LETTERS

Regional cerebral glucose metabolism in akinetic catatonia and after remission

K L Kahlbaum published in 1874 the first recorded description of catatonia. Akinetic catatonia is now defined as a neuropsychiatric syndrome principally characterised by akinesia, mutism, stupor, and catalepsy.[1] Even if some advances have been made in the recognition of catatonia, in particular by the development of different rating scales,[1] the pathophysiology of this syndrome is not clearly established.

A right handed 14 year old girl presented with akinetic catatonia during an episode of depression in the context of a bipolar type I disorder. Her catatonic status was characterised by akinesia with brief episodic spontaneous stereotyped movements, mutism, no spontaneous oral intake, catalepsy, waxy flexibility, and stupor with brief occasional eye contacts. This corresponded to a total score of 19 on the Northoff Catatonia Scale.[1] Electroencephalogram performed one day after onset of symptoms showed diffuse theta activity with sporadic diffuse delta activity. Cerebral magnetic resonance imaging was normal. Brain positron emission tomographies (PET) were obtained on a CTI-Siemens HR+ tomograph. A first PET (PET1) using [^{18}F]-fluorodeoxyglucose (FDG) was performed on day 2 in a drug free state. Thereafter, intramuscular injection of 2 mg of lorazepam induced rapid clinical remission of the akinetic phase. Oral lorazepam was then given (3.75 mg/day) during five days. On day 8, a second PET with FDG was performed while the patient was treated by olanzapine (15 mg/day) and presented hyperactivity, logorrhoea, and disinhibition characterised by uncontrolled social interactions and physical contacts. Neuropsychological testing performed some days after remission revealed no apraxia or language disturbances but dysfunction of executive tasks manifested in the revised Wisconsin card sorting, the Tower of London, Stroop, and Trailmaking tests.

Voxel based analyses comparing patient's cerebral glucose metabolism with that of 29 right handed healthy controls (16 women and 13 men, mean age 32) were performed using Statistical Parametric Mapping (SPM99) (Wellcome Department of Cognitive Neurology, London, UK). Data from each subject were normalised to a standard stereotactic space and then smoothed with a 12 mm full width half maximum isotropic kernel. The analysis identified brain regions where glucose metabolism was significantly changed in each patient scan compared with the control group. All results presented are significant at $p<0.05$ corrected for multiple comparisons over the entire brain volume. In regions where we had a priori hypothesis—that is, regions implicated in awareness and motor control—we also considered results significant at $p<0.05$ after small spherical volume correction (radius 20 mm). PET2 analysis showed a relative decrease of metabolism in the precuneus, lateral parietal cortices (Brodmann area 40) and in the right superior frontal circumvolution (Brodmann area 6), see table 1. As PET2 was conducted after akinetic catatonia remission, it was used for an exclusive masking analysis of PET1 in order to search for metabolic changes characteristic of the akinetic catatonic state. This showed that a large area of the prefrontal cortex (mostly on the left side) including anterior cingulate, medial prefrontal, and dorsolateral cortices presented a relative decrease of metabolism in comparison with the control group (fig 1). This analysis also revealed relative hypermetabolism of the primary motor cortex, the rostral part of the striatum, and the vermis (fig 1). PET1 analysis also revealed that the precuneus and the left lateral parietal cortex (Brodmann area 40) presented a relative decrease of metabolism (table 1).

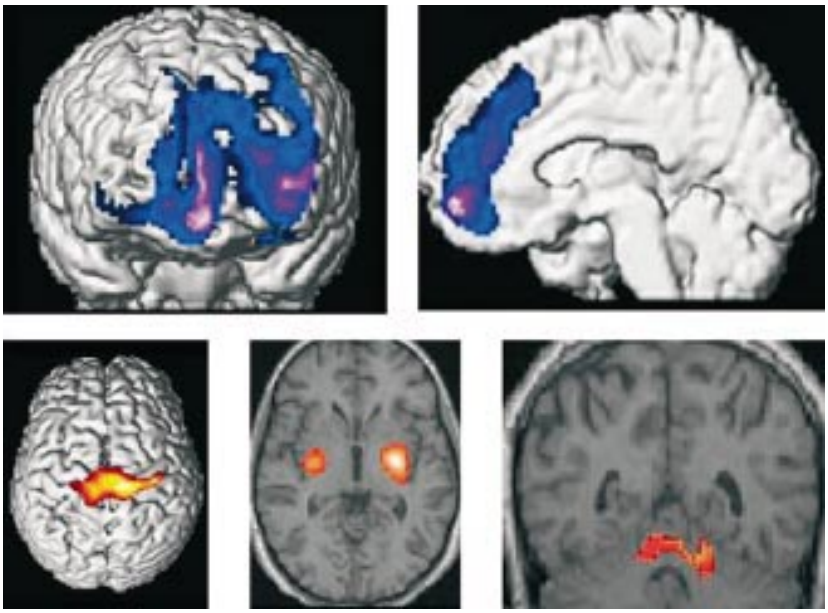

Figure 1 Results of the exclusive masking analysis showing a decrease of metabolism in a large prefrontal area (upper row, on the right), the right anterior cingulate and the right medial frontal cortices (upper row, on the left). This analysis also showed a relative increase of metabolism in primary motor cortices (lower row, on the left), in the rostral part of the striatum (lower row, in the middle), and in the vermis (lower row, on the right). Dysfunctional brain areas have been coregistrated to the patient's magnetic resonance imaging.

In our opinion, these results might shed some light on the pathogenesis of akinetic catatonia. Indeed, exclusive masking analysis allowed us to determine in this case the metabolic changes characteristic of akinetic catatonia. Prefrontal cortical areas like anterior cingulate, dorsolateral, and medial prefrontal cortices are implicated in the planning, initiation, generation of voluntary movements and executive functions in general. Hypofunction of these brain areas, as demonstrated in our patient, could therefore explain symptoms such as akinesia, mutism, and absence of spontaneous oral intake, which are usual features of akinetic catatonia.[1] Moreover, the increased activity in primary motor cortices, the rostral part of the striatum and the vermis, associated with the deficit of internal initiation and generation of voluntary movements, might account for some particular motor features of catatonic states. These are

Table 1 Results of SPM analysis of PET1 and 2

	Hypermetabolism					Hypometabolism				
	Cluster level		Voxel level			Cluster level		Voxel level		
PET	p	Cluster size	p	Z	Coordinates x,y,z (mm)	p	Cluster size	p	Z	Coordinates x,y,z (mm)
1	0.001	885	0.008	4.97	30, –8, –2	0.039	354	0.015	4.83	46, 18, 0
	<0.001	2485	0.024	4.71	10, –24, 72	<0.001	1752	0.001*	4.49	–4, –54, 30
	<0.001	977	0.003*	4.27	12, –52, –1	<0.001	8720	0.002*	4.40	–24, 56, 18
	0.008	549	0.004*	4.24	–30, –12, –2	0.002	733	0.004*	4.21	–50, –60, 18
2						0.005	628	0.016	4.81	40, –60, 44
						<0.001	1589	0.002*	4.43	–4, –54, 30
						<0.001	1057	0.005*	4.16	–48, –64, 32

*After small spherical volume correction (radius 20 mm).

the occurrence of episodic spontaneous stereotyped movements and the prolonged maintenance of posture (catalepsy). Previous functional cerebral imaging studies have reported the implication of the vermis in the maintenance of standing postures.[2] The high metabolic activity observed in the motor cortex could be related to reduced neuronal inhibition. Indeed, reduced density of inhibitory GABA receptors in this area has been reported in catatonia.[3] Previous imaging studies found dysfunctional posterior lateral parietal cortex in the catatonic state.[4] PET1 analysis showed hypofunction of this left region which persisted after clinical remission. So, this regional dysfunction is not sufficient to lead to akinetic catatonia but it might have participated in the disturbance of executive tasks planning.

Patients with akinetic catatonia are classically unresponsive to their environment.[1] This symptom characterises the stuporous state encountered in this syndrome. The exclusive masking analysis demonstrated reduced activity in the medial prefrontal cortex during akinetic catatonia. Previous functional imaging studies showed that the ventral medial prefrontal cortex is implicated in the integration of the visceromotor aspects of emotional processing with information gathered from the internal and external environments.[5] The dorsal medial prefrontal cortex has been involved in explicit representations of states of the "self".[5] Dysfunction of these brain areas might therefore explain the stuporous state observed in akinetic catatonia. Activity within the precuneus has been implicated in the representation of the world around us and the lateral parietal cortex is known to participate in conscious awareness.[5] PET1 analysis showed that these two regions presented a decrease of metabolism that persisted on PET2. This persistence could be related to the hypomaniac state presented at the time of PET2, a state, which differs from the resting state of the control subjects. Indeed, high level of glucose metabolism in the precuneus and lateral parietal cortex is the metabolic hallmark of the normal resting state.[5] Despite its persistence after catatonia remission, dysfunction of these regions during the akinetic catatonic state may be a prerequisite for the establishment of its stuporous aspect, as supported by studies on patients with reduced level of consciousness.[5]

In conclusion, some motor symptoms usually encountered in akinetic catatonia may be related to dysfunction of prefrontal cortical areas but also primary motor cortex, striatum, and vermis. This case of akinetic catatonia also brings new clues for the involvement of the medial prefrontal cortex in conscious awareness.

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Mirth and laughter arising from human temporal cortex

Laughter and mirth are essential in our enjoyment of daily life and in facilitating communication. Various studies have been done relating to the emotional processing that takes place in the human cerebral cortex, but few have explored the cerebral origins of mirth. Some reports on pathological laughter have implicated the hypothalamus, brain stem, and temporal lobe.[1–3]

As part of the presurgical evaluation of patients with epilepsy, electric cortical stimulation is used to delineate the functional cortical areas, and sometimes this elicits various emotional responses.[4] However, only two stimulation studies[2 5] have been conducted with a focus on mirth and laughter. Arroyo *et al* suggested that the motor act of laughter and the processing of its emotional content were separately represented in, respectively, the anterior cingulate area and the basal temporal area (the fusiform gyrus or parahippocampal gyrus, or both).[2] Fried *et al* suggested not only that laughter and mirth were represented in the presupplementary motor area, but also that there was close linkage between the motor, affective, and cognitive components of laughter.[5]

We report a patient in whom electric cortical stimulation applied to the inferior temporal gyrus produced mirth alone or laughter preceded by mirth, depending on the intensity of the stimulation.

Case report

A 24 year old right handed woman with medically intractable complex partial seizures underwent implantation of subdural grid electrodes on the cortical surface of the left temporal cortex and a depth electrode into the right mesial temporal cortex. Long term video/EEG monitoring with scalp electrodes done before this invasive monitoring showed late ictal lateralisation at the left anterior temporal area, and thus a right temporal onset could not completely be excluded. Magnetic resonance imaging showed high intensity and atrophy in the left anterior and right posterior hippocampus. Interictal FDG-PET (fluorodeoxyglucose positron emission tomography) showed hypometabolism in the left temporal lobe. An intracarotid amobarbital test revealed the dominance of language and memory in the left hemisphere.

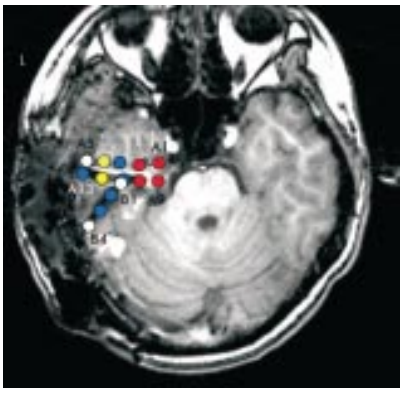

Figure 1 Brain magnetic resonance imaging showing the arrangement of electrodes on the surface of the left basal temporal cortex. A11 and B1 are overlapping. The electrodes A4 and A12 (yellow) are located on the basal aspect of inferior temporal gyrus where the electric stimulation induced mirth with or without laughter. A1, A2, A9, and A10 (red) were epileptogenic foci and were ultimately resected. Electrical stimulation of blue electrodes disrupted or arrested speech and other language tasks.

The seizures started with an epigastric rising sensation, followed by loss of awareness combined with hand and oral automatisms. Laughter or the feeling of mirth was not seen during the patient's habitual seizures. Video/EEG monitoring showed that the epileptogenic focus was in the left mesial temporal cortex (A1, 2, 9, and 10) (red electrodes in fig 1). Electrical cortical stimulation (50 Hz, alternate polarity of square pulses) was done to delineate the functional areas, with special emphasis on language function.

Stimulation of the basal aspect of the inferior temporal gyrus between A4 and A12 (yellow electrodes in fig 1) at low intensity and short duration (5 mA, 1 s) consistently produced mirth without laughter, and it was always accompanied by a melody that she had heard in a television programme in her childhood. The duration and intensity of the mirth increased in proportion to the duration and intensity of stimulation (15 mA, 3 s), and she eventually smiled during the latter part of a 5 second stimulation. The patient said that the tune appeared funny to her and made her feel amused, but only during the electrical stimulation, and we were able to confirm this. When maximum intensity at longer duration (15 mA, 5 s) was applied, it disrupted a variety of language tasks, but neither alternating hand and foot movements nor vocalisation was disturbed. During this maximum stimulation condition, the patient felt mirth, but the performance of various language tasks obscured apparent laughter. Stimulation of the adjacent pairs of electrodes (A3–A11, A6–A13, and B2–4) (blue electrodes in fig 1) affected only language tasks but was not consistently accompanied by a feeling of mirth.

Comment

Our observations suggest that mirth is represented in a relatively small distinct area in the temporal neocortex (the basal surface of the inferior temporal gyrus), which is in part consistent with the observations of Arroyo *et al*.[2]

Our study clearly showed that mirth was represented in the inferior temporal gyrus, and was closely linked with a particular context (a certain tune in this patient). This association with a specific event was not observed in the patients reported by Arroyo *et al*.[2] Because the temporal lobe is involved in memory function in human, it is reasonable that both the context of the mirth and laughter and the induced mirth and laughter are represented. In the present case, we could not identify any site where the electric stimulation elicited laughter without mirth. Importantly, the fact that the stimulation with higher intensity and longer duration elicited mirth with laugher more effectively suggests different thresholds for mirth and laughter, postulating a hierarchical organisation or serial processing of mirth and laughter in the human temporal cortex. Laughter might be situated at a higher order than mirth, at least in the temporal neocortex. It is possible that laughter might be caused by further activation of the frontal motor cortices, including the anterior cingulate gyrus, through corticocortical projections, such that electrical cortical stimulation could elicit laughter without mirth.[2]

With regard to the characteristics of induced mirth in this patient, the melody which made her feel funny was not amusing by itself in the absence of electrical stimulation, raising the possibility that stimulation changed the internal standard of her amusement through an undetermined process.

Although it should be taken into account that the mirth elicited in the present case might not necessarily have reflected the representation of mirth and laughter in the normal brain, no mirth was seen during the patient's habitual seizures, and neither electrode A4 nor electrode A12 was included in the epileptogenic foci. Thus this particular area (A4–A12) producing mirth on stimulation can be judged to reflect normal function in this patient.

In the present case, mirth is represented in the temporal lobe and may be stored together with the context inducing mirth in the same area, suggesting a close relation between mirth and memory function. As far as the temporal neocortex in the present patient is concerned, laughter seems to be situated at a hierarchically higher order than mirth.

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How valid is the clinical diagnosis of Parkinson's disease in the community?

In a population based study on the prevalence of Parkinson's disease in London, Schrag *et al* reported on the data of a long term clinical evaluation of 202 patients.[1] The initial diagnosis of probable Parkinson's disease was later confirmed in 83%, plus 2% each with atypical features and possible Parkinson's disease. In 15% the initial diagnosis was later rejected, while 19% of patients not diagnosed as Parkinson's disease were later found to have the disorder. Their conclusion was that in 15% of the cases the clinical criteria of Parkinson's disease were not followed, in accordance with previous retrospective clinicopathological studies of parkinsonism, in which the rate of false positive diagnosis ranged between 22–24%[2 3] and 15–18%.[4 5] Using more strict diagnostic criteria by movement disorder experts, this figure could recently be further reduced to around 10%, with a positive predictive value (PPV) for idiopathic Parkinson's disease of 98.6%, and for other parkinsonian syndromes 71.4%—for example, for multisystem atrophy (MSA), 85.7%, and for progressive supranuclear palsy (PSP), 80%.[6 7]

Referring to these data, Schrag *et al* suggested that at least 10% of the patients with a final clinical diagnosis of Parkinson's disease may have other disorders.[1] In pathological series, the incidence of atypical parkinsonism is substantial; for example, PSP is found in 6–22% of necropsy cases, MSA in 5–11.4%, vascular parkinsonism in 2–3%, and Alzheimer's disease in demented Parkinson's disease patients in 2–6%[5 6] (see table 1).

Although samples from brain banks and specialised institutions are considered to overrepresent atypical disorders owing to the referral bias inherent in such samples,[7] these data are, at least in part, confirmed by a large consecutive clinicopathological study of 260 elderly patients with a clinical diagnosis of parkinsonism derived in the years 1989 to 2001 from three large community hospitals in Vienna, two with acute and one with chronic care facilities (table 1). The concordance of the clinical diagnosis with the necropsy findings in this cohort was much better than in previous series[5] (table 2), which, unfortunately, was not considered or quoted by Schrag *et al*. In our recent necropsy series, the mean incidence of Lewy body disease, including Parkinson's disease, was 78%; of other neurodegenerative disorders masquerading as Parkinson's disease (for example, PSP, MSA, and so on), around 12%; while other disorders referred to as secondary parkinsonism (essential tremor, drug induced parkinsonism) accounted for 8.4% (table 1). The initial rate of misdiagnosis in the overall group of 750 cases was around 17%, and, owing to more precise diagnostic criteria, this finally fell to 11.5% (table 2).

A review of the clinical and pathological diagnoses of 160 non-demented patients with parkinsonism (85 men, 75 women; mean (SD) age, 76.6 (8.3) years, range 52 to 96)—the majority of whom had been examined in hospitals by neurologists experienced

Table 1 Incidence of different types of Parkinsonism in necropsy series (percentages)

	Schrag *et al*[1] (clinical PD)	Hughes *et al*[2]	Jellinger[5] (1957–70)	Jellinger[5] (1971–88)	Jellinger (1989–2001)	
					n	%
Idiopathic Parkinson's disease	61.4	50.0	75.3	77.0	151	57.6
(Brainstem LB disease)	(2.0)					
Lewy body dementia		–	2.7	5.8	53	20.4
Lewy body disease (total)			78.0	82.8	204	78.0
Other degenerative parkinsonism		33.0	10.0	8.9	34	13.2
Multiple system atrophy	1.5	22.0	4.6	2.3	9	3.5
Progressive supranuclear palsy	3.0	11.0	3.6	2.6	8	3.1
Pick disease, corticobasal degen	–	?	0.9	0.5	2	0.8
Alzheimer's disease	–	?	0.9	3.5[a]	15	5.7
Secondary parkinsonism		17.0	12.0	8.3	22	8.4
Vascular parkinsonism (MIE, SAE, MIX)	5.5	?	3.0	4.2	8	3.1
Postencephalitic parkinsonism	–	?	6.3	1.9	0	0
Symptomatic (JCD, tumours, etc)	3.5	?	0	0.3	3	1.1
Toxic/drug induced parkinsonism	–	?	0.9	0.3	3	1.1
Post-traumatic/boxer dementia	–	?	0.9	0.3	0	0
Unclassified/no lesion ("tremor")	22.8	?	0.9	1.3	8	3.1
Total	**202**	**143**	**110**	**380**	**260**	**100.0**

[a]With SN lesion 3.0.
JCD, Jakob-Creutzfeldt disease; LB, Lewy body; MIE, multi-infarct encephalopathy; MIX, Alzheimer's disease plus vascular encephalopathy; PD, Parkinson's disease; SAE, subcortical arteriosclerotic encephalopathy.

Table 2 Misdiagnosis in necropsy series of clinical Parkinson's disease (with or without dementia)

Pathology	Hughes *et al*[2] (n=100)	Rajput *et al*[3] (n=41)	Jellinger (1971–88)[5] (n=380)	Jellinger (1989–2001)[5] (n=260)		Hughes *et al*[6] (n=143)
				n	%	
Alzheimer's disease	6	2.0	2.6	5	1.9	?
Vascular encephalopathy	0	2.0	3.5	2	0.8	?
Progressive supranuclear palsy	8	0.0	1.8	3	1.1	3.5
Multiple system atrophy	5	10.0	2.2	3	1.1	3.0
Nigral atrophy (unclassified)	2	2.0	0.5	1	0.4	
MIX encephalopathy (AD+VaE)	0	0.0	0.5	1	0.4	
Lewy body dementia	1	0.0	3.6	12	4.6	
Pick's disease, corticobasal degeneration	0	0.0	0.2	0	0	8.7
Normal (essential tremor?)	1	0.0	0.3	2	0.8	
Others (pallido-nigral degeneration, toxic, etc)	0	2.0	0.3	1	0.4	
Postencephalitic parkinsonism	1	4.0	0	0	0	
Total	**24**	**22.0**	**15.3**	**30**	**11.5**	**15.2**

Values are % unless stated.
AD, Alzheimer's disease; VaE, vascular encephalopathy.

in movement disorders over a 12 year period from 1990 to the end of 2001—gave the following results: 129 were clinically diagnosed as probable idiopathic Parkinson's disease without severe dementia, and 21 as having atypical parkinsonian syndromes. The PPV of the clinical diagnosis for the whole group was 89.4% (143/160); for idiopathic Parkinson's disease, 94.2% (131/139); for PSP, only 50% (4/8); for MSA, 57.1% (4/7); and for vascular parkinsonism, 66.7% (4/6). The sensitivity for idiopathic Parkinson's disease was 94.2% owing to eight false positive cases, mainly dementia with Lewy bodies (DLB), and two cases of PSP.

The diagnostic accuracy of 89.4% for the whole cohort was higher than in the group described by Hughes *et al* (85.3%),[2] and was similar to that of our own total group of 260 parkinsonian cases without and with dementia, where the rate of false clinical diagnosis was 11.5 % (table 2). This was lower than in previous clinicopathological series from the same hospitals and the same neuropathology department (table 2).

It is of interest that the majority of cases with a false clinical diagnosis of idiopathic Parkinson's disease in our cohort had a final pathological diagnosis of DLB—mainly "pure" DLB cases which often initially present with parkinsonism.[9 10] These were not included or mentioned in either of the British series.[1 3 6 7] In our recent consecutive necropsy series of 260 parkinsonian cases, DLB accounted for around 20% which, owing to improved neuropathological techniques and knowledge, was much higher than in previous series (table 1). The reason for the differences between the British series and our own is a matter for debate.

The recent British studies and our own studies imply that neurologists with particular expertise in the field of movement disorders may be best at recognising the clinical syndromes of parkinsonism. However, they also show clearly that neuropathological examination using modern immunohistochemical methods still represents the gold standard for the final diagnosis which, even after examination of the patients by very experienced clinicians, may differ by around 10% from the final clinical diagnosis. Improvement in the clinical consensus criteria and expertise may further reduce the rate of false clinical diagnosis of these devastating disorders—a possible basis for further improvements in treatment strategies.

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Smoking and cognitive change from age 11 to age 80

Age related cognitive decline affects people's quality of life and their ability to live independently.[1] A recent review stated, "[we] are aware of no studies on the relationship between smoking and cognitive decline associated with normal aging or studies of the effect of smoking on cognition in normally aging individuals."[1] Some previous studies examined smoking in relation to pathological cognitive aging, but lacked cognitive data before the initiation of smoking, and used crude clinical cognitive assessments.[2–4] Among middle aged subjects, current smoking was associated with poorer cognitive performance on tasks of psychomotor speed and cognitive flexibility.[5] Smoking has been identified as a possible risk factor for accelerated cerebral degenerative changes, cognitive decline, and dementia.[6] Here we show that smoking contributes to normal cognitive change from age 11 to age 80.

Participants, methods, and results

The Scottish Mental Survey of 1932 (SMS1932) tested mental ability in people born in 1921 (n = 87 498). The SMS1932's Moray House test (MHT) was validated against the Stanford Binet test and includes verbal reasoning, numerical, spatial, and other items. From 1999 to 2001 we traced and retested 550 people from Edinburgh who were born in 1921 (the Lothian birth cohort 1921). All lived independently. We excluded people with mini-mental state examination scores below 24 and those with known dementia. We traced their scores on the MHT from SMS1932, readministered the MHT using the same instructions and time limit as the SMS1932, and collected information on smoking. In all, 470 people (194 men) provided full data.

We examined the effect of smoking on cognitive change from age 11 to age 80 using general linear modelling (analysis of covariance; SPSS version 11). Age corrected MHT score at age 80 was the dependent variable, smoking (never (n = 205); current (n = 34); ex-smoker (n = 231)) and sex were between subject variables, and age corrected MHT score at age 11 was a covariate. Among the current smokers the mean (SD) age at starting smoking was 18.9 (5.5) years (range 9 to 40). The ex-smokers' mean age at starting smoking was 18.2 (5.2) years (range 7 to 60), and the mean age at stopping smoking was 49.6 (16.1) years (range 19 to 79 years). Only six of these ever-smokers (current and ex-) began smoking before the age of 11. The mean (SD) MHT scores for each smoking related subgroup at age 11 and age 80 are shown in table 1. MHT scores at age 11 had a large effect on scores at age 80 ($F_{1,463} = 332.2$, $p < 0.001$, $\eta^2 = 0.418$). There was a significant, independent effect of smoking ($F_{2,463} = 3.3$, $p = 0.039$, $\eta^2 = 0.014$), but not of sex

Table 1 Moray House test scores at age 11 and age 80 by smoking status

	n	IQ age 11 (SD)	IQ age 80 (SD)
Never smoked	205	101.6 (13.8)	100.8 (14.5)
Ex-smoker	231	99.8 (15.2)	100.3 (14.1)
Current smoker	34	98.4 (15.5)	94.3 (17.5)

Scores were converted to IQ-type scores (mean = 100; SD = 15) at each age separately.

($F_{1,463}$ = 3.1, p = 0.079, η^2 = 0.007).[2] The sex by smoking interaction was not significant ($F_{2,463}$ = 1.7, p = 0.17, η^2 = 0.007). Current smokers had significantly lower MHT scores at age 80 than never smokers (p = 0.013; mean difference = −5.2, 95% confidence interval (CI) −9.4 to −1.1) and ex-smokers (p = 0.016; mean difference = −5.0, 95% CI −9.0 to −0.9). These group comparisons remained similar in effect size and significance after entering years of full time education to the model.

Comment

Smoking affects cognitive change detrimentally from age 11 to age 80, with an effect that is similar in size to other contributors, such as the ϵ4 allele of the APOE gene.[7] An advantage of this study is that the initial cognitive assessments were made when only a tiny percentage of the subjects had begun smoking. This finding adds to those of a previous study which found that, among middle aged participants, current smokers had reduced cognitive performance when compared with never smokers.[5] In the present study, a history of having smoked and then given up smoking was not associated with any lowering of cognitive scores in old age. At age 80 there are survivor effects on cohorts owing to factors—such as death and illnesses—that are related to smoking. It might be expected that smokers in our cohort would be biased toward being especially fit and cognitively able. Thus selection bias could lead to our underestimating the effect of smoking on cognitive aging. The effect of smoking on cognitive aging might be direct, associated with, for example, biochemical factors such as antioxidant defences; neuropathological changes including acceleration of perfusional decline, cerebral atrophy, and polioaraiosis and leucoaraiosis (thinning of grey and white matter densities, respectively)[6]; or smoking related disease—though smoking did not explain the effect of cardiovascular disease on cognition in the Rotterdam study,[4] nor unequivocally in the Zutphen study.[3] It might also be indirect, being an indicator of a general tendency toward healthy lifestyle choices and responsiveness to health education. These possibilities notwithstanding, our data add to the reasons for giving up smoking, irrespective of age.

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