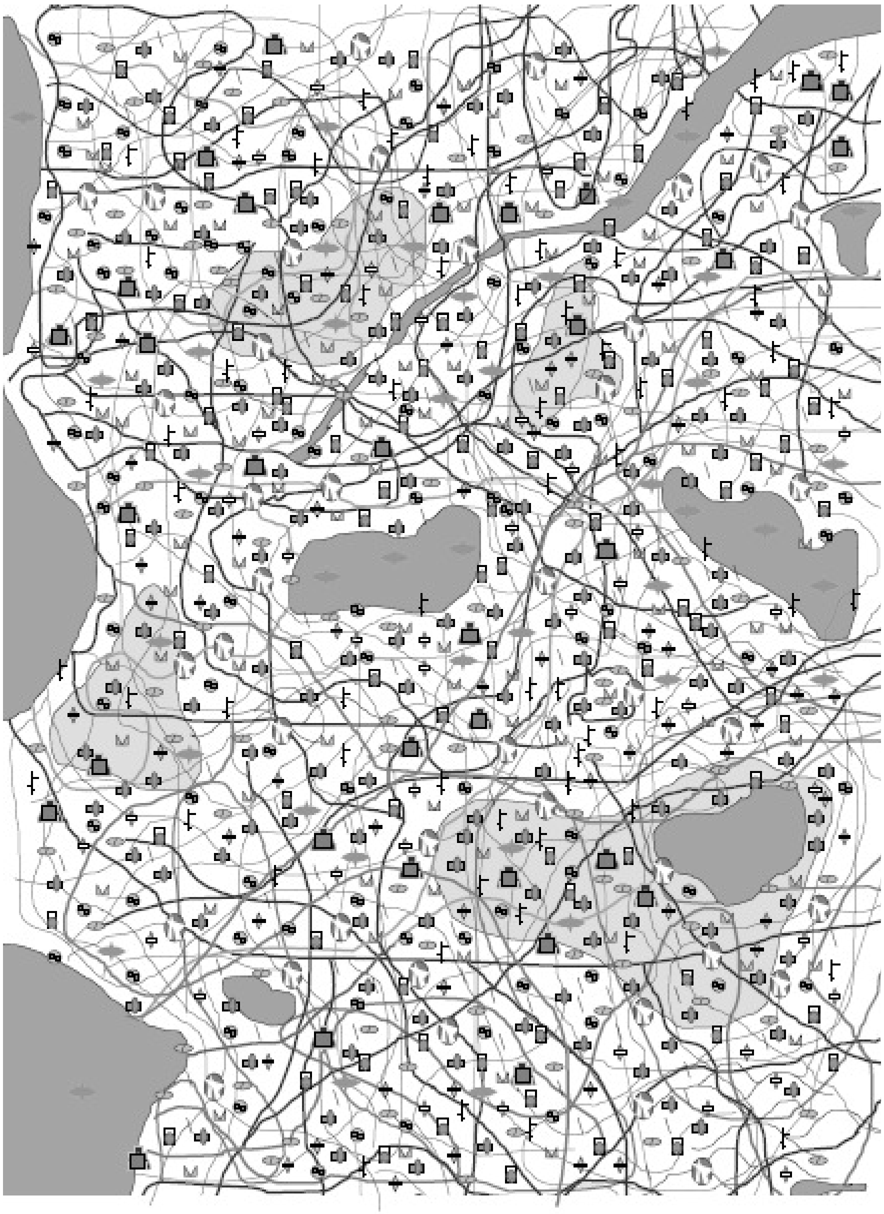
Succulents are the true specialists of arid regions. The most amazing of all is the miracle plant which can live for 1,000 years. Also called the 'living fossil', this plant, found in the deserts along the southern shore of South Africa, consists of two huge leaves which grow out flat to the sand in the opposite directions from a low woody stem. These leaves can be up to 3 m long and over 1 m wide. The plant gains water from sea frogs, driven in land by winds from the Atlantic – these same winds disperse the plan's seeds across the hot desert sands. There are a total of 1,650 known cactus species. Many of these can be found in the arid deserts of Mexico, including Button cacti which live on drops of moisture from beneath the desert rocks, and protect themselves from hungry animals by looking just like stones. One cactus which inhabits the totally arid Atacama Desert in Chile never receives any rain, only the damp mist from the Pacific.

Action beneath the surface

Using extremely long roots to get to any available water is a survival strategy common to the most resilient of desert plants. In the sandy Arabian Desert, the long, deep roots of sledge plants are so substantial that locals use them for firewood. The banana plant has an underground stem that sustains it safely through the dry season. This stem sends out a sturdy shoot that consists of thick leaf stalks, arranged one inside the other, and ends on an oblong leaf blade. When the rain comes, this shoot finds the water and a flower stem emerges from its centre.

Taken from: *The Guinness book of amazing nature* (1998). Guinness publishing ltd. Pp.153-154.

Appendix H: Map – Experiment 9



Original map = A3