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Emotion Regulation in Multiple Sclerosis

Bogumila Radlak

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D. Clin. Psychol. Declaration of own work

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Title of Work: Research Portfolio: Emotion Regulation in Multiple Sclerosis

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RESEARCH PORTFOLIO ABSTRACT

Introduction: The objective of this thesis was to examine aspects of emotion regulation in Multiple Sclerosis (MS). A systematic review was carried out of studies investigating the prevalence of alexithymia in individuals with MS, and its relationship with anxiety and depression. An empirical study was conducted to explore whether there were differences in emotion regulation abilities in individuals with different variants of MS, compared to healthy individuals.

Methods: Twelve journal articles were identified via systematic search utilising predefined criteria. Seventy nine individuals with relapsing-remitting type of MS, and 38 individuals with chronic progressive type of MS were recruited to the empirical study. Participants filled in self-report questionnaires measuring difficulties in emotion regulation, illness severity, illness representations and quality of life. Also, 55 healthy volunteers took part in the current study.

Results: The estimate of prevalence of alexithymia in MS was approximately twice as high as in general population. Positive relationships between alexithymia and/or anxiety and depressive symptoms were found. Those with MS reported difficulties accepting emotional distress which, to some extent, were predicted by strong illness identity and negative emotional responses to having MS. These findings were independently of illness severity, and type of MS. Perceptions of negative consequences of MS were the only partial mediator of the relationship between illness severity and quality of life.

Conclusions: Larger and more representative samples are needed to clarify the impact of alexithymia on the clinical presentations of patients with MS. Psychological interventions targeting non-acceptance of emotional distress and negative illness perceptions are warranted to support those with MS.

THE PREVALENCE OF ALEXITHYMIA AND ITS ASSOCIATION WITH ANXIETY AND DEPRESSION IN MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW

Bogumila Radlak[1*] and Paul G. Morris[2]

[1] Department of Clinical Neuropsychology, NHS Grampian, Aberdeen, AB25 2ZA, UK

[2] The School of Health in Social Science, the University of Edinburgh, Edinburgh, EH8 9AG, UK

* Corresponding author email address; bogumila.radlak@nhs.net; tel.: 0044 1224 559352; fax: 01224 661587

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Systematic Review Abstract

Objective: Large body of evidence across health conditions shows that the presence of alexithymia can adversely impact on functional and treatment outcomes. The main purpose of this review was to investigate the prevalence of alexithymia in Multiple Sclerosis and its relationship with mood difficulties, specifically anxiety and depressive symptoms.

Method: A literature search for studies assessing alexithymia in Multiple Sclerosis was conducted. The following major electronic databases were systematically searched until 10th March 2017: EMBASE (from 1947), MEDLINE (from 1946), PsychINFO (from 1806) and SCOPUS (from 1960), with secondary sources sought, including references in primary articles. Relevant first authors were contacted. Attempts were made to obtain any existing grey literature.

Results: Twelve observational studies met inclusion criteria. Presence of alexithymia, as determined by cut-off scores, was measured using self-report instruments, i.e. the Toronto Alexithymia Scale (by 10 studies) and the Bermond- Vorst Alexithymia Questionnaire (by two studies). Given methodological and reporting limitations, the most adequate estimate of prevalence of alexithymia in Multiple Sclerosis was 23%, and ranging from 10% - 31.6%. The balance of evidence indicated positive relationships between alexithymia and/or anxiety and depressive symptoms.

Conclusions*:* Levels of alexithymia are significantly higher in Multiple Sclerosis, compared to rates of approximately 10% in general population. Thus, it might prove beneficial to target alexithymic features in psychological treatment of Multiple Sclerosis. Yet, further studies with larger and more representative patient samples are required to clarify the impact of alexithymia on the clinical features of patients with MS.

Keywords: emotion regulation, illness representations, multiple sclerosis

Introduction

The importance and prevalence of mood disturbance in Multiple Sclerosis (MS) has previously been highlighted in research literature on MS (Feinstein & Feinstein, 2001; Mohr & Cox, 2001; Dahl, Stordal, Lydersen, & Midgard, 2009), with the prevalence of anxiety and depressive symptoms estimated to be approximately 34% and 35% respectively (Boeschoten et al., 2017), compared to the prevalence of anxiety and depressive disorders in MS estimated at 10% and 21% respectively (Boeschoten et al.,, 2017). Other emotional difficulties in MS are reported, such as emotional lability, pathological laughing and crying, as well as alexithymia (Montreuil & Petropoulou 2003; Montel & Bungener, 2007). It is important, from a clinical point of view, to investigate whether alexithymia is common in individuals with MS, since the presence of alexithymia is shown to affect suitability and outcomes to different types of psychological treatments, as well as has prognostic implications for those affected (Lumley, Neely, & Burger, 2007).

Further, alexithymia has been conceptualised as a vulnerability factor for the appearance of psychiatric and psychosomatic symptoms (Franz et al., 2008), being strongly related to depression and anxiety in the general population (Honkalampi, Hintikka, Tanskanen, Lehtonen, & Viinamäki, 2000; Marchessi & Maggini, 2001). There is also some evidence of the relationship between the presence of alexithymia and poorer therapeutic outcomes (Lumley et al., 2007). Thus, further exploring the evidence for the relationship between alexithymia and depression or anxiety in studies on MS might shed some light on whether alexithymic traits should be considered in the treatment of mood disorders in MS.

Definition of alexithymia

The alexithymia construct was first coined by Sifneos (1973) to capture a cluster of traits which were key to the clinical presentation of patients with psychosomatic disorder who were found not to benefit from insight- oriented psychotherapy approaches. The original view of alexithymia, which is widely acknowledged in contemporary research and theory (Taylor, Bagby, & Parker, 1997), is of emotional blindness; entailing a cluster of cognitive traits such as, difficulties with identifying and describing own emotional states to others, as well as having a predominantly externally-oriented thinking and reduced imaginative capacity. Therefore, individuals having alexithymia struggle with recognising and communicating how they feel, display little insight into their internal emotional states, subsequent symptoms and physical manifestations of their feelings (Nemiah, Freyberger, & Sifneos, 1976). Much less recognised alternative view of alexithymia is that of a global emotional processing impairment which restricts recognition and expression of one's feelings (Lane, Sechrest, Riedel, Shapiro, & Kaszniak, 2000). Nevertheless, both constructs approve of alexithymia being an inability, deficit or deficiency in emotional processing rather than an active defensive process or maladaptive emotion regulation strategy (such as e.g. emotion suppression, inhibition or denial etc.), which limits the experience or expression of emotion (Lumley et al., 2007). Other emotion-related construct that is commonly mistaken for alexithymia is emotion regulation. Emotion regulation is a broader concept than alexithymia that encompasses a wide array of processes, such as accessing and expressing emotions, monitoring and controlling one's feelings and accepting one's emotional states (Dahl, 2003). The current systematic review article is focused solely on the original definition of alexithymia, for which a very large body of literature has been produced, primarily in physical and psychiatric health, with less focus being on neurological conditions such as MS.

Measurement issues in alexithymia

Assessment tools of alexithymia have been developed over the past four decades with questionable psychometric properties, thus, resulting in clinical and research practice call for the development of measures that are shown to be valid and reliable. Given that the critical review of assessment measures of alexithymia is beyond the scope of this review, the reader is referred to several such reviews, comprehensively covering assessment methods that are interview-based, collateral informant-based, and self-reports (see e.g. Linden, Wen, & Paulhaus, 1994; Taylor, Bagby, & Luminet, 2000; Taylor et al., 1997; Lumley et al., 2007). The current review focuses on two alexithymia self-report tools used in research with participants with MS, namely the 20-item Toronto Alexithymia Scale (TAS-20; Bagby, Taylor, & Parker, 1994), as well as the Bermond- Vorst Alexithymia Questionnaire (BVAQ; Bermond & Vorst, 1998).

Overall, self-report measures are the most extensively used in the assessment of alexithymia (Lumley et al., 2007). The Toronto group developed the TAS-20 to measure three aspects of alexithymia on a 5-point Likert-type scale, namely difficulty recognising own emotions (e.g. "*I have feelings that I can't quite identify*"), difficulty describing feelings (e.g. "*People tell me to describe my feelings more*"), and externally oriented thinking (e.g. "*I prefer to analyse problems rather than just describe them*"). TAS-20 has an empirically–derived cut-off score that classifies people into having alexithemia (61-100), being borderline alexithymic (52-60), or non-alexithymic (20-51) despite scores being continuous. This measure has been utilised widely in both nonclinical and clinical populations, and has been, to our knowledge, the most extensively employed measure in alexithymia research as a whole, as well as in MS research. There is a wealth of data to support its convergent and discriminant validity, as well as to predict clinical criteria and basic emotional processes involved in alexithymia (Bagby et al., 1994; Parker, Taylor, & Bagby, 2003; Zech, Luminet, Rimé, & Wagner, 1999).Given the

extensive validation of TAS-20, its brevity, ease of employment, and the possibility of comparison across various studies when utilising a common tool, the TAS-20 has become the golden standard in alexithymia evaluation in the literature. Yet, this measure is not without limitations. The three cognitive aspects of alexithymia captured by the TAS-20 have different number of items, with some aspects loading more than others to the total score which is used for the diagnosis of alexithymia. It has also been argued by some (e.g. Vorst & Bermond, 2001) that other essential aspects of alexithymia, such as 'limited fantasizing', as well as 'limited experiencing of emotional states' that are not included in this measure, ultimately limit the operationalization of this tool, providing a limited assessment of alexithymia.

More recently developed BVAQ captures same aspects of alexithymia as the TAS-20 (identifying, verbalizing and analysing), with an additional assessment of 'emotionalizing' and 'fantasizing' (Vorst & Bermond, 2001), thus, arguably being a more comprehensive measure of alexithymic traits. These five aspects of alexithymia are measured on a 5-point Likert-type scale. 'Emotionalizing' refers to the degree of arousal caused by emotional events (e.g. "*When something unexpected happens, I remain calm and unmoved*"), 'fantasizing' is the propensity to engage in daydreaming and imaginative thinking (e.g. "*I have few daydreams and fantasies*"), 'identifying' is defined as one's capability to recognise own emotional states (e.g. "*When I am tense, it remains unclear from which of my feelings this comes*"), 'analyzing' is defined as one's eagerness to seek out reasons for own emotional responses (e.g. "*I hardly ever consider my feelings*"), and 'verbalizing' is one's ability to label or communicate own feelings (e.g. "*I find it difficult to express my feelings*"). The scale consists of two parallel versions (A and B) of 20 items each, with version B shown to be more psychometrically sound (Zech et al., 1999). There is substantially less studies supporting evidence of adequate validity and reliability of BVAQ, despite moderate correlations of the BVAQ with the TAS-20 (Morera,

Culhane, Watson, & Skewes, 2005). The empirically derived cut-off score for determining the presence and absence of alexithymia is over 52 and below 44 respectively (Gay et al., 2017). Importantly, to best of our knowledge, the psychometric properties have been evaluated only for the TAS-20 in a sample of individuals with MS (Fernandez-Jimenez et al., 2013). Factorial validity and reliability were adequate, supporting the three factor structure of the Spanish adaptation of this measure.

Prevalence in general population and non-neurological conditions

It is believed that the prevalence of alexithymia in the general population is approximately 10%, with somewhat higher rates for men (9% - 17%) than for women (10%-15%; Mattilaa, Salminenc, Nummia, & Joukamaa, 2006). Alexithymia appears to be normally distributed in both genders and therefore regarded by some as a personality dimension (Franz et al. 2008). Although some evidence suggests that alexithymia tends to be more prevalent in advanced age, in men rather than women (Honkalampi et al., 2000; Mattilaa et al., 2008), and in those with low educational level and socioeconomic status (Franz et al., 2008), the sizes of these relationships tend to be variable.

Aggravated rates of alexithymia are found in patients with psychosomatic disorders (40-60%; Taylor et al., 1997), autism spectrum disorder (40%-60%; Berthoz & Hill, 2005), depressive disorders (32 - 51%; Marchesi et al., 2000; Saarijarvi, Salminen, & Toikka, 2001), anxiety disorders (13% - 58%; Da & Taylor, 1993; Marchesi, Brusamonti, & Maggini, 2000), eating disorders (24% - 77%; de Zwaan et al., 1995), addictive disorders (30% - 50%; Evren et al., 2008), and obsessive-compulsive disorder (11% - 36%; Grabe et al., 2006). Thus, it appears that individuals with various psychiatric conditions are at the higher risk of having alexithymia.

Prevalence of alexithymia in neurological conditions

Alexithymia appears to have been most widely investigated in traumatic brain injury (TBI), with 30%-60% of those with TBI also meeting criteria for the diagnosis of alexithymia (Ricciardi, Demartini, Fotopoulou, & Edwards, 2015). Individuals with epileptic seizures were also found to have aggregated levels of alexithymic traits, ranging from 29% to 76% (Ricciardi et al., 2015). Recent systematic review of 11 studies on the prevalence of alexithymia in Parkinson's disease, reported its prevalence to be between 18% - 23.8% (Assogna et al., 2016). Similarly to non-neurological conditions, the prevalence of alexithymia appears to be markedly higher in those aetiologically distinct neurological conditions. Yet, there is a body of evidence that these conditions, similarly to MS, are associated with the presence of various emotional difficulties other than alexithymia (Beyenburg et al., 2005; Fann, Hart, & Schomer, 2009; Péron et al., 2012).

Moreover, there is neuroimaging evidence (Moriguchi & Komaki, 2013) that alexithymia is associated with reduced neural responses to emotional stimuli, and with decrease activity during imagery, in the limbic and paralimbic areas (i.e., anterior/posterior cingulate cortex, amygdala, insula). In contrast, alexithymia is also known to be associated with enhanced neural activity in somatosensory and sensorimotor regions, including the insula. As most of these areas have been found to be adversely affected by early stages of MS (Audoin et al., 2010), it seems reasonable to assume that the prevalence of alexithymia will also be heightened in people with MS.

Rationale for the review:

A large body of evidence across health conditions shows that the presence of alexithymia may adversely impact on functional outcomes (Lumley et al., 2007), and predicts patients' prognosis in psychiatric, behavioural as well as medical treatments. Following from that, alexithymia

predicts poorer treatment outcomes, not only for somatoform disorders (Bach & Bach, 1995) and mixed psychiatric disorders (McCallum, Piper, Ogrodniczuk, & Joyce, 2003), but also for anxiety and depression (Ogrodniczuk, Piper, & Joyce, 2004). Since it appears likely that alexithymia hinders adjustment to illness and/or recovery, it is possible that it will also impact on rehabilitation treatment which is commonly offered to those with MS (and with other neurological conditions). It is therefore important to investigate the prevalence of alexithymia in MS.

Moreover, taking into account alexithymic traits of individuals with MS and understanding their relationship with depression and anxiety can aid neuropsychological assessment and possibly result in treatment plans becoming more effective. This might be particularly relevant for psychological interventions which focus on close rapport with a therapist, rely on high degree of insight and emotional awareness, such as cognitive-behavioural therapy (CBT), acceptance-commitment therapy (ACT), as well as psychodynamic psychotherapy. Hence, the purpose of this review is to explore further the evidence for alexithymia in MS and its relationship with depression and anxiety.

Methods

Review aim:

The primary aim of this review was to investigate the prevalence of alexithymia in individuals in MS. It was hypothesised that the prevalence of alexithymia would be heightened in people with MS, compared to the general population.

The secondary aim was to investigate the relationship between alexithymia and mood difficulties, specifically anxiety and depressive symptoms, in MS.

Search strategy:

Searches were carried out within the domains of keywords, title and abstract. The following major electronic databases were systematically searched until 10th March 2017: EMBASE (from 1947), MEDLINE (from 1946), PsychINFO (from 1806) and SCOPUS (from 1960). The following key terms were utilised in a search string: ("multiple sclerosis" OR "MS" OR "neurological disease") AND ("alexithymia" OR "alexithymic" OR "emotion regulation" OR "emotion* dysregulation" OR "emotion* functioning" OR "emotion* recognition" OR "emotion* perception" OR "emotion* identification" OR "emotion* awareness" OR "emotion* unawareness" OR "emotion* blindness " and " emotion* lability"). Also, the Cochrane Database of Abstracts of Reviews of Effects (DARE) was searched to ensure that a similar review had not been carried out recently, using the same key terms.

Inclusion/exclusion criteria for the assessment of included studies:

It has been suggested by the Centre for Reviews and Dissemination (CRD; 2009) that poorer quality studies tend to report more favourable outcomes than high quality studies. This, however, might be an artefact of publication bias, with poorer quality studies being less likely to publish at all if they do not report favourable outcomes- such that similar quality studies that indicate no effect are not published. Studies exploring prevalence of alexithymia and group differences in alexithymia, as compared to general population, are mainly observational: case-control or cross-sectional in design. Moreover, strong inferences about causality of effects or associations found cannot be made considering that variable are not manipulated under

experimental conditions, and participants are not randomly selected. Thus, these studies are placed at the lower end of evidence quality hierarchy (CRD, 2009).Yet, it is important to consider whether strategies to improve confidence in the results and to attempt reducing a risk of bias (by e.g. blind assessments of outcome or careful matching etc.) have been employed by those studies.

The literature search, as well as consultation of the CRD (2009), Cochrane Collaboration (2011) and the Agency for Healthcare Research and Quality guidelines (AHRQ; 2012) revealed no particular recommended tool for evaluating risks of bias in observational studies. The aforementioned resources recommend employment of a domain-based evaluation tool (The Cochrane Collaboration, 2011), and question using a scale or a checklist that utilises summary scores, as such scores imply that all biased items are of similar risk to study's findings. The CRD recommend the AHRQ tool for the quality assessment of observational studies, and to tailor it to best meet the requirements of the systematic review in question. This systematic review adopted the aforementioned quality assessment tool (see Table 1 in appendix A), with review criteria following internationally recognised guidelines produced by both, the Centre for Reviews and Dissemination (CRD), The University of York (www.york.ac.uk/inst/crd/), as well as the Scottish Intercollegiate Guidelines Network (SIGN 50, 2015). The quality assessment tool covers the domains of: detection bias, selection bias and confounding, validity and reliability of measures, statistical power, and method of analysis.

The PCOS format (Population, Comparators, Outcomes, Study Design; CRD, 2009) was employed. Each quality criterion was given a rating of 'yes', 'partially', 'no', or 'unclear', with a rationale for the decision noted (see Table 2 below). Quality criteria 1, 2, 5 and 6 were relevant to the first aim of the review, with all of the criteria being relevant to the second aim of the review. An overall quality category was applicable only to those included studies which helped to address the secondary aim of the current review. An overall quality category, instead of a single summary score, was utilised with four possible ratings of:

- 'excellent', i.e. All but one of the criteria are well covered, with up to one partially addressed. Limitations of the study are thought to be very unlikely to have affected the findings or conclusions drawn.
- 'very good', i.e. All but two of the criteria are well covered, with up to two partially addressed. Limitations of the study are thought to be unlikely to have affected the findings or conclusions.
- 'reasonable', i.e. At least 70% of criteria are either partially addressed or well covered , with up to one criterion being unmet or unclear. Limitations of the study may have modestly affected the findings or conclusions.
- 'limited', i.e. Many or most criteria were partially addressed with some criteria being unmet and unclear. Limitations of the study are thought likely or very likely to have affected the findings or conclusions.

An independent rater reviewed the quality of 50% of included studies, selected randomly. Exact agreement was achieved on 68% (54/80) of methodological quality ratings, with a difference of one point (e.g. yes versus partially or partially versus no) on 25% (20/80) of items and of two points (e.g. partially versus unclear) on 7% (6/80) of items. All differences between raters were discussed and amended where appropriate.

Table 2.
Study Characteristics and Main Findings

Author(s) and country of origin	Participants	Participants with MS eligibility criteria	Study Design	Outcome measures	Key Results
Cecchetto et al., (2014) **Italy**	**RRMS** = 30 (70% females), **Age** *M* = 34.2 (*SD* = 6.2), **YoE** *M* = 14.7 (*SD* = 2.0), **MS duration** *M* = 9.1 (*SD* = 6.7), **EDSS** *M* = 2 (*SD* = 1.0)	McDonald criteria for diagnosis EDDS ≤ 4.5, age 20-40, IQ ≥ 80, no other neurological or psychiatric disorder	Case-control study	**TAS-20** **BDI**	The prevalence of alexithymia was 10% (n = 3) of MS group met thr There were no participants meeting Alexithymia scores significantly co = .51, *p* = .004).
Gleichgerrcht et al., (2015) **Argentina**	**RRMS** = 38 (87.3% females) **Age** *M* = 42.3 (*SD* = 11.3), **YoE** *M* = 15.4 (*SD* = 2.8) **EDSS** *M* = 1.66 (*SD* = 1.6), **MS duration** *M* = 1.6 (*SD* = 8.7, range 1.38-39.3 years), **MSSS** *M* = 2.35 (*SD* = 2.4)	McDonald criteria for diagnosis, no other neurological or psychiatric disorder, no TBI, no alcohol/drug abuse	Case-control study	**TAS-20**	The prevalence of alexithymia was
Kuloglu et al., (2012) **Turkey**	**MS** = 60 (66.7% females), RRMS &SPMS-percentage not reported **Age** *M* = 35.2 (*SD* = 8.9, range 18-25), **YoE** – no data, **MS duration** *M* = 5.4 (*SD* = 4.5), **EDSS** *M* = 1.31 (*SD* = 1.07)	McDonald criteria for diagnosis for RRMS or SPMS, no psychiatric or other neurological disorder, no drug/alcohol abuse	Case-control study	**TAS-20**	The prevalence of alexithymia was
Patil et al., (2016) **Argentina**	**RRMS** = 38 (86.8% females), **Age** *M* = 42.3 (*SD* = 11.3), **YoE** *M* = 15.4 (*SD* = 2.8), **MS duration** *M* = 10.60 (*SD* = 8.7), **EDSS** *M* = 1.66 (*SD* = 1.6), **MSSS** *M* = 2.35 (*SD* = 2.4)	McDonald criteria for diagnosis for RRMS, no psychiatric disorder, drug/alcohol abuse, TBI, MMSE >24 Inclusion criteria for HC: no neurological or psychiatric disorder,	Case-control study	**TAS-20**	The prevalence of alexithymia was

		drug/alcohol abuse, TBI			
Prochnow et al., (2011) **Germany**	**MS** = 35 (34.3% females; SP = 29 (83%), RR = 5 (14%), PP = 1 (3%), **Age** *M* = 48.2 (*SD* = 10.2), **YoE** *M* = 10.8 (SD = 2.3), **MS duration** *M* = 9.2 (*SD* = 8.4), **EDSS** *Median* = 6.0 (range 0-7.5)	McDonald criteria for diagnosis: no psychiatric or other neurological disorder	Case-control study	**TAS-20** **BDI**	The prevalence of alexithymia was According to the cut-off scores 1 classified as depressed, 28.6% (n = 45.7% (n =16) as not depressed. Mi Correlational analysis between ale was not performed/reported.
Bodini et al., (2008) **Italy**	**RRMS** = 58 (56.9% females), **Age** *M* = 34.8 (*SD* = 9.3, range 28-80), **YoE** – no data, education levels reported instead, **EDSS** *Median*= 1.5 (range 0-6.0), **MS duration** *M* = 9.1 (*SD* = 5.5). Marital status reported	McDonald criteria for diagnosis for RRMS, MMSE ≥24, no psychiatric or other neurological condition	Cross-sectional study	**TAS-20** **BDI**	Alexithymia was found in 13.8% of Significantly higher levels of depr found in alexithymic patients (n = alexithymic patients (n = 37).TAS- subscale was associated with BDI s the strongest factor associated with Among the alexithymic group, 6 (BDI ≥ 13), compared to 7 out of 3 group (p = .02). Significant correlation between (rho = .37, p <.004)
Chahraoui et al., (2008) **France**	**MS** = 61 (68.8% female; RR = 46 (75 %), SP = 6 (9.8%) PP = 9 (14.8%), **Age** *M* = 41.1 (*SD* = 10.8), **YoE** – no data, education levels reported instead, **MS duration** *M* = 9.28 (*SD* = 7.51), **EDDS** *M*= 2.9 (*SD* = 2.19)	Posner criteria for diagnosis, no history of psychiatric disorder	Cross-sectional study	**TAS-20** **BDI** **STAI**	The prevalence of alexithymia was Alexithymics were significantly mo than borderline alexithymics (d = 0.71) with MS. Alexithymics were significantly m 0.01,) than borderline alexithymics (d = 0.89) with MS. Alexithymics were significantly m 0.003) than borderline alexithymics (d = 0.84) with MS. The prevalence of depression wa 44.3%, and state anxiety was 29.6% Positive correlations between anxi scores were found: the TAS-20 DIF with BDI (r =.31, p = .05), STAI-S (r =.43, p = .01), and STAI-T (r =.43, p =.01). The TAS-20 DDF subscale signific =.28, p = .05), and STAI-T (r =.31, Depression, state and trait anxiety alexithymia scores.
Fernandez-Jimenez et al., (2013) **Spain**	**MS** = 221(63.03% female; RR = 172 (77.8%); SP =39 (17.7%), PP = 10 (4.5%),	McDonald criteria for diagnosis, no psychiatric or other neurological disorder, no	Cross-sectional study	**TAS-20**	High degree of alexithymia was pre Reliability and the three factor m scale.

	Age *M* = 40.61 (*SD* = 9.65), **YoE** – no data, education levels reported instead, **MS duration** *M* = 8.45 (*SD* = 6.23), **EDDS** *M*= 3.04 (*SD* = 1.83)	cognitive impairment			
Gay et al., (2010) **France**	**MS** = 115 (68.6% females), **Age** *M* = 47.2 (*SD* = 10.9, range 20-80), **YoE** – no data, education levels reported instead, **MS duration** *M* = 15.3 (*SD* = 10.05), **EDDS** *M* = 4.75 (*SD* = 2.45)	Inclusion criteria: not stated	Cross-sectional study	**TAS-20** **DRS** **STAI**	Alexithymia, and satisfaction with mediators of the relationship betwe MS. Those variable explain 56.7% 20.5% of individuals with MS had 5.4% severe depressive symptoms, state anxiety, 43.8% trait anxiety, a Depressive symptoms strongly asso *r* = .50, *p* <.001
Chahraoui et al., (2014) **France**	**MS** = 66 (62% female, RRMS = 41, (80.6%)), **Age** *M* = 41. 4 (*SD* = 10.86, range 20-77), **YoE** = no data, **MS duration** *M* = 10.9 (*SD* = 8.66), **EDDS** = 3.07 (*SD* = 2.20)	McDonald criteria for diagnosis	Longitu-dinal Study	**TAS-20** **BDI** **STAI**	Alexithymia positive linked to trai depression (*r* = .27, *p* < .05). Moderate trait anxiety in 15 (24.2 (19.4%). Moderate depression in 20 (32.3 (8.1%).
Dulau et al., (2017) **France**	**MS** = 60 (58% females, RR = 30 (50%), SP = 15 (25%), PP = 15 (25%) **Age** *M* = 46.5 (*SD* = 10.6, range 18-60), **YoE** *M* = 12.9 (*SD* = 3.3), **MS duration** *M* = 14.4 (*SD* = 9.4, range 2-18 years), **EDDS** *Median* = 4 (range 0-6)	McDonald criteria for diagnosis psychiatric comorbidity, history of drug/alcohol abuse, neurological impairment (MMSE <24), EDDS > 6	Case-control study	**BVAQ-** unclear which version used (A or B) **BDI** **STAI**	The prevalence of alexithymia was No significant relationships betwe anxiety were found; *pearson's r* = BVAQ and z-score of BDI; pearson' of BVAQ and z- score of STAI-T.
Gay, Bungener, Thomas, Vrignaud, Thomas, et al. (2017) **France**	**MS** = 189 (64% female; RR = 108 (57 %); SP = 54 (29%), PP = 28 (15%)), **Age** *M* = 44.2 (*SD* = 12.5), **YoE** – no data, **MS duration** *M* = 15.0 (*SD* = 9.29, range 2-18 years),	McDonald criteria for diagnosis	Cross-sectional study	**BVAQ** - version B **HADS**	The prevalence of alexithymia was Self-reported levels of anxiety (*M* = (*M* = 8.0, *SD* = 4.19) were in the n 16/189 (8.5%) had both anxiety an anxiety, 37/189 (19.6%) had depres No statistically significant differen depressed in terms of alexithymia, between anxious and non-anxious a *p* = .14

	EDDS *M*= 4.7 (*SD* = 2.37)				Alexithymia did not correlate with correlated significantly with anxiety

Population

Selected studies were based exclusively on human adults (age range of 18–65 years) with a clinical diagnosis of MS, regardless of nationality, race or gender. Studies that included individuals with other degenerative conditions of the Central Nervous System (e.g. dementia) were excluded, unless data of participants with MS were reported separately.

Comparators

Studies with and without healthy control (HC) groups were included. Data of HC was not considered, as it was not essential to answer review's aims.

Outcomes

Presence of alexithymia, as determined by adequate cut-off scores, was the outcome of interest. Thus, only studies that included at least one validated observer and/or self-report measure of alexithymia were included in the review of the primary aim. Moreover, to be included in the review of the secondary aim, studies also required a measure of anxiety and/or depression.

Study Design

Studies included were in English and presented original data. Studies were selected based on the basis of study design, including observational investigations with cross-sectional or longitudinal design. Relevant first authors were contacted for additional information/data when needed. Conference abstracts were excluded unless additional details could be found. To reduce the impact of potential publication bias, B.R. contacted the primary authors of relevant conference abstracts to include any suitable unpublished studies. Eleven authors were

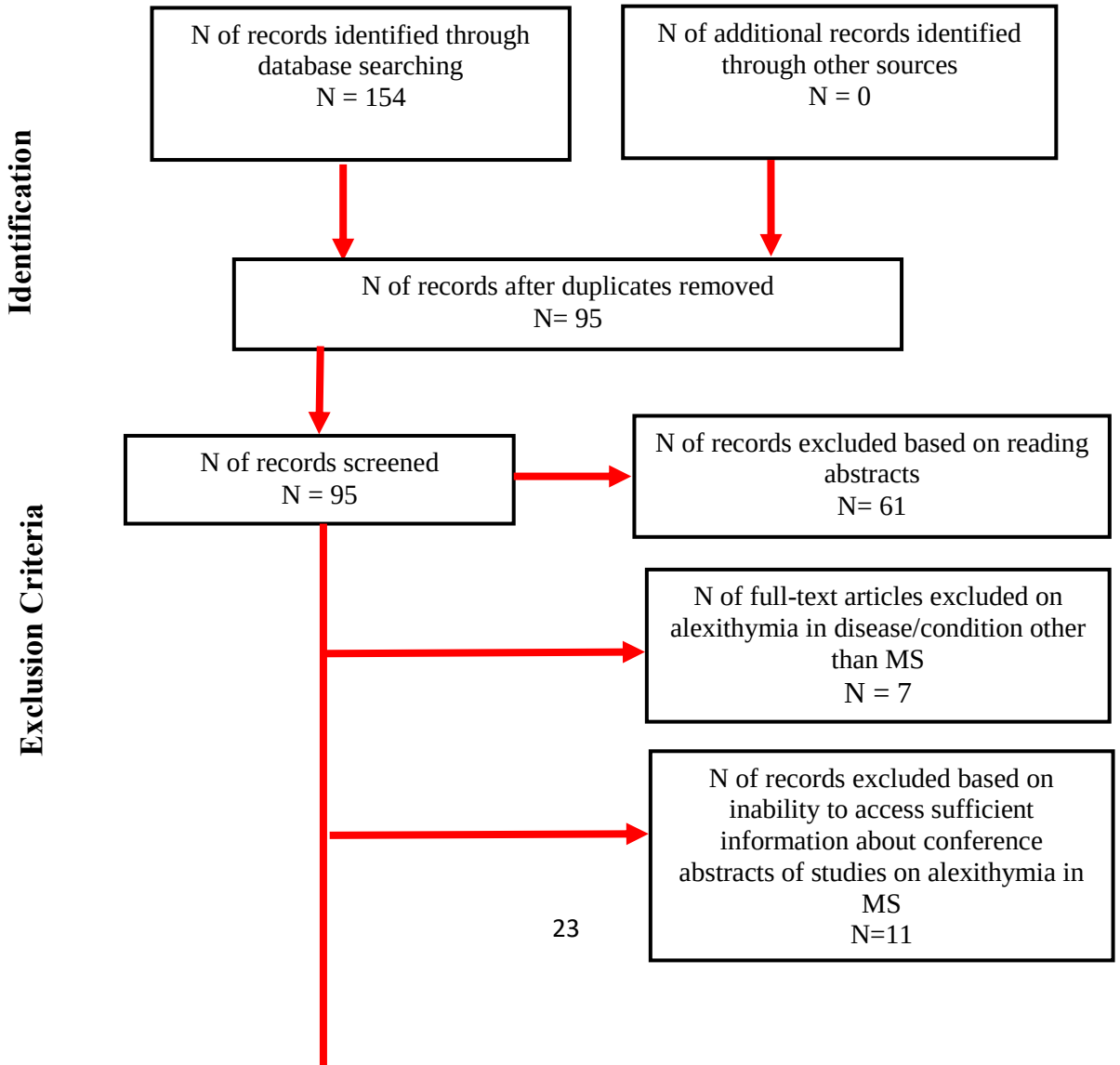
approached, of whom six did not respond, three could not be contacted, and two did not have the data presented in a reviewable format (i.e. manuscript, thesis etc.). Further attempt was made to include 'grey literature' into the current review by using the reference lists of published studies, searching on Google Scholar and greylit.org for published reports/ academic theses using same abovementioned key terms. No further studies were found which could had been considered for inclusion.

Results

Characteristics of included studies

The search process initially identified 95 studies (after excluding 59 duplicates). Both, titles and abstract of these 95 studies were investigated for their suitability, accounting for the inclusion and exclusion criteria detailed below. This resulted in 12 studies being retained for the systematic review (Bodini, Mandarelli, Tomassini, Tarsitani, Pestalozza et al., 2008; Cecchetto, Aiello, D'Amico, Cutuli, Cargnelutti et al., 2014; Chahraoui, Pinoit, Viegas, Adnet, Bonin et al., 2008; Chahraoui, Duchene, Rollot, Bonin, & Moreau, 2014; Dulau, Deloire, Diaz, Saubusse, Charre-Morin, et al. 2017; Fernandez-Jimenez, Perez-San-Gregorio, Taylor, Bagby, Ayearst et al., 2013; Gay, Bungener, Thomas, Vrignaud, Thomas, et al., 2017; Gay, Vrignaud, Garitte, & Meunier, 2010; Gleichgerrcht, Tomashitis, & Sinay, 2015; Kuloglu, Saglam, Korkmaz, Saglam, Gurok et al., 2012; Patil, Young, Sinay, & Gleichgerrcht, 2016; Prochnow, Donell, Schafer, Jorgens, Hartung, 2011). The pathway of the literature review process in illustrated in Figure 1 below. Main characteristics and key findings of interest to this review are reported in Table 2 in Appendix A. Six studies were case-control studies, comparing individuals with MS to healthy controls, further five were cross-sectional observational studies, and one study was longitudinal observational in design, with individuals with MS only. Ten of

these studies used the TAS-20 to measure alexithymia in MS, with further two studies employing the BVQS. Seven of these studies further investigated the relationship with alexithymia and depression in MS. Five of these studies further investigated the relationship between alexithymia and anxiety in MS. The number of participants with MS varied in the studies from 30 to 221. Altogether, 971 individuals with MS (635 females; 65.4%) took part in these studies, with three of the studies (Chahraoui, et al., 2014; Gay et al., 2010; Kuloglu et al., 2012) not reporting the exact figures for different clinical types of MS (n = 240). Based on the data reported in the remaining nine studies (n = 731), 525 individuals had RRMS (72%), 143 had SPMS (19%), and 63 had PPMS (9%). These figures are similar to the distribution of clinical types in MS population **(**Neild, 2006). The included studies dated from 2008 to 2017, were published in English and originated from Argentina (2), France (5), Germany (1), Italy (2), Spain (1) and Turkey (1).



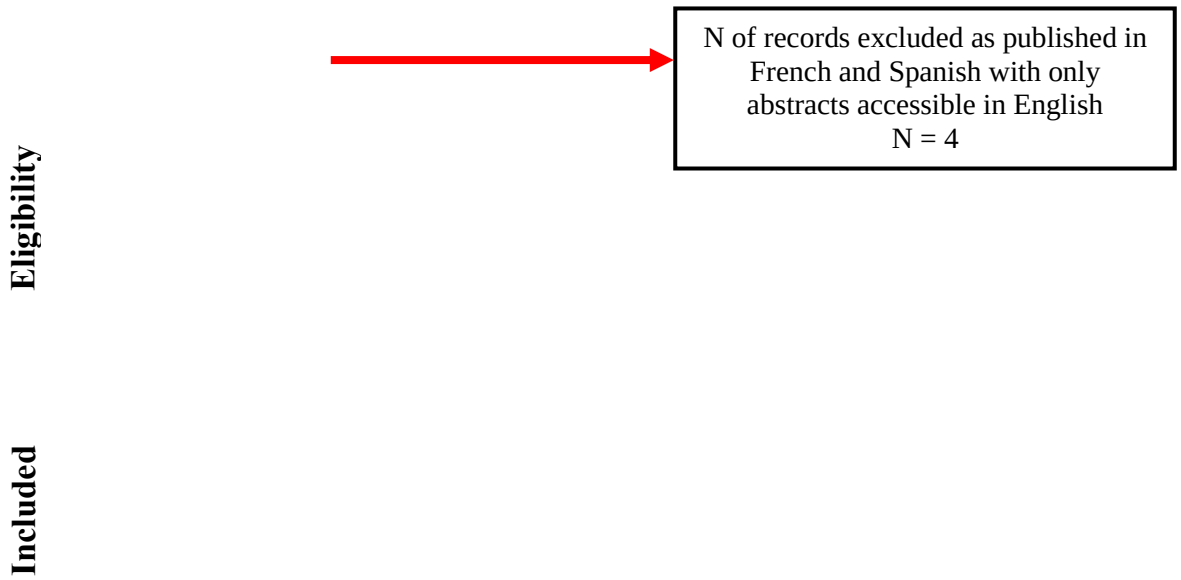


Figure 1. The pathway of the literature review process.

Quality assessment of included studies

Evaluation of the methodological strength of the aforementioned studies using the AHRQ quality assessment was conducted by applying the quality criteria outlined in Table 1 above to each of the studies, with quality ratings presented in Table 3 below. This assessment highlighted key areas which are likely to have introduced bias into the studies and impacted on the results obtained. Five out of twelve studies (Chahraoui et al., 2008; Fernandez-Jimenez et al., 2013; Gay et al., 2010, 2017; Kuloglu et al., 2012) met criteria for 'reasonable' quality, with remaining seven having 'limited' quality (Bodini et al., 2008; Cecchetto et al., 2014; Gleichgerrcht et al., 2014; Chahraoui et al., 2014; Dulau et al., 2017; Patil et al., 2016; Prochnow et al., 2011). Studies with 'reasonable' quality tended to be characterised by more representative samples and more sufficient power to detect moderate effects.

Table 3.
Quality Criteria of Included Studies in MS

Study	Quality Criteria							
	1. Selection of the cohort is unbiased*	2. Validated measure of alexithymia*	3. Validated measure of depression	4. Validated measure of anxiety	5. Sufficient Power*	6. Performance bias: outcome assessment blind to exposure*	7. Appropriate analytical methods	Quality 'Category' to address second aim (Excellent, Very Good, Reasonable, Limited)
Case-control studies measuring alexithymia with TAS-20								
Cecchetto et al. (2014)	PARTIALLY	PARTIALLY	PARTIALLY	N/A	NO	UNCLEAR	N/A	LIMITED
Gleichgerrcht et al. (2015)	PARTIALLY	PARTIALLY	N/A	N/A	NO	UNCLEAR	N/A	LIMITED
Kuloglu et al. (2012)	PARTIALLY	PARTIALLY	N/A	N/A	PARTIALLY	UNCLEAR	N/A	REASONABLE
Patil et al. (2016)	PARTIALLY	PARTIALLY	N/A	N/A	NO	UNCLEAR	N/A	LIMITED
Prochnow et al. (2011)	PARTIALLY	PARTIALLY	PARTIALLY	N/A	NO	UNCLEAR	N/A	LIMITED
Observational studies measuring alexithymia with TAS-20								
Bodini et al. (2008)	PARTIALLY	PARTIALLY	PARTIALLY	N/A	NO	UNCLEAR	YES	LIMITED
Chahraoui et al. (2014)	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	NO	NO	YES	LIMITED
Chahraoui et al. (2008)	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	UNCLEAR	YES	REASONABLE
Fernandez-Jimenez et al. (2013)	PARTIALLY	YES	N/A	N/A	PARTIALLY	NO	YES	REASONABLE

Gay et al. (2010)	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	REASONABLE
Observational studies measuring alexithymia with BVAQ								
Dulau et al. (2017)	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	NO	UNCLEAR	YES	LIMITED
Gay et al. (2017)	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	PARTIALLY	NO	PARTIALLY	REASONABLE

Note. Criteria 1, 2, 5 and 6 only were relevant to the first aim of the current review, with all of the criteria being relevant to the second aim.

Areas of strength

Most studies provided sufficient detail regarding the MS cohort, with key baseline demographics and appropriate inclusion/exclusion criteria being well specified, with recruitment settings reported. This enabled an understanding of the composition of the samples across the studies. The measures used for the assessment of alexithymia, depression and anxiety in MS were generally well validated (often in MS population) and reliable, with adequate analytical techniques and reporting of statistical data.

Areas of weakness

Although most studies used adequate inclusion/exclusion criteria and described key demographic variables of the sample, the samples were likely to be of limited representativeness of MS population. Five out of 12 studies had homogenous samples, included people with RRMS only, with lower neurological disability (i.e. MS severity as measured by the EDDS) and shorter MS duration. Likewise, most of the remaining studies predominantly included people with RRMS which reflects the prevalence of different types of MS in the population, and clinical accessibility to those with this most prevalent type of MS. Yet, having the majority of studies conducted on people with the RRMS will unavoidable limit the generalisability of the findings to other types of MS, such as SPMS and PPMS. More importantly, there appeared to be a lack of a priori power calculations to establish sample sizes needed to achieve sufficient statistical power. The majority of the studies were underpowered which further limits the representativeness of their small samples and their ability to reliably obtain the results they reported. Only five out of 12 studies had sufficient power to detect large to moderate effect sizes, with no studies having large enough samples to detect small magnitude of the effects. In sum, the risk of sampling and detection bias was high in the included studies.

Aligned to the abovementioned limitations, is the issue of sampling procedures not being specified by most of the studies, with four reporting convenience sampling procedure (Chahraoui et al., 2014; Fernandez-Jimenez et al., 2013; Gay et al., 2010, 2017). It is very likely that members of the target population did not have equal chances of being selected, as no forms of randomisation were reported and most studies recruited their participants from clinical settings; outpatient and inpatient MS clinics and university hospitals (see Table 4 in appendix B for more details). Thus, there is a lack of population-based studies in this area of research, with only one study (by Gay et al., 2010) recruiting individuals with MS from various MS associations. However, individuals with MS who are recruited from clinical setting rather than the community might not be necessarily less representative of the population, since MS is a disease variable in its course and progression, with a vast majority of those in the community, regardless of the type of MS, requiring inpatient care at various points in their lives (Boeschten et al., 2017). Taken together, where recruitment and sampling procedures for individuals with MS are not clearly stated which was often the case for the majority of the studies, adequate representativeness of the samples and future replication of these studies is limited.

Although, the measures used for the assessment of alexithymia (the TAS-20, the BVAQ), depression (the BDI, the DRS, the HADS) and anxiety (the HADS, the STAI) were all psychometrically sound measures (with English versions evaluated in many clinical populations), only one study reported psychometric properties for the language appropriate adaptations of these measures in MS population (Fernandez- Jimenez et al., 2013). However, most of the studies provided references for validation studies conducted on samples from language-appropriate general populations, for alexithymia measures; the TAS-20 and the BVAQ. Only the studies of Gay et al. (2010, 2017) referred the reader to the validation studies of the depression measures used; the DRS was validated on English-speaking general

population, the HADS was validated on MS English-speaking population, and separately on French-speaking general population (see Table 4 in appendix B for more details). Yet, none of those were reported to be validated on MS French-speaking population, as required for these studies. Similarly, only the studies of Chahraoui et al. (2008, 2014) and Gay et al. (2010, 2017) referred the reader to the validation studies of the anxiety measures used; the STAI was validated on the French-speaking general populations, and the HADS on MS English-speaking population, with none of those reported to be validated on MS French-speaking population, as again required for these studies. None of the studies using the BDI for the assessment of depression, reported or referred the reader to appropriate validation studies of this measure. Hence, we independently examined the psychometric properties for the BDI and found evidence of adequate validity and reliability for MS populations for English, French and Italian adaptations of the BDI (see Hind et al., 2016 for a review). It is likely that there is evidence for validity and reliability of all the language-specific adaptations of the measures used by the studies, for MS population, and simply they were not reported due to journal's stringent word limits. Alternatively validation studies for use of these measures in other languages could had been published in those languages rather than English. Hence, we were unable to access and verify such studies.

Related to the aforementioned issue is the application of adequate cut-off scores. All studies reported the cut-off scores utilised to assess the presence of alexithymia. However, this was rarely the case for the studies that also investigated anxiety and depression in MS, making it impossible to reliably estimate the presence of depression and anxiety in those studies. Ten out of 12 studies used the TAS-20 to investigate the prevalence of alexithymia in MS, yet with somewhat different cut-off scores. As detailed in table 5 in appendix C, the cut-off scores for the presence of alexithymia were largely the same (equal or larger than 61, out of 100) across

different empirically derived scoring criteria, such as the Toronto team cut-off values, the internationally accepted cut-off values, and the North American cut-off values. The French cut-off values were more inclusive, with a cut-off score equal to or larger than 53 out of 100. Only one (Chahraoui et al., 2008) out of five French studies (Chahraoui et al., 2008) used the French cut-off. Yet, the original thresholds proposed by the Toronto team (Bagby et al., 1994) are also validated for the use with the French adaptation of TAS-20 (Loas et al., 1996), and the use of these thresholds would largely facilitate comparisons with other studies. There were more significant differences for cut-off scores differentiating those with borderline alexithymia and those with absence of alexithymia across those different scoring criteria applied by the included studies. Hence, it was impossible to reliably estimate the percentage of people with borderline alexithymia in MS. It is unclear whether the remaining two studies (Dulau et al., 2017; Gay et al., 2017) which employed the BVAQ to assess alexithymia, used same cut-off scores. Gay et al. (2017) applied the cut-off score of 52 and over as indicative of the presence of alexithymia, whereas Dulau et al. (2017) employed a cut-off score that was less than the 5th percentile of the matched HC score (-1.64 SD), without specifying the actual value of the score.

Finally, it is unclear whether the majority of included studies used blinding procedures, suggesting they were not used. Only the study by Gay et al. (2010) reported that participants were blinded to the actual research questions, with no studies reporting an application of a double-blinded procedure. It would be difficult for the researchers not to realise which participants were the ones with MS, considering the prominent gait difficulties of many people with MS. On the other hand, measures of mood difficulties, such as of anxiety and depression have a questionable face validity, with many participants being able to guess, at least to some extent, the constructs being measured. However, attempting to utilise double-blinded procedures should be sought to minimise the influence of potential confounding variable, such

as various assumptions of emotional difficulties in those with MS that might be unintentionally projected by the researcher to the participant, or similar illness beliefs of the participants with MS affecting the ratings on mood questionnaires.

Prevalence of Alexithymia in Multiple Sclerosis

The key aim of this systematic review was to explore the prevalence of alexithymia in individuals with MS. Table 4 in appendix B reports percentages of alexithymia in all studies, according to the measures used and adopted cut-off scores. The data shows that the prevalence of alexithymia vary widely in individual studies, ranging from 10% to 53%. Overall, 277 out of 971 individuals with MS were classified as alexithymic which equates to 28.5% of the total sample.

More specifically, studies (n = 10) which used TAS-20 to measure alexithymia, found the prevalence to range between 10% and 42.6%. The 42.6% prevalence was reported in the study by Chahraoui et al. (2008) who applied French cut-off value for presence of alexithymia which is five points lower than the cut-off value of 61+ used by the rest of the studies. The authors argue that the French cut-off value of 56+ is more appropriate for the French version of the instrument. Yet, as mentioned earlier, the original thresholds proposed by the Toronto team (Bagby et al., 1994) are also validated for the use with the French adaptation of TAS-20, which largely facilitate comparisons with other studies. It is also possible that the less restrictive French cut-off controls less well for type II error. The nine studies (n = 661; 64% females) which used the same cut-off score of 61 + for the presence of alexithymia, reported the prevalence to be significantly lower, ranging from 10% - 31.6%. It was found that 151 (23%) out of 661 individuals with MS who took part in those nine studies were classed as alexithymic.

Only two studies used the BVAQ to estimate the prevalence of alexithymia in MS, showing discrepant levels of alexithymia, of 12% (n = 60; 58% females) in a study by Dulau et al. (2017), and of 53% (n = 189; 64% females) in a study by Gay et al. (2017). However, the study by Dulau et al., (2017) did not report their actual cut-off score. It is possible that they utilised a more restrictive cut-off score, since it was less than the 5th percentile of the matched HC score (-1.64 SD). This discrepancy highlights the importance of establishing specific cut-off scores of the presence of alexithymia for the BVAQ which can be universally applied for an ease of comparison across the studies. Given the methodological and reporting limitations described, it appears that the most adequate estimate of prevalence of alexithymia in MS is the one based on the aforementioned nine studies, estimated at 23%, and ranging from 10% - 31.6%. Thus, levels of alexithymia seem to be indeed higher in those with MS, compared to rates of approximately 10%, previously reported in the literature on general population (Mattilaa et al., 2006).

Considering the limited power of all of these studies to detect effects and issues regarding sample representativeness and cut-off scores applied (as shown by the quality assessment in table 3, with quality criteria 1, 2, 5 and 6 being relevant to the assessment of prevalence) these results should be treated with caution. In particular, studies utilising much bigger samples of individuals with different clinical subtypes of MS and recruited from multiple settings should be conducted to more accurately estimates prevalence in alexithymia in MS.

Relationship between Alexithymia, Depression and Anxiety in MS

The second purpose of this review was to investigate the nature of the relationship between alexithymia, depression and anxiety in MS.

Most studies (n = 8) employed the Beck's Depression Inventory (BDI; Beck, Ward, Mendelson, Mock & Erbaugh, 1961) to investigate depressive symptoms in MS, with one study (Gay et al., 2017) utilising the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) and another study (Gay et al., 2010) using Depression Self-Rating Scale (DRS; Zung, 1965). All these measures were reported showing sound psychometric properties, with the BDI being one of the most frequently used measure of depression in MS and being validated in this population (Hind et al., 2016). Similarly, the HADS has been validated for use in MS population (Honarmand & Feinstein, 2009). Yet, some of the studies did not report whether the versions adopted for the local language were psychometrically assessed for use in MS populations.

Seven studies investigated the relationship between alexithymia and depression in MS (Bodini et al., 2008; Cecchetto et al., 2014; Chahraoui et al., 2008; 2014; Dulau et al., 2017; Gay et al., 2010; 2017), with Prochnow et al. (2011) reporting levels of depression and alexithymia but not exploring the relationship between the two. Data on depressive symptoms was reported for a total of 594 individuals with MS, with data missing for 3% (n = 16) of the total sample of 610 individuals. The study of Dulau et al. (2017) did not report depressive symptoms at the individual level. The reported prevalence of moderate to severe depression varied between studies from 10% to 34.4%, with an overall estimate equating to 27%. Thus, 161 individuals out of 594 were reported as showing moderate to severe symptoms of depression. Although, this estimate needs to be taken with caution, since it is unclear whether the studies applied same

cut-off scores, the figure is similar to recently reported figures on depressive symptoms in MS. Boeschoten et al., (2017), in their systematic review of 58 studies with a total sample of 87,765 patients with MS, estimated the prevalence of depressive symptoms in MS at 30.5%. The difference might be due to the limited size and representativeness of samples included in our studies, as well as potentially different cut-off scores, as highlighted by the quality assessment.

Moderate to large positive relationships between alexithymia and depression scores were found. The TAS-20 total score correlated significantly with the BDI score in the study of Bodini et al. (2008), rho = .37, p <.004, Chahraoui et al. (2014), r = .27, p < .05, Cecchetto et al., (2014), r = .51, p = .004, and Gay et al. (2010), r = .50, p <.001. Gay et al. (2010) found that alexithymia and social support explain 56.7% of the variance in depression scores. Chahraoui et al. (2008) found depression and anxiety scores to predict 20% of variance in alexithymia scores. They further established a relationship between the TAS-20 subscales and depression score, and found moderate positive relationship between the DIF subscale and the BDI score, r =.31, p = .05. Likewise, Bodini et al. (2014) found, by means of a stepwise regression analysis that the DIF subscale was the strongest factor associated with depression. These findings suggest that those with MS who had difficulties identifying own feelings, had more depressive symptoms. Additional analysis of Bodini et al. (2014) indeed showed that individuals with MS and alexithymia (n = 8) were significantly more depressed (p <.007, d = 1.06) than those without (n = 37). Same finding was reported by Chahraoui et al. (2014), where significantly higher levels of depression (p = 0.02, d = 0.71) were reported in those with alexithymia (n = 26), as opposed to those without (n=15).

Contrary to these findings, Dulau et al. (2017) reported no relationship between alexithymia scores and depression in their sample of individuals with MS (r = .21, p = 0.12). Similarly, Gay

et al. (2017) reported no relationship between alexithymia scores and depression (r = .07, p > .05) in their study, further showing that depressed individuals with MS (n = 37) showed similar levels of alexithymia, compared to those who were not depressed (n= 128), F = (2, 186) = 1.36, p = .26. Interestingly, the only feature differentiating those two studies from the rest of the studies that found the relationship between alexithymia (as measured by the TAS-20) and depressive symptoms, was the measure used to assess alexithymia, namely the BVAQ. Although the majority of studies found a positive relationship between alexithymia and depression, more studies with larger representative samples are warranted to replicate these findings.

Five out of 12 studies further investigated the relationship between anxiety and alexithymia, with four of them (Chahraoui et al., 2008, 2014; Dulau et al., 2017; Gay et al., 2010) employing the French adaptation of the State- Trait Anxiety Inventory (STAI; Spielberger, 1983) to investigate anxiety symptoms in MS, and one (Gay et al., 2017) utilising the French adaptation of Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) Both measures were reported showing sound psychometric properties (see Santangelo et al., 2016 for the STAI), with the HADS being validated for use in MS population (Honarmand & Feinstein, 2009). Yet, it is unclear whether the French adaptations of the measure were psychometrically assessed for use in individuals with MS whose first language is French. We independently searched for such studies with no success.

Data on anxiety symptoms was reported for a total of 431 individuals with MS. The study of Dulau et al. (2017) did not report anxiety symptoms at the individual level. The reported prevalence of state anxiety (i.e. temporarily induced anxiety by situations perceived as threatening, as measured by the STAI) ranged from 29.6% in the study by Chahraoui et al.

(2008) to 36.4%, in the study by Gay et al. (2010), with 60 out of 176 individuals with MS having this type of anxiety. The prevalence of trait anxiety (i.e. enduring, chronic anxiety as measured by the STAI) was similarly prevalent across three studies and equal to 43.6% in the study by Chahraoui et al. (2014), 43.8% in the study by Gay et al. (2010), and 44.3% in the study by Chahraoui et al. (2008), with 106 out 242 individuals with MS having this type of anxiety. Gay et al. (2017) found anxiety symptoms (as measured by the HADS) to be prevalent in 12.7% of their MS sample, with 24 out of 189 individuals having anxiety symptoms. Thus, 159 out of 431 individuals with MS had some anxiety symptoms, which equates to 36.8% of the total sample for which this data were reported. Although this estimate needs to be taken with caution, since the anxiety symptoms were measured by a small number of studies, with potentially different cut-off points, the figure is similar to the estimate found by Boeschoten et al., (2017). Their systematic review of 58 studies with a total sample of 87,765 patients with MS, estimated the prevalence of anxiety symptoms in MS at somewhat lower level of 34%. The difference might be due to the limited size and representativeness of samples included in a small number of studies, as well as potentially different cut-off scores, as highlighted by the quality assessment.

Some studies found small to moderate relationships between alexithymia and anxiety, with the study of Chahraoui et al. (2014) reporting trait anxiety to be moderately correlated with alexithymia, $r = .40$, $p < .01$. These results are in line with the findings of Charhraoui et al. (2008) who found much higher levels of state anxiety in alexithymics with MS ($F = 4.62$, $p = 0.01$) compared with borderline alexithymics ($d = 0.70$) and non-alexithymics ($d = 0.89$), with MS. Even bigger differences were found in relation to trait anxiety and alexithymia, ($F = 6.13$, $p = 0.003$), with alexithymics showing much higher ratings of trait anxious than borderline alexithymics ($d = 0.93$) and non-alexithymics ($d = 0.84$) with MS. Furthermore, at the whole

group level, ratings on the DIF subscale of TAS-20 correlated moderately with both, state (r =.43, p = .01) and trait (r =.43, p =.01) anxiety, whereas ratings on the DDF subscales correlated modestly with state anxiety (r =.28, p = .05), and moderately with trait anxiety (r =.31, p =.05). Further analysis revealed that depression, as well as state and trait anxiety predicted 20% of variance in alexithymia scores. These finding suggest that individuals with MS and higher levels of anxiety also present with difficulties in identifying and describing their emotional states. Also, the study of Gay et al (2010) have shown that alexithymia is a partial mediator of the relationship between trait anxiety and depression in MS. However, most recent studies do not entirely support those findings, with Gay et al. (2017) showing a very small relationship between alexithymia and anxiety symptoms, r = .18, p < .05. When they compared non-anxious individuals with MS to anxious ones, they found no significant differences in their levels of alexithymia, F(2,186) = 1.99, p = .14, suggesting that the presence of alexithymic traits is not higher in those with more anxiety symptoms in MS. Finally, the study of Dulau et al. (2017) found a small relationship between alexithymia levels and trait anxiety in MS which was only approaching significance (r = .22; p= .09).

Although the majority of studies found a positive relationship between alexithymia and anxiety, similar to studies investigating the relationship between alexithymia and depression, more studies with larger representative samples and sufficient power to detect such relationships are warranted. This is crucial in order to produce a consistent pattern of findings in this area of research before we can conclude with confidence that the presence of alexithymic traits in people with MS plays a role in the levels of anxiety and depression or vice versa.

Discussion

Summary of findings

The primary aim of this review was to draw together current data on alexithymia in individuals with MS, hypothesising that the prevalence of alexithymia will be heightened in people with MS.

This review systematically evaluated twelve studies which investigated the construct of alexithymia in MS, with the estimated prevalence of 23%, and ranging from 10% to 31.6%. This is a more conservative estimate, based on nine out of those 12 studies, for reasons discussed in the result section of this review. It is still markedly higher compared to the prevalence of alexithymia in general population (approximately 10%), somewhat higher than in other neurodegenerative disorder, such as Parkinson's disease (18% - 23.3%; Assogna et al., 2016). Yet, it is noticeably lower than in other neurological conditions, such as TBI (30% - 60%) or epilepsy (29% - 76%). Since several studies suggested that men score higher than woman on alexithymia questionnaires (Levant et al., 2006; Levant, Hall, Williams, & Hasan, 2009), our results can, to some extent, reflect the composition of our total sample, which included 65.4% of females. It is possible that our estimate would be higher if more men would be included. This, however, would not be representative of the population of MS, which includes almost twice as much women (Milo & Kahana, 2010). Also, our total sample included predominantly individuals with RRMS (72%) and therefore, the results from this review are most probably best generalised to those with RRMS, and modest to moderate levels of neurological disability, rather than chronic types of MS, such as SPMS or PPMS.

Since research on alexithymia in MS, to date, has consisted of relatively small and mostly underpowered cross-sectional studies, conducted largely on individuals with RRMS with lower levels of disability, future research should consider including more individuals with chronic types of MS, which are characterised by higher levels of neurodegeneration and sustained disability that is likely to expand to social, emotional and cognitive impairments (Cotter et al., 2016). The present review highlights the need for research investigating chronic types of MS in order to establish the extent to which the findings of our systematic review generalise to these particular individuals.

The relationship between alexithymia, anxiety and depression in MS

The secondary aim of this review was to evaluate whether alexithymia was associated with higher levels of anxiety or depression.

The relationship between alexithymia, anxiety and depressive symptoms in MS warrants further assessment, and would potentially benefit from longitudinal investigation. It is encouraging that small to large relationships between alexithymia and depression or anxiety symptoms were found in the reviewed studies. Yet, these results should be treated as preliminary due to methodological limitations of the studies, discussed in detail in the result section of the review. In summary, the current review highlight the need for larger and more representative samples of individuals with MS, with sufficient power to detect such relationships. Thus, it would be recommended for future studies to obtain population-based data records from general practitioner-practices, hospital databases, health surveys, various MS societies and support groups, as well as reliable webpages, such as the web portal of the UK MS Register. Such a recruitment and selection process would potentially allow for some form

of random selection, at least at the level of invitation for taking part, and end up reaching a more representative number of individuals with MS; in terms of clinical types of MS, MS duration and severity, and sociodemographic variables.

Strengths and Limitations of the Systematic Review

The main strength of this review is a systematic and comprehensive search strategy and an assessment of risk of bias to aid interpretation of the findings. The tool used for an assessment of the study quality was adopted from an existing AHRQ tool and further amended in order to assess the methodological aspects of studies more precisely, as opposed to assessing their reporting quality. Although, the validity of this tool in its current form has not been investigated, the current guidance of the CRD suggests that AHRQ developed for the quality assessment of observational studies should be amended to suit the research being assessed (CRD, 2009).

The potential limitation of the current review is that the quality ratings were carried out by one individual, with the other rater rating only 50% of the studies included. However, the inter-rater reliability for the quality of those studies was relative high, with the percentage agreement in ratings equating to 68%. The study most probably is vulnerable to publication bias, since only the published studies were assessed in this review. We acknowledge the importance of including unpublished data in such reviews, yet most of the researchers that were contacted with regards to their published conference abstracts, did not reply to our request or did not have the data presented in a form of a manuscript. Also, this review was restricted to articles published in English, excluding a number of potentially relevant studies.

Clinical Implications

The rationale for this review stemmed from the evidence that alexithymia adversely impacts on adjustment to illness and/or recovery in various psychological conditions (Bach & Bach, 1995; McCallum et al., 2003) and can hinder therapeutic outcomes (Lumley et al., 2007). Also, alexithymia is strongly linked to anxiety and depression in general population (Honkalampi et al., 2000). Since individuals with MS also present with high levels of depression and anxiety (Boeschoten et al., 2017), it was plausible that higher traits of alexithymia would be found. The present review highlighted that individuals with MS indeed reported more alexithymic traits, and the link between alexithymia, anxiety and depression symptoms in MS has been found in the reviewed studies. Thus, there will be individuals with MS who are at the higher risk of having alexithymia, as well as anxiety and depressive symptoms for which they might seek treatment.

Such individuals need to be especially considered, in the context of neuropsychological rehabilitation and other psychological interventions, such as CBT or ACT which target mood difficulties in the context of adjustment to chronic illness. The effectiveness of these therapeutic approaches is reliant on close rapport with a therapist and a degree of insight into their internal emotional processes which, arguably those with high levels of alexithymia do not have. To best of our knowledge, studies on non-pharmacological or pharmacological treatment of alexithymia in MS are non-existent. Studies which explored non-pharmacological treatment of alexithymia were not carried out specifically on individuals with MS, but rather on individuals with various psychiatric disorders, such as anxiety and adjustment disorders, depressive disorders, and somatoform disorders to name a few (Grabe et al., 2008). For

instance, psychodynamic group therapy was shown to significantly reduce alexithymic features, as well as psychological distress in psychiatric inpatients (Grabe et al., 2008).

As previously noted, the presence of alexithymia was associated with poor outcome in supportive therapy, as well as more traditional psychodynamic therapy (Ogrodniczuk, Piper & Joyce, 2011), with reduced access to one's emotions, with difficulties identifying, differentiating and articulating own feelings, as well as lack of imagination typically seen in alexithymic patients. These presenting symptoms were considered to possibly reduce successful engagement in therapy. It is likely that some patients with MS will demonstrate similar presentation of symptoms in neuropsychological setting. Such clinical presentation of alexithymic features should be recognised and incorporated into psychological case formulation of the patient, by the clinical (neuro) psychologist who delivers the interventions. This might possibly prevent drop-out rates of such individuals and enhance therapeutic alliance with the group members and the psychologist.

Further, there is some evidence showing that alexithymic symptoms can be reduced by other types of psychological approaches that can arguably be more easily incorporated into neuropsychological rehabilitation than psychodynamic group therapy. The controlled study of Beresnevaite (2000) aimed to reduce alexithymic traits and investigate whether this reduction would mediate the effects of treatment on health outcomes in 37 post cardiac arrest patients with elevated alexithymia scores. They were randomly allocated to either four months of weekly group therapy or two sessions of psychoeducation control group. The group therapy incorporated relaxation strategies, techniques aimed to increase emotional awareness and communication of one's feelings, imagery, music therapy and psychoeducation/ strategies on nonverbal emotional expression. Significant reduction in the TAS scores were reported for the treatment group only, and this reduction in alexithymic symptoms predicted better

cardiovascular outcomes 24 months later. This study provides sound empirical evidence that alexithymia traits can be reduced and should be addressed by psychological treatments, as they can otherwise hinder health outcomes. Such psychological approaches aimed at reducing alexithymia traits should be developed and incorporated into neuropsychological interventions and, subsequently, adequately evaluated to expand the evidence base for the treatment of alexithymia in people with neurological conditions, such as MS.

In terms of the pharmacological treatments of alexithymia, one study reported an improvement in alexithymic features in post-stroke depressed individuals after treatment with venlafaxine, a nonadrenergic and serotoninergic reuptake inhibitor (Cravello, Caltagirone, & Spalletta, 2009). To best of our knowledge, no such studies has been carried out in MS.

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APPENDIX A: Quality Assessment Criteria of Observational Studies

Table 1.
Quality Assessment Criteria of Observational Studies

1. Selection of the cohort is unbiased*	The sample is likely to be representative of the target population. Type of recruitment strategy is less likely to introduce bias. Key baseline demographics (age, gender, years of education, ethnicity, setting, IQ) of the cohort are adequately specified (>4). Clearly determined inclusion criteria, including all of the following: type of MS, severity of MS, time since diagnosis, no co-morbid neurological or psychiatric conditions. For control group information: no neurological or psychiatric conditions,	Yes
	The sample is less likely to be representative of the target population. Type of recruitment strategy is more likely to introduce bias. Key baseline demographics are less well specified (≤3) Meets all but one of the following: type of MS, severity of MS, time since diagnosis, no co-morbid neurological or psychiatric conditions. For control group information: no neurological or psychiatric conditions.	Partially
	The sample is unlikely to be representative of the target population. Type of recruitment strategy is likely to introduce bias. Poor description of key baseline demographics (≤2). Some information is provided on inclusion and exclusion criteria but it is not clear, no consideration given to type/severity of MS and time since diagnosis. Would be difficult to replicate study on basis of details given. No clear criteria for control group.	No

	This information is not reported or it is not applicable in this case.	Unclear
2. Validated method of evaluating the presence of alexithymia*	This measure has been translated to a language spoken by the target population (i.e. MS) and has evidence of good validity and reliability in the study population. Psychometric properties of outcome measure of alexithymia are clearly reported or the reader is referred to an adequate source.	Yes
	The measure has evidence of acceptable validity and reliability in other populations than MS or in a language not spoken by the target population. Psychometric properties of outcome measure of alexithymia are discussed less clearly and it is not possible to independently verify an adequate source.	Partially
	The outcome measure has not been described in detail and have not undergone psychometric evaluation.	No
	This information is not reported or it is not applicable in this case.	Unclear
3. Validated method of evaluating the presence of depression symptoms.	This measure has been translated to the language spoken by the target population (i.e. MS) and has evidence of good validity and reliability in the study population. Psychometric properties of outcome measure of depression are clearly reported or the reader is referred to an adequate source.	Yes
	The measure has evidence of acceptable validity and reliability in other populations than MS or in the language not spoken by the target population. Psychometric properties of outcome measure of depression is discussed less clearly and it is not possible to independently verify an adequate source.	Partially
	The outcome measure has not been described in detail and have not undergone psychometric evaluation.	No
	This information is not reported or it is not applicable in this case.	Unclear

4. Validated method of evaluating the presence of anxiety symptoms	This measure has been translated to the language spoken by the target population (i.e. MS) and has evidence of good validity and reliability in the study population. Psychometric properties of outcome measure of anxiety are clearly reported or the reader is referred to an adequate source.	Yes
	The measure has evidence of acceptable validity and reliability in other populations than MS or in the language not spoken by the target population. Psychometric properties of outcome measure of anxiety is discussed less clearly and it is not possible to independently verify an adequate source.	Partially
	The outcome measure has not been described in detail and have not undergone psychometric evaluation.	No
	This information is not reported or it is not applicable in this case.	Unclear
5. Sufficient power*	G*Power 3.1.6 (Faul, Erdfelder, Lang & Bucher, 2007) was employed to calculate sample sizes needed for sufficient power. For correlational analyses it is required to recruit 614 individuals to detect a small effect size (r=0.1), 62 individuals to detect a moderate effect size (r =0.3), and 21 individuals to detect a large effect size (r=0.5), with the statistical power of 0.8 at an alpha level of 0.05. For group differences, it is required to recruit 310 in each group to detect a small effect size (d=0.2), 51 to detect a moderate effect size (d=0.5), and 21 to detect a large effect size (d=0.8), with the statistical power of 0.8 at an alpha level of 0.05.	
	A sample size is sufficiently large to detect small to moderate correlations (r=0.1-0.3) or group differences (d=0.2-0.5), with the statistical power of 0.8 at an alpha level of 0.05.	Yes
	A sample size is sufficiently large to detect moderate to large correlations (r=0.3-0.5) or group differences (d=0.5-0.8), with the statistical power of 0.8 at an alpha level of 0.05.	Partially

	A sample size is sufficiently large to detect only large to very large correlations or group differences with the statistical power of 0.8 at an alpha level of 0.05.	No
	This information is not reported or it is not applicable in this case.	Unclear
6. Performance bias: outcome assessment blind to exposure*	Examiners were not aware of the health status of the participants with MS during outcome assessment and scoring of measures. Participants with MS were blind to the research question.	Yes
	Either examiners who assessed outcomes were blind to the health status of the participants or the participants were blind to the research question.	Partially
	The study examiners who assessed outcomes were not blind to the health status of the participants. The participants were not blind to the research question.	No
	Examiner's awareness of group membership is not reported or not described clearly enough to work out or no applicable in this case.	Unclear
7. Appropriate analytic methods	Analysis conducted is clearly appropriate to answer aims of the current review. Statistics, such as P-values e.g. effect sizes can be calculated if not reported.	Yes
	Analysis conducted is appropriate, with some limitations, e.g. not controlling for covariates or multiple comparisons. The findings are not reported in sufficient detail and effect sizes may not be calculated from data.	Partially
	Analysis conducted appears inappropriate to answer the research question and does not provide meaningful results.	No
	This information is not reported or it is not applicable in this case.	Unclear

* *Note*. Criteria 1, 2, 5 and 6 only were relevant to the first aim of the current review, with all of the criteria being relevant to the second aim.

APPENDIX B: Decision Narrative in Quality Assessment

Table 4.
Decision Narrative in Quality Assessment

	Quality Criteria						
Study	1. Selection of the cohort is unbiased	2. Validated measure of alexithymia	3. Validated measure of depression	4. Validated measure of anxiety	5. Sufficient Power	6. Performance bias: outcome assessment blind to exposure	7. Appropriate analytical methods
Cecchetto et al. (2014)	**Partially:** - RRMS only, aged 20-40 only, minimal neurological impairment only EDDS ≤ 4.5 - Sampling procedure not specified - Recruited from one hospital unit - Key baseline demographics adequately specified - Clearly determined inclusion criteria	**Partially:** -Psychometric properties not reported for Italian adaptation - Referred to appropriate study showing adequate validity and reliability of an Italian adaptation of TAS-20 in general population (Bressi et al. 1996)	**Partially:** -Psychometric properties not reported for Italian adaptation - Referred only to studies which used same measure in MS population - Although not discussed, BDI-II has demonstrated adequate psychometric properties in MS Italian population (e.g. Hind et al., 2016)	N/A	**No:** - MS = 30 - Sufficient only to detect large to very large effect sizes	**Unclear:** - No information provided	N/A - Descriptive analysis only

Gleichgerrcht et al. (2015)	- **Partially:** RRMS, minimal neurological impairment, EDDS *M* = 1.6 - Sampling procedure not described - Recruited procedure not specified - Key baseline demographics less well specified (age, education, gender only) - Clearly determined inclusion criteria	**Partially:** -Psychometric properties not reported for Spanish adaptation but stated that the version was validated for Spanish language - Referred to the original source demonstrating adequate psychometric properties of TAS-20 in general population (Bagby et al. 1994)	N/A	N/A	**No:** - MS = 38 - Sufficient only to detect large to very large effect sizes	**Unclear:** - No information provided	N/A - Descriptive analysis only
Kuloglu et al. (2012)	- **Partially:** - RRMS and SPMS only, aged 18-25 only, minimal neurological impairment only EDDS *M* = 1.31 - Sampling procedure not described - Recruited from one Neurology Clinic of university hospital- participants hospitalised or	**Partially:** -Psychometric properties not reported for Turkish adaptation - Referred to study on reliability and validity of Turkish adaptation of TAS-20 (details not discussed; Sayar & Gulec, 2001)	N/A	N/A	**Partially:** - MS = 60 - Sufficient to detect large to moderate effect sizes	**Unclear:** - No information provided	N/A: - Descriptive analysis only

	treated as outpatients - Key baseline demographics adequately specified - Clearly determined inclusion criteria	- English version of Sayar et al. (2001) paper not available					
Patil et al. (2016)	**Partially:** -RRMS only, aged 20-40 only, minimal neurological impairment EDDS *M* = 1.66 - Sampling procedure not specified - recruitment procedure not specified - Key baseline demographics adequately specified - Clearly determined inclusion criteria	**Partially:** -Psychometric properties not reported for Spanish adaptation - Referred to study on reliability and validity of Spanish adaptation of TAS-20 -English version of Martinez-Sanches, 1996 not available	N/A	N/A	**No:** - MS = 38 - Sufficient only to detect large to very large effect sizes	**Unclear:** - No information provided	N/A - Descriptive analysis only
Prochnow et al. (2011)	**Partially:**	**Partially:** - Referred to appropriate study showing adequate	**Partially:** -Referred to study on German test manual of BDI	N/A	**No:** - MS = 35	**Unclear:** - No information provided	N/A - Descriptive analysis only

	-predominantly SPMS, majority males - Sampling procedure not specified - recruitment procedure not specified - Key baseline demographics adequately specified - Clearly determined inclusion criteria	validity and reliability of German adaptation of TAS-20 in general population (Franz et al. 2008).	without discussing details and English version not available (Hautzinger et al. 1995)		- Sufficient only to detect large to very large effect sizes		- Correlations between TAS-20 and BDI not performed
Bodini et al. (2008)	**Partially:** - RRMS only, minimal neurological impairment EDDS M = 1.5 - Sampling procedure not specified - Recruited from one outpatient MS centre - Key baseline demographics adequately specified - Clearly determined inclusion criteria	**Partially:** -Psychometric properties not reported for Italian adaptation -Referred to appropriate study showing adequate validity and reliability of an Italian adaptation of TAS-20 in general population (Bressi et al. 1996)	**Partially:** -Psychometric properties not reported for Italian adaptation - Although not discussed, BDI has demonstrated adequate psychometric properties in MS Italian population (Hind et al., 2016)	N/A	**No:** - MS = 58 - Sufficient only to detect large to very large effect sizes	**Unclear:** - No information provided	**Yes:** - Adequate analysis to investigate group differences based on level of alexithymia in MS (ANOVA), and associations between variables (Spearman's correlation and multiple logistic regression - Not stated whether data met assumptions for parametric tests - p-values and CI stated, effect sizes possible to calculate

Chahraoui et al. (2014)	**Partially:** - RRMS only, minimal neurological impairment EDDS M = 1.5 - Convenience sampling procedure - Recruited from two outpatient MS centres- – those who had regular follow-up consultations approached by post - Key baseline demographics adequately specified - Clearly determined inclusion criteria	**Partially:** -Psychometric properties not reported for French adaptation - Referred to appropriate study showing adequate validity and reliability of French adaptation of TAS-20 in general population (Lous, Fremaux, & Merchard 1995)	**Partially:** -Psychometric properties not reported for French adaptation - Although not discussed, BDI has demonstrated adequate psychometric properties in MS French population (e.g. Hind et al., 2016)	**Partially:** -Psychometric properties not reported for French adaptation - Referred to study on reliability and validity of French adaptation of STAI (details not discussed; paper not available in English) Bruchon-Schweitzer & Paulhan, 1993)	**No:** - MS = 61 - Sufficient only to detect large to very large effect sizes	**No:** - Participants informed about the study by the neurologist - The researcher not blinded, trained for the study, obtained written consent and participants medical information	**Yes:** - Adequate analysis of T1 and T2 data using Wilcoxon test to account for nonparametric data. - Spearman's correlation used adequately - p-values stated, effect sizes possible to calculate
Chahraoui et al. (2008)	**- Partially:** - All types of MS represented -Sampling procedure not described - Recruited from one MS clinic or one university hospital	**Partially:** -Psychometric properties not reported for French adaptation - Referred to appropriate study showing adequate validity and reliability of French adaptation	**Partially:** -Psychometric properties not reported for French adaptation - Although not discussed, BDI has demonstrated adequate psychometric	**Partially:** -Psychometric properties not reported for French adaptation - Referred to study on reliability and validity of French	**Partially:** - MS = 66 - Sufficient to detect large to moderate effect sizes	**Unclear:** - No information provided	**Yes:** - Adequate analysis to investigate group differences based on level of alexithymia in MS (ANOVA), and associations between variables (Spearman's correlation and multiple logistic regression - Not stated whether data met assumptions for parametric tests

	- Key baseline demographics are poorly specified (only age and gender) - All required inclusion criteria but one-not stated if comorbid neurological conditions excluded	of TAS-20 in general population (Lous, Fremaux, & Merchard, 1995)	properties in MS French population (e.g. Hind et al., 2016)	adaptation of STAI (details not discussed; paper not available in English) Bruchon-Schweitzer & Paulhan, 1993)			- p-values stated, effect sizes possible to calculate
Fernandez-Jimenez et al. (2013)	- **Partially:** - All types of MS represented Convenience sampling technique - recruitment from one university hospital – those who were coming for routine medical check-ups - Key baseline demographics adequately specified - Clearly determined inclusion criteria	**Yes:** -Adequate psychometric properties reported for Spanish adaptation - Study investigated and demonstrated validity and reliability of an Spanish adaptation of TAS-20 in MS	N/A	N/A	**Partially:** - MS = 221 - Sufficient to detect large to moderate effect sizes	**No:** - Not stated whether participants were blinded to research question - The researcher not blinded obtained written consent and participants medical information	**Yes:** - adequate descriptive statistics (means and standard deviations) - investigation of prevalence of alexithymia in MS only, hence no further analysis
Gay et al. (2010)	- **Partially:** - All types of MS represented, wide range of ages,	**Partially:** -Psychometric properties not reported for French adaptation	**Partially:** -Psychometric properties not reported for French adaptation	**Partially:** -Psychometric properties not reported for French	**Partially:** - MS = 115 - Sufficient to detect large to	**Partially:** - Participants were blinded to research question	**Partially:** Adequate use of statistical methods of Pearson's correlations and SEM to answer research questions

	disability status and MS duration - Convenience sampling technique - recruitment from various MS associations, hospitals and private neurologists, all lived in the community - Key baseline demographics adequately specified - Inclusion criteria not stated	- Referred to appropriate study showing adequate validity and reliability of French adaptation of TAS-20 in general population (Lous & Fremaux, 1995)	- Referred to the original study showing adequate validity and reliability of DRS (Zung et al., 1965) - Although not discussed, DRS has demonstrated adequate psychometric properties in other neurological conditions such as Parkinson's Disease (Torbey et al., 2015)	adaptation - Referred to study on reliability and validity of French adaptation of STAI (details not discussed; paper not available in English) Bruchon-Schweitzer & Paulhan, 1993)	moderate effect sizes	- The researcher was not blinded- obtained written consent and participants medical information	- Not stated whether data met assumptions for parametric tests - No correction for multiple comparisons was not applied - p-values stated, effect sizes possible to calculate
Dulau et al. (2017)	- **Partially:** - All types of MS represented, wide range of ages, those with higher disability status excluded (EDDS > 6) - Sampling procedure not specified - recruitment from one MS clinic in university hospital	**Partially:** -Psychometric properties not reported for French adaptation - Referred to appropriate study showing adequate validity and reliability of French adaptation of BVAQ in general population	**Partially:** -Psychometric properties not reported for French adaptation - Referred to original source only Although not discussed, BDI has demonstrated adequate psychometric	**Partially:** -Psychometric properties not reported for French adaptation Referred to original source only	**No:** - MS = 60 -Sufficient to detect only large to very large effect sizes	**Unclear:** - No information provided	**Yes:** - Accounting for nonparametric data - Bonferroni correction used for multiple comparisons Adequate use of Pearson's correlation and multiple linear regressions - p-values stated,

	- Key baseline demographics adequately specified - All required inclusion criteria but one-not stated if comorbid neurological conditions excluded	(Vorst & Bermond, 2001)	properties in MS French population (e.g. Hind et al., 2016)				
Gay et al. (2017)	**- Partially:** - All types of MS represented - Convenience sampling technique - recruitment from three university hospitals - Key baseline demographics less well specified (e.g. education) - Inclusion criteria not stated	**Partially:** - Some psychometric properties reported for French adaptation - Referred to appropriate study showing adequate validity and reliability of French adaptation of BVAQ in general population (Zech et al., 1999)	**Partially:** - Some psychometric properties reported for French adaptation in general population – referred to adequate source (Untas, et al. 2009) - Referred to appropriate study showing adequate validity and reliability of HADS in MS but not for French adaptation (Honarmond &Feinstein, 1999)	**Partially:** - Some psychometric properties reported for French adaptation in general population – referred to adequate source (Untas, et al. 2009) - Referred to appropriate study showing adequate validity and reliability of HADS in MS but for English, not French adaptation (Honarmond &Feinstein, 1999)	**Partially:** - MS = 189 Sufficient to detect large to moderate effect sizes	**No:** - Participants informed about the study by the neurologist - The researcher not blinded, trained for the study, obtained written consent and participants medical information	**Partially:** - Appropriate use of ANOVA and Pearson's correlations but no correction for multiple comparisons - Not clearly stated whether data met assumptions for parametric tests - p-values stated, effect sizes possible to calculate

APPENDIX C: Prevalence of Alexithymia in Multiple Sclerosis

Table 5.
Prevalence of Alexithymia in Multiple Sclerosis

Author(s)	**Sample**	**Cut-off scores applied**	**Alexithymia**	**Borderline Alexithymia**	**No Alexithymia**
Gleichgerrcht et al., (2015)	RRMS = 38	**Toronto team cut-off values:** Alexithymia: score: 61-100 Borderline Alexithymia: score: 52-60 No alexithymia: score: 20-51	RRMS = 12 (31.6%)	RRMS = 10 (26.3%)	RRMS = 16 (42.1%)
Cecchetto et al., (2014)	RRMS = 30	**International cut-off values:** Alexithymia: score: 61-100 Borderline Alexithymia: score of 51-60 No alexithymia score: 20-50	RRMS = 3 (10%)	RRMS = 4 (13.3%)	RRMS = 23 (76.6%)
Patil et al., (2016)	RRMS = 38	**Toronto team cut-off values:** Alexithymia score: 61-100 Borderline Alexithymia score: 52-60 No alexithymia score: 20-51	RRMS = 12 (31.6%)	RRMS = 10 (26.3%)	RRMS = 16 (42.1%)
Kuloglu et al., (2012)	MS = 60	**North American cut-off value:** Alexithymia score: 61-100 No alexithymia: score 20-60	MS = 14 (23.3%)	No data	MS= 46 (76.6%)
Prochnow et al., (2011)	MS = 35	**Toronto team cut-off values:** Alexithymia score: 61-100	MS = 9 (25.8%)	MS = 13 (37.1%)	MS = 13 (37.1%)

		Borderline Alexithymia score: 52-60 No alexithymia score: 20-51			
Bodini et al., (2008)	MS = 58	**International cut-off values:** Alexithymia score: 61-100 Borderline Alexithymia score: 51-60 No alexithymia score: 20-50	MS = 8 (13.8%)	MS = 13 (27.6%)	MS = 37 (58.6%)
Gay et al., (2010)	MS = 115	**North American cut-off value:** Alexithymia: score: 61-100 No alexithymia: score: 20-60	MS = 27 (23.2%)	No data	MS = 88 (76.8%)
Chahraoui et al., (2014)	T1: MS = 66	**International cut-off values:** Alexithymia score: 61-100 Borderline Alexithymia score: 51-60 No alexithymia score: 20-50	MS = 19 (30.6%)	MS = 19 (30.6%)	MS = 24 (38.7%)
Fernandez-Jimenez et al., (2013)	MS = 221	**Toronto team cut-off values:** Alexithymia score: 61-100 Borderline Alexithymia score: 52-60 No alexithymia score: 20-51	MS = 40 (18.1%)	MS = 45 (20.4%)	MS = 136 (61.5%)
Chahraoui et al., (2008)	MS = 61	**French cut-off values:** Alexithymia score: 56-100 Borderline Alexithymia score: 45-55 No alexithymia score: 20-44	MS = 26 (42.6%)	MS = 20 (32.8%)	MS = 15 (24.6%)
Gay et al., (2017)	MS = 189	Alexithymia score 53-100	MS = 100 (53%)	N/A	MS = 89 (47%)
Dulau et al., (2017)	MS = 60	Alexithymia score was less than the 5th percentile of the matched HC score (-1.64 SD).	MS = 7 (11.7%)	N/A	MS = 53 (87.3%)

APPENDIX D: Archives of Clinical Neuropsychology: Instructions for Authors

PREPARATION OF MANUSCRIPTS

- Manuscripts should be prepared carefully according to the *American Psychological Association Manual of Style* (6th ed). Italics are not to be used for expressions of Latin origin, for example, in vivo, et al., per se. Use decimal points (not commas); use a space for thousands (10 000 and above). Please avoid full justification, i.e., do not use a constant right-hand margin. Ensure that each new paragraph is clearly indicated. Present tables and figure legends on separate pages at the end of the manuscript. Manuscripts should be in their final form when they are submitted, so that proofs require only correction of typographical errors. All parts of the manuscript (except figures) should be double-spaced throughout and should be in a word-processing file.

- **Sections of the manuscript:** Title page, Structured abstract, Keywords, Introduction, Methods, Results, Discussion, Funding, Acknowledgements, References, Tables, Figures (if not in a graphic-type file like PDF, tif, eps, etc.)

- **Length of manuscript:** While papers may be of any length required for the concise presentation and discussion of the data, succinct and carefully prepared papers are favored both in terms of impact as well as in readability.

- **General format:** All sections of the manuscript must be double-spaced. Margins of 1 inch should be left at the sides, top, and bottom of each page. Number each page centered at the bottom (Title Page is 1). Italicize words and letters to appear in italics. Clearly identify unusual or handwritten symbols and Greek letters. Differentiate between the letter O and zero, and the letters I and l and the number 1. Each table and figure must be called out in the text.

- **Title page:** The title should be short, specific, and informative. The first name, initial(s), and surname of each author should be followed by his or her department, institution, city with postal code, and country at the time the work was conducted. Email address, phone and fax numbers of the corresponding author should also be provided. Any changes of address may be given in numbered footnotes. The author to whom proofs and reprints should be addressed should be indicated. Please provide a running title of not more than 60 characters.

- **Abstract:** The second page of every manuscript must contain the structured Abstract, which should not exceed 250 words. The Abstract should include each of the following sections: Objective: A brief statement of the purpose of the study, Method: A summary of the participants as well as

descriptions of the study design, procedures, and specific key measures, Results: A summary of the key findings, including specific results of significance testing to the extent that space allows, Conclusions: Clinical and theoretical implications of the findings as space allows. Abbreviations and reference citations should be avoided.

- **Key words:** Up to six key words, which will appear after the abstract, should be included below the title, each separated by a semicolon (;). Keywords should be selected from the APA list of index descriptors, unless otherwise agreed with the Editor. Thus, please give them careful consideration.

- **Funding:** Details of all funding sources for the work in question should be given in a separate section entitled 'Funding'. This should appear before the 'Acknowledgements' section. The following rules should be followed: The sentence should begin: 'This work was supported by …'. The full official funding agency name should be given, i.e. 'National Institutes of Health', not 'NIH' (full RIN-approved list of UK funding agencies) Grant numbers should be given in brackets as follows: '[grant number xxxx]'. Multiple grant numbers should be separated by a comma as follows: '[grant numbers xxxx, yyyy]'. Agencies should be separated by a semi-colon (plus 'and' before the last funding agency).

- **References:** This journal follows American Psychological Association Manual of Style (6th ed.) as a guide for style and citation. Authors are responsible for the accuracy of the references. Published articles and those in press (state the journal which has accepted them and enclose a copy of the manuscript) may be included. In the text, a reference should be cited by author and date. Not more than six authors may be cited per reference; if there are more than six authors, use et al in the in-text parenthetical citation. At the end of the manuscript, the citations should be typed in alphabetical order, with the authors' surnames preceding initials. References should include, in the following order: authors' names, year, complete title of the article, journal title, volume number, inclusive page numbers, and (for books only) name and address of publisher. The name of the journal should be italicized and appear in full.

- **Tables:** Tables should be typed on separate sheets and numbered consecutively with numbers (i.e., Table 1, Table 2, etc). Tables should be self-explanatory and include a brief descriptive title. Tables can include note(s) that appear below the table. Note(s) usually include full definitions of abbreviations that appear in the table. Footnotes are also acceptable and are indicated by lowercase letters. But footnotes should not include extensive experimental detail. Tables must be called out in the text.

- **Abbreviations:** Try to restrict the use of abbreviations to those listed in the American Psychological Association Manual of Style (6th ed.) and to those abbreviations that appear as word entries in Merriam-Webster's Collegiate Dictionary. Any word you intend to abbreviate should be spelled out at first occurrence. The first spelled out occurrence should be followed by the abbreviation in parenthesis. Standard units of measurement may be used without definition in the body of the paper. Acronyms formed from phrases are unacceptable.

- **Preparing the files:** When preparing your final files, please present all sections of the paper in one word-processing file, excluding illustrations. If necessary, tables may be placed in a separate word-processing file. When creating and/or editing your manuscript, use the document mode (or equivalent) in the word-processor program. Type the title, authors, and affiliations in the journal style (i.e., in upper and lowercase), with bold font for the title and authors. The text should be typed unjustified, without hyphenation (except for compound words) and at double line spacing. Headings should be typed as follows: main (section) headings in bold upper and lowercase; subheadings in italic upper and lowercase letters with the text beginning on the next line; sub-subheadings in italic upper and lowercase letters with the text continued on the same line. Indexing flags should not be included in the text. Enter only one space at the end of sentences and after commas, semicolons, and colons. No space should be inserted before these punctuation marks. Do not use lowercase l (ell) for 1 (one) or O for 0 (zero). These may look interchangeable but they have different electronic values. Check the final copy of your paper carefully because spelling mistakes, inconsistencies, and errors will be faithfully translated into the typeset copy.

- **Supplementary data:** is supporting material that cannot be included in the printed version for reasons of space and is not essential for inclusion in the full text of the manuscript but would nevertheless benefit the reader. It should not be essential to understanding the conclusions of the paper but should contain data that is additional or complementary and directly relevant to the article content. *Examples:*more detailed methods, extended data sets/data analysis, tables, or additional figures (including color). It is standard practice for appendices to be made available online-only as supplementary material. All text and figures must be provided in suitable electronic formats. All material to be considered as supplementary material must be submitted at the same time as the main manuscript for peer review. It cannot be altered or replaced after the paper has been accepted for publication, and will not be edited. Please indicate clearly the material intended as supplementary material upon submission. Also ensure that the supplementary material is referred to in the main manuscript where necessary, for example as "(see Supplementary Material)" or "(see Supplementary Figure 1)." *Acceptable formats*: a maximum of 5 files is acceptable to make up the supplementary data unit for an article. The maximum size per file should not exceed 2 MB (though text files should

be a great deal smaller), and files must be as small as possible so that they can be downloaded quickly. An HTML index page is usually created to link the supplementary data file(s) to the article. Please provide short (2-4 word) titles for each individual file---these will be used to create links to the files from the index page.

EFFECTS OF ILLNESS REPRESENTATIONS ON EMOTION REGULATION IN MULTIPLE SCLEROSIS

Bogumila Radlak[1*], Louise H. Phillips[2], Nuno Ferreira[3], Fiona Summers[1], Paul G. Morris[3]

[1] Department of Clinical Neuropsychology, NHS Grampian, Aberdeen, AB25 2ZA, UK

[2] The School of Psychology, the University of Aberdeen, Aberdeen, AB24 3FX, UK

[3] The School of Health in Social Science, the University of Edinburgh, Edinburgh, EH8 9AG, UK

* Corresponding author email address; bogumila.radlak@nhs.net; tel.: 0044 1224 559352; fax: 01224 661587

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Empirical Paper Abstract

Objective: This study explored whether there were differences in emotion regulation abilities in individuals with different variants of Multiple Sclerosis, compared to individuals without MS. It was further investigated whether negative illness perceptions predicted emotion dysregulation in Multiple Sclerosis, independently of disease severity. Emotion regulation abilities and illness perceptions were also explored as potential mediators of the relationship between illness severity and quality of life.

Method: Hundred and seventeen individuals with a diagnosis of Multiple Sclerosis and 55 healthy controls took part in this study. The following self-reported measures were employed; the Difficulties in Emotion Regulation Scale, the Illness Perception Questionnaire-Revised, the World Health Organisation Quality of Life, and the Patient Determined Disease Steps.

Results: Individuals with Multiple Sclerosis reported difficulties accepting their emotional distress which were to some extent predicted by strong illness identity and negative emotional responses to having Multiple Sclerosis, independently of illness severity, and regardless of the relapsing-remitting or chronic nature of Multiple Sclerosis. Beliefs regarding the consequences of Multiple Sclerosis were found to be the only partial mediator of the relationship between illness severity and quality of life.

Conclusions: Given that nonacceptance of emotional distress was significantly higher in Multiple Sclerosis, and predicted by having strong beliefs about illness identity and negative emotional responses, there is a scope for psychological interventions to be effective in alleviating these difficulties.

Keywords: Emotion Regulation, Illness Representations, Multiple Sclerosis

Introduction

Different Variants of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory neurological disease of the central nervous system (CNS) which is the leading cause of neurological disability amongst younger adults (Compston & Coles, 2008). Most people are first diagnosed with a relapsing-remitting form of MS (RRMS; O'Connor, 2002), which involves attacks (relapses) followed by periods of recovery (remission). Relapses occur when inflammatory cells attack the myelin of specific nerves. Remission occurs when inflammation subsides and symptoms reduce. Although symptoms may disappear completely during remission process, after several relapses there may be residual damage to the myelin, resulting in partial recovery only (Neild, 2006). Most people initially diagnosed with RRMS later develop secondary progressive MS (O'Connor, 2002), characterised by a steady increase in disability, as symptoms do not disappear completely after a relapse. In the primary progressive MS, unlike in RRMS, the first (primary) symptoms are progressive. They get worse over time rather than appearing as sudden attacks (relapses). Symptoms may continue to worsen over time or may become stable. The hallmark of the chronic progressive forms of MS (CPMS), namely secondary progressive MS and primary progressive MS is the permanent loss of neural tissue (Neild, 2006).

The disease tends to affect not only physical health of MS sufferers but also cognitive and emotional functioning. While physical and cognitive impairments present in MS, such as restricted mobility, reduced executive control and slowed processing speed, have been extensively researched (Kalmar, Gaudino, Moore, Halper, & Deluca, 2008; Rao, 1995), less is understood about the nature of emotional difficulties present in MS. Multiple areas of

axonal demyelination are implicated in MS with many of the lesions arising in the white matter of the frontal brain regions (Brownell & Hughes, 1962). Prefrontal cortex, frontal and subcortical brain circuits have been implicated in the self-regulatory processes crucial not only to executive functioning (Stuss & Alexander, 2007) but are also likely to be involved in emotion generation and regulation processes (Ochsner & Gross, 2005). Since a great number of MS sufferers show cognitive dysregulation on executive function assessments, it is possible that emotion regulation abilities are similarly affected (Kalmar et al., 2008).

Emotion Regulation in MS

Emotion Regulation refers to a set of abilities and processes that allow for an awareness, understanding, monitoring and evaluation of affective states as they arise, together with employing various strategies to mould the inner experience of those states and to govern the outer expression of affect (Gross, Sheppes, & Urry, 2011). For instance, emotion regulation strategies, such as expressive suppression (involving active inhibiting of the overt manifestation of emotions in response to an emotional event) or cognitive reappraisal (entailing a modification of the subjective experience of emotions by changing the way one thinks about emotional event) have been found to impact on well-being, with individuals who routinely employ suppression reporting poorer life satisfaction and more depressive symptoms, compared to individuals who use reappraisal (Gross &John, 2003).

Moreover, the significance of effective emotion regulation processes and strategies has been widely acknowledged in clinical settings due to the adverse consequences of emotion dysregulation on functioning and well-being. Emotion dysregulation contributes to increased severity of anxiety, depression, as well as post-traumatic stress disorder and schizophrenia

(Liverant, Kamholz, Sloan & Brown 2010, Van der Meer, Van't Wout & Aleman, 2009; Tull, Barrett, McMillan, & Roemer, 2007). Emotion regulation is believed to be important for psychological adaptation to chronic illness, such as rheumatoid arthritis (Van Middendorp, Geenen, Sorbi, Hox, Vingerhoets et al., 2005), kidney disease (Gillanders, Wild, Deighan & Gillanders, 2008), as well as MS (Phillips, Saldias, McCarrey, Henry, Scott et al. 2009). It is also likely to decrease life satisfaction, reduce work effectiveness and adversely impact on interpersonal relationships (Gross and Munoz, 1995) (Garnefski, Koopman, Kraaij & ten Cate, 2009). Therefore, understanding the nature and cause of emotion regulation difficulties in chronic conditions such as MS is vital when designing interventions aimed at improving functional outcomes of those suffering from the disease. Moreover, treatment plans included in the NICE (186) clinical guidelines for the management of MS in primary and secondary care focus primarily on physical and cognitive rehabilitation. Therefore, more research is needed into the emotion regulation difficulties of individuals with MS in order to extend the evidence base in this area and to incorporate a wider range of emotion regulation interventions into psychological treatments offered to people with MS.

In relation to MS, the incidence of emotion regulation difficulties has been reported for over a century, with first clinical accounts describing uncontrollable laughter, as well as a dissociation between the overt displays of affect and subjective mood reports in individuals with MS (Charcot, 1887; Surridge, 1969). Some of the symptoms of emotion regulation disturbances in MS involve pathological laughter and crying, unusual feelings of euphoria, emotional incontinence (disproportional exaggerated emotional expression), pseudobulbar affect (atypical expression of affect due to involvement of cortico-bulbar pathways), as well as emotional lability (dramatic shifts of mood; Feinstein, 2004; Finger, 1998; Rabins, 1990; Schiffer, 1990). Also, alexithymia which involves inability to identify own emotional states,

together with difficulties to delineate bodily sensations of emotions from actual feelings (Mikolajczak & Luminet, 2006), has been implicated in MS (Gleichgerrcht et al., 2015) and associated with emotion dysregulation (Swart *et al*., 2009).

Most of abovementioned studies of emotion regulation in individuals with MS have employed symptom report or clinical observation to investigate the nature of emotion regulation processes in this disease. Nevertheless, it is essential to examine specific aspects of emotional appraisal, experience and perceived control as assessed by standardized measures. To date, only three studies (Phillips et al., 2009; 2014; Schirda, Nicholas & Prakash, 2015) have used standardised assessments to explore emotion regulation processes in MS. Phillips et al. (2009) measured emotion regulation strategies using the Emotion Regulation Questionnaire (ERQ, Gross &John, 2003) in 86 individuals with MS. The ERQ is comprised of two subscales measuring appraisal of emotions and expressive suppression of emotions It was found that the absence of reappraisal as a method of emotion regulation was associated with lower self-reported quality of life. Similarly, a study by Schirda et al. (2015) found that emotion dysregulation was a partial mediator in the relationship between trait mindfulness and quality of life in their sample of 95 individuals with MS. However, it is not possible to deduce whether emotion dysregulation is more common in MS, as neither of these studies employed a healthy control group. Additionally, a broader range of emotion regulation strategies (than those measured by the ERQ) needs to be explored in order to enhance an understanding of these processes in MS.

These limitations were addressed in another study by Phillips et al. (2014) who investigated a variety of emotion regulation strategies in 31 individuals with MS and 31 matched controls using the Difficulties in Emotion Regulation Scale (DERS, Gratz & Roemer, 2004). This

well-validated measure comprises multiple subscales designed to assess discrete emotion regulation processes, including acceptance of the emotion, acknowledgement and comprehension of the experienced emotional state, an ability to manage impulsive conduct in the context of negative affect, as well as an ability to employ flexible strategies to modify experienced emotions as required by the situational demands. It was found that individuals with MS reported more problems with emotion regulation than did control individuals, with a medium effect size (d = .68). A lack of interaction between the groups and DERS separate subscales, implies that different aspects of emotion regulation were similarly affected by MS. Interestingly the same emotion regulation measure was employed by Schirda et al. (2015) in their study on trait mindfulness, emotion regulation and quality of life. Yet, group differences in specific emotion regulation strategies were not possible to be explored due to a lack of control group.

One of the main limitations of the previous studies on MS is the use of heterogeneous cohort of individuals with MS. It is important to differentiate between those two heterogeneous types of the disease, since RRMS is mainly inflammatory in nature, with symptoms of the disease exacerbating and diminishing, leading to partial or complete recovery, while the CPMS forms being characteristic of permanent nerve damage, loss (Neild, 2006) and subsequent worsening of symptoms. It is therefore possible that the severity of the emotion regulation difficulties in MS is affected by the form of the disease. If individuals with different variants of MS had different patterns of emotion regulation difficulties, this could have potential implications for symptom management as well as rehabilitation and therapy goals. Furthermore, only one of the previously discussed studies (i.e. Schirda et al., 2015) on emotion regulation in MS explored psychosocial factors that can potentially impact on difficulties in emotion regulation and be possible targets of psychological intervention. They

reported that higher levels of dispositional mindfulness were significantly associated with lower levels of emotion dysregulation. Yet, it is likely that other factors, such as individuals' illness representations can adversely impact on emotion regulation in MS.

Illness Representations in MS

In the area of adjustment to chronic illness, many studies, including those on MS (e.g. Jopson and Moss-Morris, 2003), have utilised the Common Sense Model (CSM) of illness representations developed by Leventhal et al. (1984). The CSM proposes that the cognitive perceptions that individuals hold about their illness impact on their coping styles and emotional responding. This is a "parallel" processing model, meaning that both cognitive and emotional representations are formed simultaneously, in parallel and can have a direct effect at each other (Hagger & Orbell, 2003). In short, individuals who are diagnosed with a health condition, develop an organised set of beliefs about their illness. These beliefs or cognitions are defined as illness representations and include knowledge, experience, emotions, as well as illness-related perceptions (Skelton & Croyle, 1991). Studies have shown that the perceptions that individuals hold about their illness are not only a significant predictor of adjustment, but also levels of social dysfunction, self-esteem, fatigue, as well as various mood problems (Heijmans, 1998; Jopson & Moss- Morris, 2003; Murphy, Dickens, Creed, & Bernstein, 1999).

In the context of MS, few studies explored the illness perceptions of individuals with MS. Jopson and Moss-Morris (2003) employed a well-validated assessment tool of illness representations, the Illness Perceptions Questionnaire- Revised (Moss-Morris *et al.*, 2002), and reported that beliefs about MS significantly affected people's adjustment to MS. Poor

outcomes (i.e social dysfunction, role dysfunction, low self-esteem, fatigue,) were associated with strong illness identity (ascribing a label and an array of symptoms to MS), belief in serious consequences of MS, and its cyclical timeline, low understanding of MS, as well as low perceived personal control over MS. The cross sectional design of the study made it impossible to ascertain the actual direction of relationships between variables. Yet, the analyses controlled for MS severity which helped to show that the poor outcome did not simply arise from the severity of illness itself. Similarly, Vaughan *et al.* (2003) conducted a cross sectional study utilising the Illness Perception Questionnaire (Weinman *et al.*, 1996) and reported that strong MS identity, serious consequences of MS and low control levels of control over MS correlated with poor outcome (i.e. physical functioning, self-esteem, anxiety and depressive symptoms). Spain *et al.* (2007) reported similar findings in the context of health related QoL, with same dimensions of illness representations as in Vaughan *et al.* (2003) being associated with reduced QoL in MS, namely illness identity, consequences and perceived control/cure. In the most recent study by Bassi et al., (2016) strong illness identity and negative emotional representations were linked to lower psychological well-being, life satisfaction, and hedonic balance in those with MS.

Since MS is incurable, unpredictable and with substantial individual variation, it seems unsurprising that previous studies found poor outcomes in MS to be associated with less helpful illness perceptions. It is also reasonable to assume that people with MS will develop beliefs and cognitions that are either helpful or detrimental to regulating their emotional responses to symptoms and their everyday difficulties, although this has not been extensively investigated. However, no studies to date have explored the link between illness representations and emotion regulation abilities in MS more directly.

Finally, no studies to date have investigated the relationships between illness severity, emotion regulation, illness representations and quality of life of people with MS. There is evidence that MS severity is strongly associated with poor quality of life (Henriksson et al., 2001), while social dysfunction is predicted by illness representations in MS (Jopson & Moss-Morris, 2003). Moreover, previous studies showed that problems with emotion regulation predicted well-being in a range of healthy and clinical populations, including MS (Gross & John, 2003; Phillips, Henry, Hosie & Milne, 2006, Phillips et al., 2009; Phillips et al., 2014). More recently, Schirda (2015) showed via a simple mediation model that emotion regulation partially mediated the association between mindfulness and quality of life. Since adaptive emotion regulation protects against mental health difficulties and predicts higher life satisfaction (for a review see Gross and Munoz, 1995), whereas helpful illness representations may enhance adjustment to chronic illness (Jopson & Moss-Morris, 2003), it is, therefore, important to further explore the indirect effects of emotional and psychosocial factors, such as emotion regulation and illness representations, on potential relationship between illness severity and quality of life.

Rationale for the study

To address the abovementioned gaps in the literature, the current study aimed to look at the use of a broad range of emotion regulation strategies (as assessed by DERS) by exploring the effects of different types of MS on emotion regulation abilities, namely relapsing-remitting MS and the chronic progressive forms of MS, as well as healthy controls. This study extends previous research in MS by further investigating whether illness representations developed by individuals with MS impact on how they regulate their emotions, even when controlling for the severity of their condition. Few previous illness representation studies discussed above,

have attempted to account for disease severity, making it problematic to conclude whether the relationship between emotion regulation and illness cognitions results in fact, from the severity of the condition itself. The final aim of the study is to test the possible mediating effect of emotion regulation and illness representations in the relation between MS severity and quality of life. This is the first study to explore the relationships between these variables in individuals with MS.

The study will address the following research aims:

1) To explore whether individuals presenting with different variants of MS, namely RRMS and CPMS, will have different emotion regulation abilities, as compared to individuals without MS (HC).

2) To explore whether negative illness representations predict emotion dysregulation in MS, independently of disease severity.

More specifically, it was hypothesized that individuals who have a strong illness identity, a poor sense of control over their MS, strong emotional responses to their MS and believe their MS to have had detrimental consequences on their lives, will have more difficulties with emotion regulation, after controlling for the effects of disease severity.

These cognitive dimensions of illness representations were chosen based on previous findings of Vaughan *et al.* (2003) and Spain et al., 2007 (discussed above) which showed that illness identity, perceived control and consequences are associated most with key outcome variables.

3) To explore emotion regulation and illness representations as mediators of the relationship between MS severity and quality of life in MS.

More specifically, it was hypothesised that emotion regulation abilities and illness representations will be significant mediators of the relationship between MS severity and quality of life.

Methodology

Participants

Participants with MS were identified via NHS Grampian MS register. In total, 570 individuals with MS were randomly selected and invited via letter to take part in the study. 117 individuals with MS gave their informed consent and completed the questionnaires (20.5% of the original sample). The majority of the sample had a diagnosis of RRMS (n= 79; 67.5%). Secondary Progressive MS was the next most frequent type (n = 29; 24.8%), followed by Primary Progressive MS (n = 9; 7.7%). Individuals with the two progressive MS types were combined, in the analysis, into one chronic progressive group (CPMS; n = 38) introduction. Ethical approval was granted by the NHS NRES South West - Cornwall & Plymouth Research Ethics Committee (REC) (see appendix E). The inclusion criteria were: McDonald criteria for MS diagnosis (McDonald et al., 2001), as assessed by a neurologist, including lesions present on MRI, 18-65 years of age to avoid confounding effects of developmental changes in emotional skills or emotional changes due to aging. Participants were excluded if deemed not to have capacity to consent, had a pre-morbid history of neurological disease (other than MS), traumatic brain injury, psychiatric or mood disorder, severe alcohol or drug abuse, were

undergoing a relapse during testing, had poor understanding of English that would negatively affect their ability to complete questionnaires or understand instructions, had current optic neuritis, or other severe visual impairment that would negatively affect their ability to satisfactorily complete measures.

Fifty five healthy controls matched for age, gender and education were recruited from the general community via word of mouth, though collaboration with the University of Aberdeen Research Participant Panel and friends/relatives of the MS participants. The inclusion criteria were: 18-65 years of age. Participants were excluded if they had a pre-morbid history of neurological disease, traumatic brain injury, psychiatric or mood disorder, severe alcohol or drug abuse, poor understanding of English that would adversely impact on their ability to complete questionnaires or understand instructions, had severe visual impairment that would again negatively affect their ability to satisfactorily complete measures.

Demographic information

There were 76% females in the RRMS sample, 61% females in the CPMS sample, and 58% females in the HC sample. The groups did not differ significantly in terms of male-female ratio, χ^2 (2) = 5.50, p = .064. Descriptive statistics are shown in table 1 below. A main effect of group on age was found, $F(2, 169) = 3.64$, p = .028, η_p^2 = .041. Bonferroni post- hoc analysis revealed that the CPMS group was significantly older than the RRMS group (p = .034, r = .28, 95% CI [0.25, 8.95],), but not the HC group (p = .034, r = .23, 95% CI [-0.26, 9.03]). The age difference between the RRMS group and the HC group did not reach significance either (p = 1, r = .01, 95% CI [-3.65, 4.09],). The three groups did not differ significantly in estimated years of education, F (2, 169) = 2.61, p = .076, η_p^2 = .030. The mean time since clinical diagnosis (in

years) did not differ significantly between the MS groups, $t(115) = 1.32$, $p = 0.189$, $r = .13$, 95% CI [-5.17, 1.04]. The MS severity mean score on a patient-rated variant of the Disease Steps measure (Hohol, Orav, & Weiner, 1995) for the RRMS group ($M = 2.25$) was representative of mild disability, whereas for the CPMS individuals ($M = 5.24$) was representative of moderate disability. A significant difference between the groups was found, $t(52) = 8.64$, $p < .001$, $r = .65$, 95% CI [-3.67, -2.30], indicating greater MS severity in participants with the CPMS, compared to those with the RRMS.

Table 1.
Descriptive Statistics for demographic information for MS groups and HC

	RRMS Group			**CPMS Group**			**HC Group**		
	M	***SD***	***95% CI***	***M***	***SD***	***95% CI***	***M***	***SD***	***95%CI***
Age (in years)	47.3 n = 79	8.67	(45.4- 49.2)	51.9 n = 38	7.19	(49.5- 54.3)	47.5 n = 55	10.8	(44.6- 50.4)
Education (in years)	14.5 n = 79	3.33	(13.4- 15.6)	14.6 n = 38	3.00	(13.9- 15.3)	15.7 n = 55	3.26	(14.9- 16.5)
MS Duration (in years)	12.3 n = 79	8.16	(10.4-14.1)	14.3 n = 38	7.46	(11.9-16.8)	---	---	---
MS Severity (PDDS 0- 8)	2.25 n = 79	1.79	(1.85-2.65)	5.24 n = 38	1.67	(4.69-5.78)	---	---	---

Note. PDDS = The Patient Determined Disease Steps (MS severity measure)

Measures

All four validated self-report measure were completed by participants with MS. Two of these measures were MS specific (i.e. The Patient Determined Disease Steps and The Illness Perception Questionnaire-Revised) and therefore not filled in by HC. HC completed the remaining three measures (the Difficulties in Emotion Regulation and the World Health Organisation Quality of Life).

1) Brief background and demographic information: age of participant, gender, years of education, type of MS, date of first symptoms, date of diagnosis, and other neurological or psychiatric diagnosis.

2) The Patient Determined Disease Steps measure (PDDS; Hohol et al., 1995) was used to assess MS severity. This questionnaire was specifically designed for an evaluation of functional disability and disease progression in MS, based primarily on ambulation. The PDDS is an ordinal rating scale comprising nine classifications: 0 = 'Normal, mild symptoms or signs, mostly sensory', 1 = 'Mild Disability, noticeable symptoms, still minor', 2 ='Moderate disability, no gait problems, but other disabling symptoms', 3 = 'Gait disability, significant gait problems', 4 = 'Early cane, intermittent use of cane', 5= 'Late cane, cane-dependent', 6 = 'Bilateral support', 7 = 'Confined to wheelchair' and 8= 'Bedridden'. Scores range from 0-8, and they are used to classify individuals according to disability level: a score of 0-2 indicates 'mild disability' with sensory symptoms and no walking limitation; a score of 3-5 indicates 'moderate disability' with walking difficulties and need for a cane; a score of 6-8 indicates 'severe disability' with a need for bilateral support or wheelchair or being bedridden (Gulick, Namey, & Harper, 2011). Inter-rater

reliability for PDDS was found to be excellent (kappa = .80) compared to a moderate result for the Expanded Disability Status Scale (EDSS) (kappa = .54) which is the most widely employed clinical measure of severity in MS (Kurtzke, 1983). A longitudinal study conducted by Hohol et al., 1999), which compared the PDDS and the EDSS for evaluation of MS progression, showed that the two scales delivered similar evaluations and were strongly associated with each other at baseline, and over time. These findings grant further support for validity of the PDDS and its use as a simple, practical tool for evaluation of disease progression in MS (Hohol et al., 1999). The internal consistency for this measure was acceptable (cronbach's alpha = .79).

3) Emotion regulation problems were investigated using the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004). The DERS is a self-report questionnaire designed to evaluate 6 domains of emotion dysregulation using 36 items; 1) acceptance of emotion (*nonacceptance),* 2) the ability to inhibit impulses when experiencing negative emotional states (*impulse control),* 3) the ability to successfully direct behaviour towards targets and goals when distressed (*goals),* 4) the ability to be aware of own emotions (*awareness),* 5) having clarity about and understanding of emotions experienced (*clarity*) and 6) the ability to access and use emotion regulation strategies (*strategies)*. Higher scores indicate greater emotion regulation difficulties. The total score rages from 1-5. Psychometric properties of the DERS were shown to be adequate (Gratz & Roemer, 2004). The DERS was selected over other emotion regulation measures due to assessing a wider range abilities believed to be crucial for effective regulation of emotions, such as acceptance of emotional responses and awareness rather than contrasting strategies. The internal consistency for this measure was acceptable ranging from 0.59 to 0.91 for different subscales.

4) The Illness Perception Questionnaire-Revised (IPQ-R; Moss-Morris et al., 2002) - This questionnaire will be used to measure participants' various beliefs about their illness. The IPQ-R encompasses eight cognitive illness representations, including *illness identity, cause, acute/chronic timeline, cyclical timeline, consequences, personal control, treatment control and illness coherence,* and a single subscale measuring emotional representations/responses to illness (Moss-Morris et al., 2002). Illness identity and cause are divided into separate subscales. Remaining dimensions form a third subscale. Scores ranged from 0-5. Items were coded so that higher scores reflect stronger negative beliefs on a particular subscale. The IPQ-R has demonstrated good construct, criterion and known-groups validity (Moss-Morris et al., 2002). Although the participants with MS in this study completed the entire IPQ-R, only the subscales that related to the study's hypothesis were included for the analyses. These subscales were:

(1) **Illness identity** - ratings of the number of 14 symptoms that individuals with MS believed to be (or not) associated with their illness. For the purposes of the study, three additional symptoms commonly present in MS (speech distortions, numbness, clumsiness) were added to the scale, as done in previous research (Jopson and Moss-Morris, 2003) giving a score range of zero to 17.

(2) **Personal control** (6 items) - ratings of people's beliefs about their own capability to control symptoms they experience (e.g. "What I do can determine whether my illness gets better or worse").

(3) **Treatment control** (5 items) – ratings of people's beliefs regarding the effectiveness of the prescribed treatment in controlling the illness (e.g. "The negative effects of my illness can be prevented (avoided) by my treatment").

(4) **Consequences** (6 items) – ratings of people's beliefs regarding the adverse impact of their illness on their life and functioning (e.g. "My illness strongly affects the way others see me").

(5) **Emotional representations** (6 items) - ratings of people's beliefs regarding their negative emotional responses to illness (e.g. "Having this illness makes me feel anxious").

The internal consistency for different subscales was acceptable ranging from 0.75 to 0.81.

Quality of life was assessed using the self-rated World Health Organisation Quality of Life instrument (WHOQoL-BREF; Skevington, Lofty & O'Connell, 2004). This questionnaire assesses multidimensional aspects of quality of life delineated into four separate domains of psychological well-being, social relationships, physical health, and functioning in the environment, using 24 items. Higher scores are indicative of better quality of life, with scores ranging from 0-100. Adequate psychometric properties of the WHOQoL-BREF have been reported (Harper & Power, 1998). Since the WHOQoL-BREF has been found to be sensitive to physical impairments, social participation restrictions, activity limitations, and difficulties in functioning in day to day environment, it is recommended as a quality of life measure for MS population (Wynia, Middel, van Dijk, De Keyser, & Reijneveld, 2008). Moreover, the WHOQoL-BREF has been found to display adequate validity in MS by correlating with disability, depression and caregiver assessments of QoL (Alshubaili, Awadalla, Ohaeri, & Mabrouk, 2007). The internal consistency for different subscales was acceptable ranging from 0.85 to 0.90.

Statistical Analysis

Strategy for dealing with missing data

Within the final sample, 2% of variables were missing. These data were missing entirely at random, as demonstrated by Little's MCAR test. The 2% of missing values were replaced with predicted values using the expectation-maximisation (EM) algorithm. This statistical technique has been regarded as a reliable method for handling missing data (He, 2010). Cases were excluded on pairwise basis. One person with MS did not fill in their DERS and PDDS questionnaires. All participants with MS returned their IPQ-R questionnaires filled in, except for one person, and further one failed to rate the illness identity scale.

Strategy for dealing with outliers

Potential outliers were initially investigated using boxplots. Subsequently, a method of winsorising was used to deal with outlying data. This technique involves recoding outliers to the next lowest (or highest) score that cannot be classified as an outlying score. Z-scores were computed for each of the dependent variables in order to screen for existing outliers. Z-scores lower than - 3.29 and greater than + 3.29 were classed as outliers, as normally distributed data points are anticipated to fall within this range (Field, 2013). Fifteen outliers across the DERS, IPQ-R and WHOQoL-BREF were found and subsequently recoded.

Exploratory Data Analysis

Data was explored for normality, skew, kurtosis and homogeneity of variance. The

Kolmogorov-Smirnov test of normality was employed alongside QQ plots, histograms. Z-scores were computed for skew and kurtosis values; skew score was divided by the standard error, kurtosis score was square rooted (Field, 2013). Resulting z-scores were considered significant if the score was greater than 2.58 (Clark-Carter, 1997).

The three subscales of the DERS (impulse control, goals and clarity) did not meet the assumptions for parametric analysis. Successful square root transformations were conducted based on the histogram distributions (Clark-Carter, 1997). All subscales were subsequently transformed accordingly (Field, 2013) for further comparisons which enabled parametric analysis to be carried out.

Group differences between CPMS, RRMS and HC in the multiple subscales of the DERS, WHOQoL-BREF and IPQ-R were examined by conducting separate mixed design analyses of variance (ANOVAs), followed up by separate simple effects analysis (one-way ANOVAs) to delineate group differences in individual subscales where interaction effects were observed. Sample size was determined by carrying out a power analysis using G*Power 3.1, with an alpha level of 0.05, and a medium effect size (f = .25). This led to a predictive total sample size (two MS groups and HC) of 179 with an actual power of .80.

For the secondary research question, relationships of DERS scores with other measures were investigated using Pearson's correlations, employing a significance level of $p < .01$ to account for multiple comparisons. Next, hierarchical regression analysis was used to address the extent to which illness representations predict difficulties in emotion regulation in the sample of MS participants. Hierarchical regression controlled for factors such as disease severity. Sample size was determined by carrying out a power analysis using G*Power 3.1, with an alpha level of 0.05, and a medium effect size (f = .25). This led to a predictive total sample size (two MS groups and HC) of 159 with an actual power of .80.

For the final research question, multiple mediation analysis was carried out to investigate whether the relationship between illness severity and quality of life was mediated by emotion regulation and illness representations. PROCESS macro (Hayes, 2013) was employed for SPSS in order to apply bias-corrected nonparametric bootstrapping procedures (5000 resampling) to test the direct, indirect and total effects of illness severity of quality of life. Ma and Zeng (2014) showed, using Monte Carlo simulation via M*plus* that would recommend a minimum sample size of 100 participants for an adequately powered (of .80) multiple mediation analysis.

Results

Table 2 below provides a summary of descriptive statistics for each of the dependent measures employed, including emotion regulation, illness representations and quality of life.

Table 2.
Descriptive Information for Emotion Regulation, Illness Representations and Quality of Life for MS and HC groups

	RRMS Group			**CPMS Group**			**HC Group**		
	M	***SD***	***95%CI***	***M***	***SD***	***95%CI***	***M***	***SD***	***95%CI***
DERS[a] Total score 1-5									
Nonacceptance	2.50	1.09	(2.25-2.75)	2.41	0.98	(2.09-2.73)	1.86	0.72	(1.67- 2.06)
Goals	2.85	0.80	(2.67-3.03)	2.85	0.80	(2.57-3.14)	2.63	0.67	(2.45-2.81)
Impulse	1.95	0.49	(1.85-2.07)	1.94	0.57	(1.75-2.13)	1.76	0.43	(1.64-1.87)
Awareness	3.16	0.82	(2.98-3.35)	3.33	0.93	(3.03-3.64)	3.42	0.74	(3.23-3.63)
Strategies	2.07	0.66	(1.92-2.22)	2.17	0.78	(1.91-2.42)	1.89	0.47	(1.76-2.01)
Clarity	2.52	0.37	(2.44-2.61)	2.64	0.52	(2.48-2.82)	2.51	0.30	(2.43-2.59)
Total	2.48	0.44	(2.39-2.58)	2.53	0.51	(2.36-2.70)	2.31	0.36	(2.21-2.41)
IPQ-R[b] Total score 1-5									
Personal Control	3.17	.52	(3.06-3.29)	3.32	.65	(3.10-3.53)	---	---	---
Treatment Control	3.40	.46	(3.30-3.50)	3.48	.55	(3.30-3.66)	---	---	---
Consequences	3.09	.65	(2.95-3.25)	3.56	.51	(3.39-3.73)	---	---	---
Emotional Representations	2.72	.75	(2.56-2.89)	2.87	.78	(2.56-2.89)	---	---	---
Illness Identity Total score 0-17	7.72	2.86	(7.07-8.36)	8.13	3.19	(7.08-9.18)	---	---	---
Quality of Life Total score 0-100									
Physical	52.2	11.5	(49.6-54.8)	43.5	11.2	(39.8-47.2)	59.2	10.6	(56.3-62.0)
Psychological	60.1	12.7	(57.3-62.9)	53.5	16.1	(48.2-58.8)	63.9	11.3	(60.8-66.9)
Social	69.3	20.0	(64.8-73.8)	61.6	22.1	(54.3-68.9)	68.1	21.0	(63.1-74.5)
Environmental	74.8	14.4	(71.6-78.1)	65.9	15.2	(60.1-70.1)	76.7	13.5	(73.1-80.4)
Total	64.1	11.9	(61.5-66.8)	56.2	12.6	(52.3-60.0)	67.2	11.9	(63.9-70.4)

Note. DERS = Difficulties in Emotion Regulation Scale, IPQ-R = Illness Representations Questionnaire Revised, WHOQoL-BREF = World Health Organisation Quality of Life

[a] Note that higher scores on DERS imply more difficulties with emotion regulation.

[b] Note that higher scores on IPQ-R imply stronger and more negative beliefs regarding MS.

Differences in Emotion Regulation Abilities between the MS Groups and the HC

To explore whether individuals presenting with different variants of MS differed in emotion regulation abilities, as compared to HC, a 3 x 6 mixed-design ANOVA with six levels of DERS subscales (nonacceptance, goals, impulse, awareness, strategies or clarity) as the within-subject variable, and group category (RRMS vs CPMS vs. HC) as the between-subject variable was conducted. There was a significant main effect of group, $F(2, 168) = 3.60$, $p < .001$, $\eta_p^2 = .041$. There was no significant difference in overall ratings between participants with the RRMS and CPMS ($p = 1$, $r = .03$, 95%CI [-.25, .15]). There was also a significant main effect of subscale type $F(5, 840) = 110.7$, $p < .001$, $\eta_p^2 = .397$, with some subscales having higher ratings than others. Importantly, there was a significant DERS subscale type x group interaction, $F(10, 840) = 3.67$, $p < .001$, $\eta_p^2 = .042$. Post-hoc analyses using the Bonferroni method indicated that significant differences between the groups were found on the DERS nonacceptance subscale only; both the RRMS group ($p = .001$, $r = .33$, 95%CI [-1.05, -.23]) and the CPMS group ($p = .025$, $r = .30$, 95%CI [-1.04, -.52]) reported more difficulties accepting their emotions, compared to the HC group. No significant difference were found between participants with the RRMS and CPMS ($p = 1$, $r = .04$, 95%CI [-.37, .55]). Lack of interaction effects on other subscales of DERS indicate similar levels of other emotion regulation abilities in participants with different variants of MS and HC. Because participants with different variants of MS did not differ on other subscales of DERS, subsequent analyses are based on nonacceptance subscale of DERS only. Also, since there were no group difference between the RRMS and CPMS groups on DERS subscales, these groups were collated together in further analyses.

Relationships between DERS nonacceptance subscale and other variables

Pearson product-moment correlations for the MS between DERS nonacceptance scores, MS severity, and illness perception scores were conducted. Prior to these analyses, scatterplots were graphed to assess whether there were linear relationships between the variables, important for meaningful interpretation of the correlation coefficient. Linear relationships were present for all variables.

For the MS participants, the DERS nonacceptance scores correlated significantly with some subscales of IPQ-R, namely Illness Identity, r =.331, p < .001 (n = 115), and Emotional Representations, r =.481, p < .001 (n= 116), indicating small to medium size effects (Field, 2013), with Personal Control, r =.206, p = .013 (n= 116), approaching the more stringent p <.01 criterion. No significant correlations were found for Treatment Control, r =.105, p = .131 (n= 116), Consequences, r =.118, p = .104 (n= 116), or MS severity, r =.069, p = .231 (n= 116).

Further, supplementary analysis of group differences in illness representations in MS is included in appendix F (Descriptive data is reported in Table 2 above). In sum, the CPMS group rated their illness perceptions, on the whole, as significantly more negative than the RRMS group, apart from illness identity.

Regression Analyses Investigating whether Illness Representations may contribute to Predicting Emotion Regulation Difficulties Independently of MS Severity.

In order to test the hypothesis that negative illness representations predict emotion dysregulation in MS, independently of MS severity, a series of hierarchical regression analyses was carried out with DERS nonacceptance as the dependent variable. Data met all the assumptions of regression analysis. The results of the regression analyses are summarised in table 3 below. The PDDS score was entered onto the first step to control for illness severity. The illness representation dimensions were then entered on the second step to investigate whether they contributed a significant percentage of the variance in emotion dysregulation when controlling for the severity of MS.

Table 3.
Hierarchical Multiple Regression of the Illness Representation Dimensions on the DERS Nonacceptance Variable Controlling for Severity (n= 115).

	DERS nonacceptance s
Step and predictors	
(1) Control Variable	
MS Severity (PDDS)	
β	.069
R^2	.005
(2) Illness Representations	
Illness Identity	
β	.191*
Personal Control	
β	.049
Treatment Control	
β	.124
Consequences	
β	-.084
Emotional Representations	
β	.443**
$R^{2change}$	.283

* P < .05, ** P < .001.

Taken together, the MS severity variable did not contribute significantly towards a proportion of the variance in DERS nonacceptance scores. On the other hand, the illness representation dimensions did significantly predict emotion regulation difficulties, independently of MS

severity, accounting for a unique 28.3% of the variance for nonacceptance scores. The β weights show that strong negative emotional responses to illness, $t(108) = 4.91$, $p < .001$, as well as a strong illness identity, $t(108) = 2.13$, $p = .036$ were the two significant predictors of emotion dysregulation in MS. The belief that MS has severe consequences and a poor sense of personal and treatment control did not significantly predict variance in DERS nonacceptance scores.

Mediating effects of emotion regulation and illness representations on MS severity and quality of life.

Supplementary data on group differences in quality of life is presented in appendix F, with descriptive statistics being included in table 2 above. In sum, the CPMS group rated their quality of life, on the whole, significantly lower than the RRMS group, as well as the HC group. The RRMS group and the HC group did not differ significantly in their overall ratings.

The final aim of the current study was to explore emotion regulation and illness representations as mediators of the relationship between MS severity and quality of life in MS. It was hypothesised that emotion regulation abilities and illness representations will significantly mediate the relationship between MS severity and quality of life.

No significant multicollinearity between predictors was found. Correlational analyses among predictor and outcome variables were conducted and are shown in table 4 below, with medium significant relationships found between the outcome variable WHOQoL-total score and the following predictors: MS severity, DERS nonacceptance, IPQ-R Illness Identity, Consequences and Emotional Representations subscales. These significant predictors were

further included into the mediation model. Since all four WHOQoL-BREF subscales correlated significantly highly with each other (see table 5 in appendix F of the supplementary material), they were merged together into WHOQoL-Total score in order to minimise the number of comparisons in the analysis. Therefore, there was only one outcome variable to be included into the mediation model.

Table 4.
Correlational Analyses of the Predictor Variables with Outcome Variables for the MS

	WHOQoL Total
PDDS MS Severity	**-.367**** **n = 117**
DERS Nonacceptance	**-.360**** **n = 116**
IPQ-R Illness Identity	**-.356**** **n = 116**
IPQ-R Personal Control	-.215* **n = 117**
IPQ-R Treatment Control	.080 **n = 117**
IPQ-R Consequences	**-.415**** **n = 117**
IPQ-R Emotional Representations	**-.372**** **n = 117**

Note. **Correlation is significant at the 0.01 level
*Correlation is significant at the 0.05 level

Next, the multiple mediation analysis was carried out to test the hypothesis that emotion regulation and illness representations will mediate the relationship between MS severity and quality of life. The MS severity (PDDS) was entered as a predictor and WHOQoL-Total as an

outcome variable. DERS nonacceptance, IPQ-R Illness Identity, IPQ-R Consequences and IPQ-R Emotional Representation were entered into the model as potential mediators of the relationship between MS Severity and QoL. A model summary (i.e. linear regression) generated an adjusted R^2 = .34, implying that the five predictors explained 34% of variance in WHOQoL-BREF ratings, with the model reaching statistical significance, F (5,109) = 11.3, p < .001.

Significance of direct and indirect effects was determined based on the lower and upper 95% confidence interval not including zero. The total effect of the relation between MS severity (PDDS) and QoL (WHOQoL-BREF; before accounting for the effect of emotion regulation and illness representations was significant, (B = -2.19, *SE* = .50, p < .001, 95% CI [-3.17, -1.20]), such that higher levels of MS severity were associated with lower levels of QoL. Further, the direct effect of the relation between MS severity (PDDS) and QoL (WHOQoL-BREF) remained significant, (B = -1.27, *SE* = .52, p=.02, 95% CI [-2.30, -0.24]) after controlling for emotion regulation (DERS nonacceptance) and illness representations (Illness Identity, Consequences and Emotional Representations). As reported in table 6 below the total indirect effect via the mediators (the difference between the total and direct effects) was significant (point estimate of -.92, 95% CI [-1.69, -0.30]). The specific indirect effects in this mediation analysis are reported below in Table 6. IPQ-R Consequences was the only significant mediator of the relationship between MS severity and QoL in MS. This suggests that strong negative beliefs about the consequences of MS mediate the relationship between MS Severity and QoL. Since the direct effect of MS Severity on QoL remained significant in this model, the IPQ-R Consequences was a partial mediator of the relationship between severity of MS and QoL. See figure 1 below for a visual representation of the mediation analysis.

Table 6.
Specific Indirect Effects of Potential Mediators

	Point estimate of indirect effect from bootstrapping	Standard Error (*SE*)	BCBCI	
			Lower CI	Upper CI
DERS Nonacceptance	-.08	.116	-.41	0.09
IPQ-R Illness Identity	-.20	.145	-.59	0.01
IPQ-R Consequences *****	-.54	.294	-1.25	- 0.07
IPQ-R Emotional Representations	-.10	.110	-.46	0.02
Total Indirect Effect *****	-.92	.345	-1.69	- 0.30

Note. BCBCI = Bias corrected bootstrapped confidence interval with 5000 samples
* Significant mediation effect at p <.05 where lower and upper BCBCI values do not include zero.

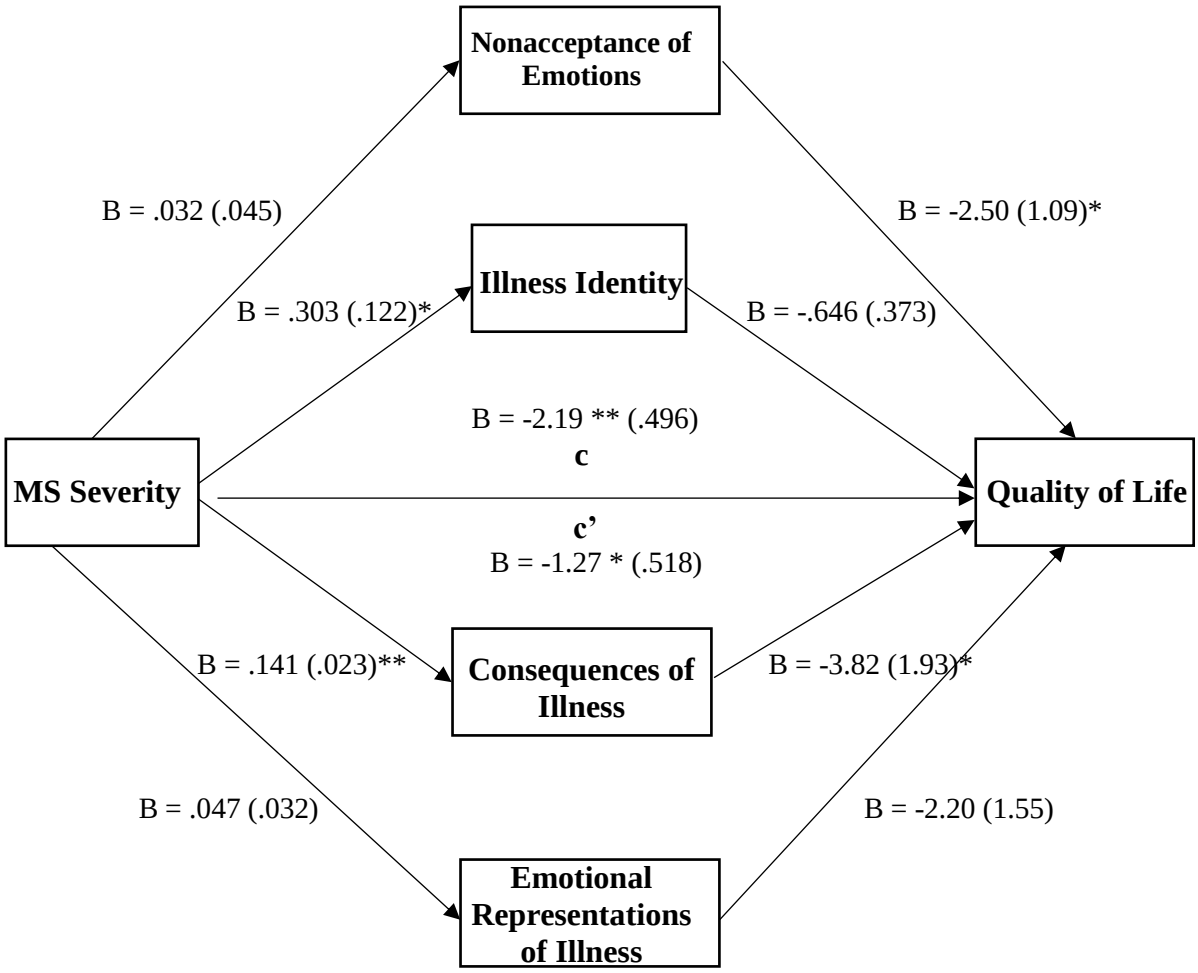

Figure 1 Mediation effects of Nonacceptance of Emotions (as measured by DERS = Difficulties in Emotion Regulation Scale) and Illness Representations (as measured by IPQ-R = Illness Representations Questionnaire Revised) on the relationship between Illness Severity (as measured by PDDS = Patient Determined Disease Step)

and Quality of Life (as measured by WHOQoL-BREF = World Health Organisation Quality of Life) in MS. All figures represent uncorrected path Beta- coefficients, with the *SE* listed in parenthesis. The results indicate that the relationship between MS Severity and Quality of Life in MS was reduced when mediators were accounted for. Bootstrapping indicated that the beliefs about the Consequences of Illness was the only significant and partial mediator of the relationship between Illness Severity and Quality of Life.
Note: ** significant at the 0.01 level, * significant at the 0.05 level

Discussion

The primary aim of this study was to investigate whether there are differences in emotion regulation strategies employed by people with relapsing-remitting MS and chronic progressive MS, as compared to healthy controls. It was further inquired whether illness representations developed by individuals with MS impact on how they regulate their emotions while accounting for the severity of their MS. The final aim was to explore the mediating effect of emotion regulation and illness representations in the relationship between the severity of MS and self-reported quality of life in MS.

Group Differences in Emotion Regulation in MS

It was found that both MS groups, the RRMS group and the CPMS group reported moderate difficulties in accepting their feelings of distress, compared to the HC group. However, no significant differences on the DERS Nonacceptence subscale were found between the MS groups, implying similar levels of difficulty with accepting emotional distress in individuals with different variants of MS. Interestingly, a lack of other significant differences on the rest of DERS subscales between individuals with MS and healthy controls suggests that other processes of emotion regulation are relatively intact in MS. These findings are partially consistent with previous literature. The study of Phillips et al. (2014) found that individuals with MS, as compared to HC, reported overall more difficulties with emotion regulation, as measured by the DERS. Yet, the different emotion regulation processes appeared to be similarly affected, as indicated by no significant group differences on the DERS subscales.

However, it is likely that the results of Phillip's study are underpowered due to a small sample size (31MS, 31HC). When exploring the reported mean statistics, the biggest mean difference between the MS and HC group in Philip's et al. (2014) study was, similarly to this study, on the Nonacceptance subscale of the DERS. Another study (Yule, 2013) on emotion regulation in chronic neurological condition, namely stroke (50 stroke, 45 HC), also found significantly higher difficulties with nonacceptance of emotions (and impulsivity) in stroke survivors, as measured by the DERS. Yet, the sizes of these effects are not reported. Interestingly, nonacceptance of emotions as indicated on the DERS has been reported previously as one of the core difficulties in alexithymia (Pandey et al. 2008), which is also found in MS (Gleichgerrcht et al., 2015). Given unpredictable occurrence and/or progression of symptoms in MS, it is not surprising that those with this chronic and, in most cases, progressive neurological condition struggle to tolerate their distress. In fact, there is evidence, particularly in the ACT literature, that non-acceptance of experiences, including emotional states, has a negative impact on functional/adjustment outcomes across conditions, such as chronic pain (McCracken & Eccleston, 2003); diabetes (Greg, Callahhan, Hayes, & Glenn-Lawson, 2007), epilepsy (Lundgren, Dahl, Yardi, & Melin, 2008), as well as MS (Pakenham & Fleming, 2010). Thus, addressing non-acceptance of emotional experiences in MS might be important in improving coping and functioning in MS.

Encouragingly, no differences between the MS groups and HC were found on other emotion regulation abilities. This was the first study to date that explored whether the severity of emotion regulation difficulties in MS was affected by the form of MS. While one could speculate whether the unpredictable trajectory of RRMS (with fluctuating functioning and recovery) or permanent neuronal loss of CPMS (resulting in progressive disability) is more

likely to lead to emotion regulation problems, it appears that the variant of MS alone is not indicative of specific emotion regulation difficulties.

Negative Illness Representations as Predictors of Emotion Dysregulation in MS

It was specifically hypothesized that individuals with MS who had a strong illness identity, a poor sense of control over their MS, strong emotional responses to their MS and believe that their MS has detrimental consequences on their lives, will have more difficulties with their emotion regulation.

First, the differences between the RRMS group and CPMS group in illness representations were explored, as this was not previously explored in the literature. It was found that overall, the CPMS group held more negative beliefs about their illness than RRMS group. However, both group also reported similar levels of illness identity. In other words, both groups were ascribing similar number of physical symptoms they experience to having MS, despite those with RRMS having lower levels of MS severity. One may assume that those with CPMS would develop a stronger and more negative identity of their illness than those with RRMS, simply because CPMS is associated with higher levels of progression and disability (Lucchinetti & Parisi, 2006).

In the context of the study's hypotheses, some aspects of Illness Representations did significantly predict 28.3% of the variance in DERS nonacceptance scores, independently of MS severity. The results indicate that those individuals with MS who have a strong and negative illness identity, as well as strong negative emotional responses to having MS, will

experience more difficulties in accepting their distress. Contrary to our hypothesis, having a poor sense of control, as well as holding negative beliefs about the consequences of having MS does not appear to contribute to nonacceptance of one's negative emotional states. This is the first study which demonstrates that the way people with MS perceive and think about their illness is linked with their emotion regulation abilities, to some extent. It is therefore possible that helping people address their negative perceptions and reactions to their illness will result in more effective emotion regulation.

These results add to previous evidence on emotion regulation in MS. Although this type of research is still in its infancy, there is evidence that factors such as low levels of dispositional mindfulness are linked to higher levels of emotional dysregulation in MS (Schirda et al., 2015). The current study shows that other psychosocial factors such as negative beliefs about one's illness are also likely to be associated with some aspects of emotion dysregulation in MS, mainly nonacceptance of one's distressing emotions. These findings also help to ascertain that problems with emotion regulation in MS do not simply arise from the severity of MS, i.e. problems with ambulation. Thus, it is important in future studies to control for factors such as MS severity.

Moreover, in the context of MS, illness representations have been mainly explored in relation to adjustment and outcome (Jopson & Moss- Morris, 2003; Vaughan et al., 2003), showing that negative illness representations are associated with poor functional outcomes, and difficult adjustment. The fact that high illness identity and negative emotional responses to having MS predicted non-acceptance of distress (as measured by DERS) further supports the aforementioned idea that intolerance of distress in MS might stem from difficulty coping and adjusting to having this unpredictable condition. A number of outcome measures has been

incorporated to study adjustment in MS, including sickness impact, mood, QoL, self-esteem, social and occupational adjustment, as well as fatigue levels (e.g. Jopson & Moss-Morris, 2003; McCabe *et al.,* 2004; van Kessel *et al.,* 2008; Vaughan *et al.,* 2003). While these biopsychosocial factors are undoubtedly important for adequate adjustment to chronic illness such as MS, we would argue that emotion regulation processes and strategies should be incorporated into current models of adjustment to MS (such as e.g. working model of adjustment to MS by Dennison *et al.,* 2009). This is so, because emotion dysregulation has been linked to lower quality of life in MS (Schirda et al., 2015), severity of anxiety and depression (Liverant et al., 2011), as well as shown to be an essential psychological adaptation to other chronic illnesses, such as rheumatoid arthritis (Van Middendorp et al., 2005), kidney disease (Gillandres et al., 2008), and Juvenile Idiopathic Arthritis (Garnefskia, Koopmanb, Kraaijb & Catec, 2009). Thus, future studies should explore more closely the emotion regulation processes (using e.g. DERS) and strategies (using e.g. ERQ) used by people with MS in relation to various aspects of outcome and adjustment.

The results of this study, so far, have shown that individuals with MS have difficulties with nonacceptance of their negative emotional experiences which are to some extent predicted by strong illness identity and negative emotional responses to having MS, independently of MS severity, and regardless of the relapsing-remitting or chronic nature of the MS.

Emotion Regulation and Illness Representations as Mediators of the Relationship between MS Severity and Quality of Life

Lastly, we hypothesized that emotion regulation abilities and illness representations will be significant mediators of the relationship between MS severity and quality of life. Since there

were no significant MS group effects on Emotion Regulation and Illness Representation measures, it was decided that the mediation analysis would be conducted on the entire MS sample.

We found that having higher MS Severity (PDDS), struggling to accept negative emotions (DERS Nonacceptance), as well as holding more negatives beliefs about own illness is associated with poorer quality of life in MS. More specifically, ascribing more symptoms to having MS (IPQ-R Illness Identity), believing MS to have serious consequences (IPQ-R Consequences) and having more negative emotional responses to having MS (IPQ-R Emotional Representations) is linked with reduced self-rated quality of life. Although, it was found that these five constructs predicted 34 % of variance in quality of life scores, only beliefs regarding the consequences of MS were found to be the partial mediator of the relationship between MS severity and quality of life. Thus, there will potentially be other factors that affect the association between MS severity and quality of life that need investigating.

MS Severity, particularly in the context of ambulatory impairment, is a common characteristic of MS, especially in its progressive forms. It has serious consequences for functioning of those with the disease and these results provide further support for previous findings of the strong relationship between MS severity (motor impairment) and reduced QoL in MS literature. It is important to explore other psychosocial factors that can mediate this relationship, as those with similar motor disturbances in MS might report reduced QoL for reasons other than the motor difficulties themselves. As demonstrated by this study, the beliefs about the consequences of MS appeared to contribute to this relationship. In other words, people with MS whose ambulation problems prevent them from having an adequate QoL, might have developed negative beliefs about the consequences of their MS which further contributes to their reduced

QoL; for instance their might think that their walking difficulties are 'too severe' to attempt leaving the house which could result in restricted social participation and reduced QoL. It is somewhat surprising that other aspects of Illness Representations (as measured by Illness Identity, Emotional Representations and Personal and Treatment Control subscales of the IRQ-R) do not further contribute to this relationship, as previous literature reported these aspects of Illness Representations to be associated and/or predict various health outcomes and adjustment to MS (Jopson & Moss- Morris, 2003; Vaughan et al., 2003). Also, emotion regulation difficulties in the form of the nonacceptance of emotions did not contribute to the relationship between MS Severity and QoL. This is contrary to previous evidence that emotion regulation difficulties predicted poorer psychological and social quality of life in MS (Phillips et al., 2014). It might be that moderate difficulties with accepting distressing feelings are not in itself severe enough to contribute to this relationship, or that there are other additional psychosocial factors, such as mood difficulties, that play a role. It might be that high levels of anxiety or depression resulting to some extent from the severity of MS might further mediate the relationship between the severity and reduced QoL. Thus, future studies, should explore the potential mediating impact of heightened levels of anxiety and depression, which are reported to be high in people with MS (Boeschoten et al., 2017)

Taken together, the findings of this study show that individuals with MS have moderate difficulties with nonacceptance of their emotional states, irrespectively of MS variant, with other emotion regulation abilities being unaffected, as compared to HC. These difficulties are to some extent predicted by having strong illness identity and negative emotional responses to having MS, independently of the severity of their illness. The beliefs about the negative consequences of having MS partially mediated the relationship between MS severity and reduced quality of life in MS.

Clinical Implications

This study found moderate difficulties in one particular aspect of emotion regulation, namely non acceptance of distress, in MS, and these difficulties were associated with reduced self-reported QoL. Although further research is warranted to assess the prevalence of emotion regulation difficulties in MS, the findings of this study are encouraging in a sense that emotion regulation difficulties might not be very severe within MS population, and possibly not dependent on MS type. However, this is surprising considering high levels of depression and anxiety in MS, and the findings that depression mediated emotion regulation difficulties in one study on MS (Phillips et al., 2014). The assumptions that high levels of depression and anxiety in MS result, at least to some extent, from poor emotion regulation processes and maladaptive strategies is still worth exploration, although our findings do not point to severe emotion dysregulation in our sample of MS participants. Since psychological interventions are commonly conducted with individuals with MS and comorbid cognitive impairments or mood disorders (such as depression and anxiety) that further impact on functioning, rather than selective emotion regulation difficulties, it might be more beneficial to explore emotion dysregulation and emotion regulatory strategies in a sample of MS individuals who also meet criteria for anxiety/depressive disorder or cognitive impairments, rather than excluding them from studies.

The National Institute of Health and Clinical Excellence (NICE, 2014) guidelines on the management of Multiple Sclerosis in adults in primary and secondary care recommend having psychologists as integral members of the neurological rehabilitation services. More specifically, different variants of Cognitive Behavioural Therapy (CBT) are recommended for the treatment of depression and/or anxiety. Also, the Matrix: A Guide to Delivering Evidence-Based Psychological Therapies in Scotland (Matrix, 2015), for neurological disorders, recommends CBT adjustment group intervention to reduce distress in MS. Yet, there are other therapeutic approaches addressing difficulties with emotion regulation, such as Dialectical Behaviour Therapy (DBT) and Acceptance and Commitment Therapy (ACT; Aldao, Nolen-Hoeksema & Schweizer, 2010) which might prove effective in MS population. Therefore, more research looking at efficacy and effectiveness of other therapeutic approaches is warranted and timely.

Given that, in the current study, nonacceptance of negative emotions was significantly poorer in MS, and predicted by having strong beliefs about illness identity and negative emotional responses, it is possible that some aspects of ACT might be effective in addressing these difficulties. ACT puts emphasis on exploring people's directions for valued living despite their illness, identifying current unworkable actions in the form of cognitive fusion (i.e. when beliefs about illness identity and consequences of MS are treated as facts) that can lead to experiential avoidance (e.g. participating in less activities to avoid unpleasant feelings of disappointment/embarrassment), and potentially exacerbating difficulties accepting such negative emotional states. ACT encourages committed actions in directions that are valued by the individual (Harris, 2009) which is an approach commonly adopted by specialist neuropsychological rehabilitation services which attempt to identify workable goals with their clients with MS to increase their functional outcomes and QoL. It would be interesting to see

whether this type of approach could improve emotion regulation by reducing the impact of illness representations in MS. Our results indicate that the relationship between MS severity and QoL is mediated by the negative beliefs about the consequences of MS. Again, ACT might prove beneficial in improving psychological flexibility and reducing narrow and/or rigit behaviours that contribute to poorer QoL in people with MS.

An ACT oriented approach to rehabilitation in MS, could affect an understanding of MS related emotional and psychosocial difficulties in all MDT members, and their subsequent responses to clients. In the context of chronic and unpredictable illness, such as MS, certain thoughts, beliefs and emotional responses are inevitable. In certain instances, active therapeutic efforts to challenge, change or discourage these experiences via e.g. CBT might prove unproductive or be simply unrealistic. Although the abovementioned applications of ACT in MS population are highly speculative at this stage, and it is important not to 'get ahead of the data', the need for further research into psychological interventions that could improve emotion regulation, illness representations and QoL in MS cannot be underestimated. Since the DERS has been shown to display sensitivity to change over time (Fox, Axelrod, Paliwal, Sleepe & Sinha, 2007), it can be utilised in future studies as an outcome measure of emotion regulation abilities and to monitor the effectiveness of psychological interventions in MS.

Limitations and suggestions for future studies

Most of the limitations and suggestions for future studies have been already discussed throughout the previous sections of this discussion. The main limitation of this study, and most psychological research in MS, is its cross-sectional design. Thus the true direction of the relationships between investigated variables cannot be guaranteed. Future longitudinal studies and interventions targeting emotion dysregulation and challenging or reducing the effects of

illness and symptom beliefs would prove key in further consolidating these results. Also, multiple assessments of emotion regulation processes and strategies, as well as social functioning, at different points in time could assist researchers and clinicians in to determining the viable and changing trajectory of MS effects on emotional and psychosocial functioning.

As abovementioned, other potential contributing factors, such MS severity, mood disorders (e.g. depression or anxiety), brain volume loss, levels of social support should be investigated when looking at differences in emotion regulation in MS, independently of MS type.

Although, the severity of MS was significantly higher in the CPMS group, compared to RRMS group in this study (i.e. moderate and mild respectively), there were significant individual differences in severity within the groups. Moreover, the PDDS measure of MS severity is based solely on ambulation. It might be useful to incorporate other indicators of severity, such as levels of fatigue, spasticity, pain, mood and/or cognitive dysfunction. Given the extensive nature of MS deficits, more comprehensive disease severity tools, such as Performance Scales (self-assessment of disease status in MS; Marrie & Goldman, 2007), may shed more light onto functional limitations that people with MS acquire and whether the extent of these limitations is associated with different level of emotion dysregulation.

Given that mood difficulties are prevalent in MS, it would be interesting to explore whether individuals with MS who have clinical levels of depression and anxiety experience greater emotion dysregulation, compared to those individuals with MS who do not report significant difficulties with mood. This study did not employed a screening instrument of depression or anxiety. However, participants were asked to report any psychiatric or mood disorders they were diagnosed with. Those who did were excluded from the study. In the context of potential

neurological contributors to emotion dysregulation, it has been shown that long-term myelin, axonal and synaptic degeneration, together with other tissue loss (such as grey matter), contribute to brain atrophy in MS (de Stefano, Battaglini & Smith, 2007). Since the lesion profile in MS is largely diffused, affecting multiple areas of both, brain and spinal cord functioning (Kantarci & Weinshenker, 2005), it might be more beneficial to look at brain volume loss, rather than lesion distribution when exploring emotion dysregulation in MS. Alternatively, it might prove advantageous in future studies to explore the links between specific neural changes resulting from MS and emotion regulation processes using imaging techniques. Given that MS may lead to disconnection in the frontal-subcortical brain tracts which are implicated in affective information processing (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000),it might be worthwhile to investigate whether emotion regulation abilities are more adversely affected in those with MS who sustained frontotemporal matter atrophy, than those without such changes.

Lastly, self-report questionnaire measures, such as DERS require individuals to consider their inner emotional processes and how these affect their outer display of emotional content and subsequent behaviour which might be problematic for people to report adequately. Moreover, although a lack of insight is not consistently reported in MS (Benedict et al., 2001; Smith & Arnett, 2010), it is possible that individuals' ratings reflected, to some extent, their desire to be perceived as having a greater control over their emotional experiences than it is actually the case. Social desirability and self-presentation bias play a role in self-report research, as adequate emotional abilities are socially highly valued, with the face validity of such tools being also high. For this reason, future studies might like to consider using informant-report measures alongside self-report measures to further increase understanding of emotion regulation difficulties in MS.

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APPENDIX E: Research Ethics Committee Approval

NHS
Health Research Authority
South West - Cornwall & Plymouth Research Ethics Committee
Level 3
Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

29 March 2016

Dr Bogumila Radlak
Trainee Clinical Psychologist
NHS Grampian
Royal Aberdeen Children's Hospital
Child and Family Mental Health Service
Westburn Rd, Forresterhill, Aberdeen
AB25 2ZG

Dear Dr Radlak

Study title:	**Effects of Illness Representations on Emotion Regulation in Multiple Sclerosis**
REC reference:	**16/SW/0082**
IRAS project ID:	**197713**

Thank you for your letter of 23 March 2016, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Georgina Castledine, nrescommittee.southwest-cornwall-plymouth@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start

APPENDIX F: Supplementary Data

Group Differences on Background Measures of Illness Representations and Quality of Life

An Independent- Samples t-test was conducted to investigate group differences in Illness Identity. No significant differences were found between participants with CPMS and RRMS, $t(114) = -0.704$, $p = .483$, $r = .06$, 95% CI [-1.58, .75] which implies that Illness Identity is similar in both MS groups.

For the assessment of the remaining IPQ-R subscales, a 2 x 4 mixed-design ANOVA with four levels of illness representations (Consequences, Personal Control, Treatment Control, or Emotional Representations) as the within-subject variable, and group type (RRMS vs. CPMS) as the between-subject variable, was conducted. This analysis revealed a significant main effect of group, $F(1, 115) = 7.96$, $p = .006$, $\eta_p^2 = .065$, indicating that the CPMS group rated their illness perceptions, on the whole, as significantly more negative than the RRMS group. There was also a significant main effect of IPQ-R domain $F(3, 345) = 25.8$, $p < .001$, $\eta_p^2 = .183$, but no significant interaction between group type x IPQ-R domain, $F(2, 345) = 2.42$, $p = .066$, $\eta_p^2 = .021$.

For the assessment of quality of life, a 3 x 4 mixed-design ANOVA with four levels of QoL domains (Physical, Psychological, Social, or Environmental) as the within-subject variable, and group type (RRMS vs. CPMS vs. HC) as the between-subject variable, was conducted. This analysis revealed a significant main effect of group, $F(2, 169) = 9.63$, $p < .001$, $\eta_p^2 = .103$. Post-hoc analyses using the Bonferroni method indicated that the CPMS group rated their quality of life, on the whole, significantly lower than the RRMS group ($p = .003$, $r = .25$, 95%CI [-13.7, -2.22]), as well as the HC group ($p < .001$, $r = .34$, 95%CI [-17.1, -4.85]). The RRMS

group and the HC group did not differ significantly in their overall ratings (p = .464, r = .10, 95%CI [-2.09, 8.14]). There was also a significant main effect of QoL domains $F(3, 507)$ = 109.2, p <.001, η_p^2 = .393, but there was not a significant interaction between group type x QoL domains, $F(6, 507)$ = 1.77, p =.102, η_p^2 = .021.

Table 5.
Correlational Analysis of WHOQoL-BREF subscales in MS (n =117)

	WHOQoL Physical	WHOQoL Psychological	WHOQoL Social
WHOQoL Psychological	.565*	___	___
WHOQoL Social	.511*	.575*	___
WHOQoL Environmental	.505*	.695*	.499*

Note. *Correlation is significant at the 0.01 level

APPENDIX G: Initial Study Proposal

Provisional Thesis Title: **Effects of Illness Representations on Emotion Regulation in Multiple Sclerosis**

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurological disease of the central nervous system (CNS) which is the leading cause of neurological disability amongst younger adults (Compston & Coles, 2008). Most people are first diagnosed with a relapsing-remitting form of MS (RRMS; O'Connor, 2002), which involves attacks (relapses) followed by periods of recovery (remission). Relapses occur when inflammatory cells attack the myelin of specific nerves. Remission occurs when inflammation subsides and symptoms reduce. Although symptoms may disappear completely during remission process, after several relapses there may be residual damage to the myelin, resulting in partial recovery only (Neild, 2006). Most people initially diagnosed with RRMS later develop secondary progressive MS (SPMS; O'Connor, 2002), characterised by a steady increase in disability, as symptoms do not disappear completely after a relapse. In the primary progressive MS (PPMS), unlike in the RRMS, the first (primary) symptoms are progressive. They get worse over time rather than appearing as sudden attacks (relapses). Symptoms may continue to worsen over time or may become stable. The hallmark of the chronic progressive forms of MS (CPMS), namely the SPMS and the PPMS is the permanent loss of neural tissue (Neild, 2006).

The disease tends to affect not only physical health of MS sufferers but also cognitive and emotional functioning. While physical and cognitive impairments present in MS, such as restricted mobility, reduced executive control and slowed processing speed, have been extensively researched (Kalmar, Gaudino, Moore, Halper, & Deluca, 2008; Rao, 1995), less is understood about the nature of emotional difficulties present in MS. Multiple areas of axonal demyelination are implicated in MS with many of the lesions arising in the white matter of the frontal brain regions (Brownell & Hughes, 1962). Frontal brain circuits have been identified in the self-regulatory process essential to executive functioning (Stuss & Alexander, 2007). Such circuits may also be implicated in emotion regulation processes (Ochsner & Gross, 2005). Since many MS sufferers display cognitive regulation difficulties

on executive function measures, it is plausible that emotion regulation capacity is similarly affected (e.g., Kalmar et al., 2008).

An ability to regulate emotions involves understanding, monitoring and evaluating one's affective states, as well as implementing a set of strategies to influence the subjective experience of emotional states, or to gain control over the outward expression of affect (Gross, Sheppes, & Urry, 2011). Various emotion regulation strategies can be exercised by individuals to manage their emotional responses and produce the desirable emotional reaction they wish to attain. The importance of adequate emotion regulation strategies has been widely recognised in clinical populations, where difficulties in emotion regulation are linked to the greater severity of depression, anxiety, schizophrenia, and post-traumatic stress disorder (Liverant, Kamholz, Sloan & Brown 2010, Van der Meer, Van't Wout & Aleman, 2009; Tull, Barrett, McMillan, & Roemer, 2007), as well as lower life satisfaction, decreased effectiveness at work and poorer interpersonal relationships (Gross and Munoz, 1995). Also, emotion regulation has been identified as an important factor in psychological adaptation to chronic illness (Garnefski, Koopman, Kraaij & ten Cate, 2009). Thus, understanding the nature and cause of emotion regulation difficulties in chronic conditions such as MS is vital when designing interventions aimed at improving functional outcomes of those suffering from the disease. Moreover, treatment plans included in the NICE (186) clinical guidelines for the management of the MS in primary and secondary care focus primarily on physical and cognitive rehabilitation. Therefore, more research is needed into the emotion regulation difficulties of individuals with MS in order to extend the evidence base in this area and to incorporate emotion regulation interventions into psychological treatments offered to people with MS.

In relation to MS, the incidence of emotion regulation difficulties has been reported for over a century, with first clinical accounts describing uncontrollable laughter, as well as a dissociation between the overt displays of affect and subjective mood reports in individuals with MS (Charcot, 1887; Surridge, 1969). Some of the symptoms of emotion regulation disturbances in MS involve pathological laughter and crying, unusual feelings of euphoria, emotional incontinence (disproportional exaggerated emotional expression), pseudobulbar affect (atypical expression of affect due to involvement of cortico-bulbar pathways), as well as emotional lability (dramatic shifts of mood; Feinstein, 2004; Finger, 1998; Rabins, 1990; Schiffer, 1990). Approximately, 10% of individuals with MS were found to experience

pathological laughing and crying at psychiatric consultation (Sá, 2008), whereas 73% were found to experience emotion dyscontrol, such as crying and irritability in the past month in the study by Feinstein and Feinstein (2001). Yet, it is impossible to determine whether these frequencies are in fact atypical due to the lack of a comparison healthy control group.

The abovementioned studies of emotion regulation in individuals with MS have employed symptom report or clinical observation to investigate the nature of emotion regulation processes in this disease. Nevertheless, it is essential to examine specific aspects of emotional appraisal, experience and perceived control as assessed by standardized measures. To date, only two studies (Phillips et al., 2009; 2014) to best of our knowledge, have used standardised assessments to explore emotion regulation processes in MS. Phillips et al. (2009) measured emotion regulation strategies using the Emotion Regulation Questionnaire (ERQ, Gross &John, 2003) in 86 individuals with MS. The ERQ is comprised of two subscales measuring appraisal of emotions and expressive suppression of emotions. Expressive suppression involves active inhibiting of the overt manifestation of emotions in response to an emotional event, whereas reappraisal modifies the subjective experience of emotions by changing the way one evaluates or think about such emotional event. Regular use of such emotion regulation strategies has been found to impact on well-being, with repeated suppression being linked to reduced psychological and social functioning in individuals with rheumatoid arthritis (van Middendorp et al., 2005). Also, similar results were found in non-clinical populations, with individuals who routinely employ suppression reporting poorer life satisfaction and more depressive symptoms, compared to individuals who use reappraisal (Gross &John, 2003). Despite no control group for comparison purposes in the study of Phillips et al. (2009), it was found that the absence of reappraisal as a method of emotion regulation was associated with lower self-reported quality of life. However, similarly to the study of Feinstein and Feinstein (2001), it is not possible to deduce whether these frequencies differ from those in the general population. Additionally, a broader range of emotion regulation strategies needs to be explored in order to enhance an understanding of these processes in MS.

These limitations were addressed in another study by Phillips et al. (2014) who investigated a variety of emotion regulation strategies in 31 individuals with MS and 31 matched controls using the Difficulties in Emotion Regulation Scale (DERS, Gratz & Roemer, 2004). This well-validated measure comprises of multiple subscales designed to assess discrete emotion

regulation processes, including acceptance of the emotion, acknowledgement and comprehension of the experienced emotional state, an ability to manage impulsive conduct in the context of negative affect, as well as an ability to employ flexible strategies to modify experienced emotions as required by the situational demands. It was found that individuals with MS reported more problems with emotion regulation than did control individuals, with a medium effect size (d = .68). A lack of interaction between the groups and DERS separate subscales, implies that different aspects of emotion regulation were similarly affected by MS.

One of the main limitations of the previous studies on MS is the use of heterogeneous cohort of individuals with MS. It is important to differentiate between those two heterogeneous types of the disease, since RRMS is mainly inflammatory in nature, with symptoms of the disease exacerbating and diminishing, leading to partial or complete recovery, while the CPMS forms being characteristic of permanent nerve damage, loss (Neild, 2006) and subsequent worsening of symptoms. It is therefore possible that the severity of the emotion regulation difficulties in MS is affected by the form of the disease. If individuals with different variants of MS had different patterns of emotion regulation difficulties, this could have potential implications for symptom management and rehabilitation goals.

Furthermore, none of the previous studies on emotion regulation in MS explored any psychosocial factors that can potentially impact on difficulties in emotion regulation and be possible targets of psychological intervention. One such a factor may be individuals' illness representations. In the area of adjustment to chronic illness, many studies, including those on MS, have utilised the illness representation model to show that the perceptions that individuals hold about their illness are a significant predictor of adjustment, levels of social dysfunction, self-esteem, fatigue, as well as various mood problems (Heijmans, 1998; Jopson & Moss- Morris, 2003; Murphy, Dickens, Creed, & Bernstein, 1999). The illness representation model proposes that individuals who are diagnosed with a health condition, develop an organised set of beliefs about their illness. These beliefs or cognitions are defined as illness representations and include knowledge, experience, emotions, as well as illness-related perceptions (Skelton & Croyle, 1991). Illness representations directly impact on people's emotional response to the disease they incurred and the coping strategies they develop in order to reduce the negative symptoms of their illness (Petrie & Weinman, 2006). At the same time, such representations affect strategies that people adopt to reduce the emotional response to the illness-related threat they perceive (Petrie & Weinman, 2006).

Since MS is incurable, unpredictable and with substantial individual variation, it seems reasonable to assume that individuals with MS will develop beliefs about their illness that will either be helpful or detrimental to regulating their emotional responses to symptoms and their everyday difficulties. Schiaffino, Shawaryn and Blum (1998) investigated the relationship between illness representations and mood in a study of individuals with MS. Beliefs associated with symptom variability were linked to higher incidence of depressive symptoms four months down the line; this was over and above initial levels of depressed mood. Thus, there is some evidence that illness representations may contribute to difficulties with emotion regulation in individuals who develop a chronic unpredictable illness, such as MS. However, no studies to date have explored the impact of illness representations on emotion regulation in MS more directly.

To address the abovementioned gaps in the literature, the current study aimed to look at the use of even broader range of emotion regulation strategies than in the previous studies by employing both of the emotion regulation measures discussed above (the ERQ and DERS) on the same sample of individuals with MS. More importantly, this study extends the previous findings by exploring the effects of different types of MS on emotion regulation abilities, namely relapsing-remitting MS (RRMS) and the chronic progressive forms of MS (CPMS), as well as healthy controls. The further objective is to investigate whether illness representations developed by individuals with MS impact on how they regulate their emotions, even when controlling for the severity of their condition. Few previous illness representation studies discussed above, have attempted to account for disease severity, making it problematic to conclude whether the relationship between emotion regulation and illness cognitions results in fact, from the severity of the condition itself..

Research Questions / Objectives:

2) What is the principal research question / objective?

To explore whether individuals presenting with different variants of MS, namely RRMS and CPMS, will have different emotion regulation abilities, as compared to individuals without MS (HC).

3) What are the secondary research questions / objectives if applicable?

To explore whether negative illness representations predict emotion dysregulation in MS, independently of disease severity.

More specifically, it was hypothesized that individuals who have a strong illness identity, a poor sense of control over their illness and believe their disease to have had detrimental consequences on their lives, will have more difficulties with emotion regulation, after controlling for the effects of disease severity

Methodology

4) Please give a full summary of your design and methodology. It should be clear exactly what will happen at each stage of the project. (Relevant to IRAS A13).

Some of the data has been previously collected by the candidate during her doctoral studies at the University of Aberdeen. However, it has not been included in the actual PhD thesis. As such, ethics applications were reviewed and approved by the NHS NRES Committee North East - Sunderland (Research Ethics Committee (REC) Reference 12/NE/0130; fully approved on 23rd March 2012). Major amendment or new ethical application will be submitted to the REC in order to be able to further recruit participants with MS and Healthy Controls.

General aspects of the research design:

The basic principle of the study method is to use standardised self-report questionnaires that participants will fill in in the comfort of their own home. It will take 30-50 minutes for the questionnaires to be filled in. No risk is associated with the measures used. All questionnaires were well standardised and validated and have been used in previous studies with other clinical populations, including MS.

Participants:

In total, 270 individuals with MS listed on the Department of Neurology (NHS Grampian) MS database were contacted by means of an Invitation Letter, Participant Information Sheet, and

Reply Form, with stamped addressed envelopes being sent to their home address. Out of these, 42 invitations were declined, 9 were undelivered, 145 were not returned, and 74 consented to participate (43% response rate: composed of invitations consented and declined) Out of the initial 74 potential participants, seven were unable to take part as they experienced a relapse, and nine further declined due to unforeseen circumstances. The remaining 58 MS participants were assessed in this study. Another two participants were excluded on the basis of co-morbidity. Thus, data from 56 individuals with MS were included in the analysis. 31 HC participants were recruited from the general community via word of mouth, friends/relatives of MS participants, and the Aberdeen University Participation Panel.

Further recruitment of participants with MS:

Potential participants with MS will be identified by the MS Nurse using the Department of Neurology's MS Patient Database at Aberdeen Royal Infirmary. An Invitation Letter outlining the purpose of the research will be sent to potential participants by the Consultant Clinical Neuropsychologist. An enclosed Information Sheet will provide details about participation. A Reply Form requesting volunteers' contact details will be attached to this letter, together with a Consent Form. A stamped, addressed envelope will be provided to enable participants to return their Reply and Consent Forms. The researcher will telephone those individuals who express an interest in the study to discuss any questions they might have about the research and to clarify whether they are still willing to participate. After receiving a signed Consent Form, the participant will then be sent a set of questionnaires (with an allocated study number) to fill in and return in the envelope provided.

Further recruitment of participants without MS:

HC participants matched for age, gender and education will be further recruited though collaboration with the University of Aberdeen Research Participant Panel and friends/relatives of the MS participants. HC participants will be initially contacted by phone. Once they agree to participate, an enclosed Information Sheet, Consent Form, as well as stamped, addressed envelope will be sent. The researcher will telephone those individuals who return their signed Consent Forms to discuss any remaining questions they might have about the research. Each participant will then be sent a set of questionnaires (with an allocated study number) to fill in and return in the envelope provided.

Materials

These are discussed in section 6

5) Please list the principal inclusion and exclusion criteria

For MS participants, the following inclusion criteria were applied:

1. Must meet McDonald Criteria for MS diagnosis (Relapsing-remitting or progressive types, as defined by a Consultant Neurologist – to ensure that participants met clinically accepted MS diagnostic criteria.
2. Aged 18+ - to avoid confounding effects of developmental changes in emotional skills and cognitive function.

Participants were excluded if they met any of the following criteria:

1. Deemed not to have capacity to consent- to avoid problematic issues of consent in this population.
2. A pre-morbid history of neurological disease (other than MS), traumatic brain injury, psychiatric disorder, severe alcohol or drug abuse - to avoid these as confounding factors.
3. Poor understanding of English that would negatively affect their ability to complete behavioural tasks, questionnaires or understand test instructions.
4. Current optic neuritis, or other severe visual or hearing impairment, and severe motor disturbances that would negatively affect their ability to satisfactorily complete measures or understand test instructions.

For Healthy Control participants, the following inclusion criteria were applied:

1. Aged 18+ - to avoid confounding effects of developmental changes in emotional skills and cognitive function.

Participants were excluded if they met any of the following criteria:

1. A pre-morbid history of neurological disease, traumatic brain injury, psychiatric disorder, severe alcohol or drug abuse - to avoid these as confounding factors.
2. Poor understanding of English that would negatively affect their ability to complete behavioural tasks, questionnaires or understand test instructions.
3. Severe visual or hearing impairment and severe motor disturbances that would negatively affect their ability to satisfactorily complete measures or understand test instructions.

6) How will data be collected?

The following self-report measures were chosen as they were shown to have good psychometric properties and have been commonly used to measure emotion regulation, illness representations and disease severity, respectively, in MS.

1) The Difficulty in Emotion Regulation Scale (DERS; Gratz, & Roemer, 2004) is a 36-item, self-report measure designed to assess multiple aspects of emotion dysregulation. The DERS was chosen to reflect difficulties in 6 domains of emotion regulation: 1) acceptance of emotion (*nonacceptance),* 2) the ability to refrain from impulsiveness when experiencing negative moods (*impulse),* 3) the ability to direct behaviour towards goals and targets despite experiencing negative emotions (*goals),* 4) awareness of emotions (*awareness),* 5) understanding and clarity about emotions experienced (*clarity*) and 6) the ability to access emotion regulation strategies (*strategies).* Participants are required to read a series of statements regarding their emotions and feelings and they must circle the response that most accurately describes them. Higher scores are indicative of greater difficulties in emotion regulation. The DERS was found to have high internal consistency, $\alpha = .93$ (Gratz & Roemer, 2004), with the six scales forming replicable factors that show adequate evidence of external validity (Weinberg & Klonsky, 2009), as well as a prediction of behavioral assessments of emotion regulation (Vasilev, Crowell, Beauchaine, Mead, & Gatzke-Kopp, 2009).

2) The Emotion Regulation Questionnaire (ERQ; Gross & John, 2003) measures the habitual use of two most frequently applied emotion regulation strategies, namely cognitive reappraisal (e.g. 'When I want to feel more positive emotion, I change what I'm thinking about') and expressive suppression (e.g. 'I keep my emotions to myself'). Six questions aim

to assess cognitive reappraisal which involves changing one's perspective on the situation. The remaining four questions assess expressive suppression which involves executing some control over one's emotions by not openly expressing them. It is a 10-item scale. Participants are asked to indicate the extent to which they agree with each statement. Higher scores indicate more frequent use of each strategy. This questionnaire has been found to display adequate psychometric properties of validity and reliability (Gratz & Roemer, 2004; Ehring et al., 2008).

3) The Illness Perceptions Questionnaire-Revised (IPQ-R; Moss-Morris et al., 2002) is one of the most widely used instruments that measure patient's illness perceptions. It is composed of two sections; the first section includes eight subscales that assess cognitive representations of the illness, while the second section evaluates emotional responses to the disease on a single subscale. Different dimensions of cognitive representations include *cause, timeline, identity, consequences,* and *control*. The *control* aspect of the IPQ-R is subsequently divided into *treatment* and *personal control* beliefs. *Personal control* beliefs represent individual's conviction about their own capability to exert control over their symptoms, whereas *treatment control* beliefs refer to the people's level of certainty in their treatment as an effective way of controlling the condition. *The timeline* dimension is further split into an acute, chronic and cyclical subscales (i.e., whether the individual perceives their condition and symptoms as short- term, long-term, or recurring in nature). A new dimension of *illness coherence* assesses the degree to which individuals think they hold a coherent understanding of their illness. All items are rated on a five-point Likert scale, ranging from *strongly agree* to *strongly disagree,* with the exception of items included in the *identity* dimension. The *identity* dimension requires the rater to indicate on a yes/no scale whether they believe a set of frequently occurring symptoms to be related to their condition.

   For the purposes of the current study, three additional MS-specific symptoms, namely speech distortions, clumsiness and numbness, were included in the initial 14-item identity list. These items are coded in a way that high ratings reflect strong beliefs on the specific dimension. Hence, high ratings on the *timeline, identity,* and *consequences* subscales represent the chronicity of the disease, the negative convictions about some symptoms related to MS, as well as the negative impact of the consequences of having the conditions, respectively. High ratings on the *coherence* and *control* dimensions reflect how well

individuals feel they understand their illness, as well as more positive beliefs about how manageable they feel their condition is. Higher ratings on the emotional representation subscale represent a strongly negative emotional reaction to the condition. The IPQ-R has shown good criterion, construct and known-groups validity (Jopson & Moss-Morris, 2003).

4) The Patient Determined Disease Steps (PDDS) questionnaire was specifically constructed for an assessment of MS progression and functional disability resulting from MS Hohol, Orav and Weiner (1995). It is based primarily on ambulation. Hohol et al., (1995) noted at the time that clinical scales of MS were too often complex to administer without adequate and costly training, were insensitive to disease progression, as well as unacceptable levels of inter-rater variability. Hence, they designed the PDDS which is an ordinal rating scale comprised of nine classifications: 0 = 'Normal, mild symptoms or signs, mostly sensory', 1 = 'Mild Disability, noticeable symptoms, still minor', 2 ='Moderate disability, no gait problems, but other disabling symptoms', 3 = 'Gait disability, significant gait problems', 4 = 'Early cane, intermittent use of cane', 5= 'Late cane, cane-dependent', 6 = 'Bilateral support', 7 = 'Confined to wheelchair' and 8= 'Bedridden'. Ratings range from 0-8, and their aim is to categorise individuals into three groups, in accordance with their disability level: a score of 0-2 reflects 'mild disability' characterized by no walking limitation but some sensory symptoms; a score of 3-5 reflects 'moderate disability' characteristic of walking difficulties, and a need for a cane; a score of 6-8 is reflective of 'severe disability' indicating a need for bilateral support, use of wheelchair or being bedridden (Gulick, Namey, & Harper, 2011). Hohol et al. argue that raters were able to quickly and easily categorise the standardisation sample of 1323 individuals with MS using the PDDS.

Inter-rater reliability for the PDDS in a sample of 60 patients was excellent (kappa = .80), as compared to a moderate result for the Expanded Disability Status Scale (EDSS) (kappa = .54) which is the most frequently employed clinical outcome measure in MS (Kurtzke, 1983). A longitudinal study, which used the PDDS and EDSS for an assessment of MS progression, found similar evaluations resulting from the two measures, as well as strong associations with each other at baseline (Spearman r = .94, n = 789, p = .0001), and over time: at 1 year, r = .55, n = 658, p = .0001; at 2 year, r = .64, n = 507, p = .0001; and at 3 year, r = .62, n = 330, p = .0001 (Hohol, Orav, & Weiner, 1999). These findings support the validity of the PDDS and its employment as a practical and simple tool for an evaluation of MS progression (Hohol et al., 1999).

7) What sample size is needed for the research and how did you determine this?

Estimation of the sample size depends on the strength of the relationship that is being explored (effect size) and the amount of statistical power required to be able to detect such effects (Field, 2013). To address our primary research questions (differences in emotion regulation abilities in different variants of MS, as compared to HC) would require conducting a series of one-way ANOVAs comparing the MS groups to the HC participants on different emotion regulation abilities. Therefore, a sample size was determined by carrying out a power analysis using G*Power 3.1, with an alpha level of 0.05, and a medium effect size (f = .25). This led to a predictive total sample size (two MS groups and HC) of 159 with an actual power of .80. Our actual total sample size was 87, with 30 participants with RRMS, 26 participants with CPMS and 31 HC participants. Thus, further 72 participants (MS = 50, HC = 22) will need to be recruited through the Department of Neurology research database at Aberdeen Royal Infirmary. This database currently contains details on over 600 MS patients whereas a required response rate for this study is 8.3%. Thus, we do not anticipate major difficulty in achieving appropriate recruitment rates.

In order to address our secondary research question (whether negative illness representations predict emotion dysregulation in MS, independently of disease severity), hierarchical regression will be conducted. Therefore, a sample size was determine by carrying out a power analysis using again G*Power 3.1, with an alpha level of 0.05, a medium effect size (f^2 = .15), and 4 predictors (illness identity, control, consequences and disease severity). This led to a predictive total sample size (two MS groups and HC) of 85 with an actual power of .80. As discussed above, we do not anticipate major difficulty in achieving appropriate recruitment rates.

Although, to our knowledge, there are no published studies of emotion regulation to date that distinguished between different types of MS and HC, the typical sample sizes in behavioural studies of emotional skills is 20- 40 for MS participants (Banati et al., 2010; Jehna et al., 2010).

8) Outline reasons for your confidence in being able to achieve a sample of at least this size. (e.g. by giving details of size of known available sample(s), percentage of this type of sample that typically participate in such studies, opinions of relevant individuals working in that area)

Data from 87 participants (MS = 56, HC = 31) has already been collected. Thus, further 72 participants (MS = 50, HC = 22) will need to be recruited through the Department of Neurology research database at Aberdeen Royal Infirmary. This database currently contains details on over 600 MS patients whereas a required response rate for this study is only 8.3%. Thus, we do not anticipate major difficulty in achieving appropriate recruitment rates. Control participants, matched for age, gender and education will be further recruited though collaboration with the University of Aberdeen Research Participant Panel and friends/relatives of the MS participants. Also, the project timescale dedicates a significant timescale of 5 months for the recruitment.

Analysis

9) Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Initially data will be analysed using descriptive statistics and will be graphed and explored using the Statistical Package for Social Sciences (SPSS) to see whether the data is meeting the necessary assumptions for the use of parametric testing.

The main research question will be analysed using one-way Analysis of Variance (ANOVA).

For the secondary research question, the data will be initially inspected by graphing scatterplots to assess whether there is a linear relationship between the variables, important for meaningful interpretation of the correlation coefficient.

Further, hierarchical regression analysis will be used to address the extent to which illness representations predict difficulties in emotion regulation in the sample of MS participants. Hierarchical regression will control for factors such as disease severity.

Management of Risks to Project

10) Please summarise the main potential risks to your study, the perceived likelihood of occurrence of these risks and any steps you will or have taken to reduce these risks. Outline how you will respond to identified risks if they should occur.

1. There is a potential risk that the amendment to this study or new application will not be approved by the REC or will require some alterations in order to be granted an approval. The perceived likelihood of occurrence of this risk is rather small due to the following factors; the time taken to complete the study will be significantly reduced from over two hours to approximately 50 minutes. Participants will be able to complete the study in the comfort of their own home, without incurring additional time and travel costs. The measures that have been chosen have been selected to minimise the duration of testing. They are not assessing particularly sensitive or upsetting issues, yet there are a few questions contained within questionnaires which do deal with personal issues. However, as all these measures have been used with many clinical populations, including the MS population previously, therefore, we do not anticipate any difficulties arising with the chosen measures. Moreover, the questionnaires sent will be anonymised. Once participants consented to take part in the study (by filling in and sending back the reply form and consent sheet), they will be assigned individual study numbers that will be put onto all questionnaires and send to the participant in a separate letter to ensure confidentiality. No identifiable, sensitive information will be posted with the questionnaires. Feedback from supervisors will be sought before submission of the amendment to the REC. Lastly, a generous amount of time has been allocated to the ethical approval process (5 months) should any difficulties arise.

2. There is a potential risk that the number of participants (total sample size = 159) required for statistical power of .8 will not be achieved. The perceived likelihood of this risk is again low. Data from 87 participants (MS = 56, HC = 31) has already been collected. Thus, further 72 participants (MS = 50, HC = 22) will need to be recruited through the Department of Neurology research database at Aberdeen Royal Infirmary. This database currently contains details on over 600 MS patients whereas a required response rate for this study is 8.3%. Thus, we do not anticipate major difficulty in achieving appropriate recruitment rates. Control participants, matched for age, gender and education will be further recruited though collaboration with the University of Aberdeen Research Participant Panel and friends/relatives of the MS participants. Also, the project timescale dedicates a significant timescale of 5 months for the recruitment.

Knowledge Exchange

11) How do you intend to report and disseminate the results of the study?

This study will be written up in a format of a doctoral thesis and submitted to the Doctorate of Clinical Psychology Programme at the University of Edinburgh. The thesis will be composed of a systematic review and a journal article which will be subsequently submitted to the Multiple Sclerosis Journal, a peer-reviewed international journal focused on all aspects of Multiple Sclerosis. The finding from this study will be presented locally within NHS Grampian and the Neuropsychology Department, as well as in the local Stuart Resource Centre for people with MS. The candidate also intends to present the findings at the MS Frontiers Conference in 2017.

13) What are the anticipated benefits or implications for services of the project? (E.g. If this is an NHS based project, in what way(s) is the project intended to benefit the NHS?)

This study will provide reliable and valid information on the nature of emotion regulation difficulties that people with different types of MS experience in their everyday life. Very little is known regarding emotion regulation in MS, and these difficulties do not seem to be targeted by current psychological interventions. Current psychological treatments focus primarily on cognitive rehabilitation in MS. Therefore, this research project will benefit the NHS Grampian Neuropsychology Department by increasing an understanding of the potential emotion regulation difficulties in MS and provide basis for designing an intervention that can target such difficulties. If illness representation underlies emotion dysregulation in MS, adjusted CBT treatments can be designed to help challenge unhelpful illness cognitions, which in turn, might help manage emotion regulation problems in this patient group.