Regional cerebral glucose metabolism in akinetic catatonia and after remission

K L Kalibbaum 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 catatypia. Even if some advances have been made in the recognition of catatonia, in particular by the development of different rating scales, 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. 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+ tomoscan. A first PET (PET1) using $^{18}$F-fluorodeoxyglucose (FDG) was performed on day 2 in a drug free state. Therafter, 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, agitation, 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. Neurophysiological 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.

Table 1 Results of SPM analysis of PET1 and 2

<table>
<thead>
<tr>
<th>PET</th>
<th>Hypermetabolism</th>
<th>Hypometabolism</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cluster level</td>
<td>Vox level</td>
</tr>
<tr>
<td>1</td>
<td>Clusters size</td>
<td>p</td>
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<tr>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>2</td>
<td>Clusters size</td>
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<tr>
<td></td>
<td></td>
<td>0.003*</td>
</tr>
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<td></td>
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</tr>
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</table>

*After small spherical volume correction (radius 20 mm)

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 (table 1).

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

Patients with akinetic catatonia are classically unresponsive to their environment. 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. The dorsolateral prefrontal cortex has been involved in explicit representations of states of the “self”.

 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 this left region which participates in conscious awareness. PETI analysis showed that these two regions presented a decrease of metabolism that persisted on PET2. This persistence could be related to the hypometabolism 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. 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.

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.

### 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 area. Long term video/EEG monitoring with scalp electrodes done before this invasive monitoring showed lateral ictal lateralisation at the left anterior temporal area, and thus a right temporal onset could not be completely 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 amobarital test revealed the dominance of language and memory in the left hemisphere. The seizures started with an epiclastic 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 at 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.

### References


### 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.”

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. However, only two-stimulation studies 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). 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.

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.

### Figures

- **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.
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.1 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 laughter might suggest 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 mirth and memory function. As far as the area, suggesting a close relation between the temporal lobe and may be stored together in this patient.

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References

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 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%1 and 15–18%.3 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%.7

Referring to these data, Schrag et al showed 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%.4 (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, 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 diagnosis of Parkinson’s disease with the pathological diagnosis was 96% (SD) age, 76.6 (8.3) years, range 52 to 96—95.4% of the patients had a clinical diagnosis of Parkinson’s disease, 3.5% had another neurological disease; SAE, subcortical arteriosclerotic encephalopathy.

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

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<td>Parkinson’s disease</td>
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<td>50.0</td>
<td>75.3</td>
<td>77.0</td>
<td>151</td>
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<tr>
<td>(Brainstem LB disease)</td>
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<td>Lewy body dementia</td>
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<td>2.7</td>
<td>5.8</td>
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<tr>
<td>Pick disease, corticobasal degen</td>
<td>0.9</td>
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<td></td>
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<td>Alzheimer’s disease</td>
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<td>0.9</td>
<td>0.5</td>
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<td>Secondary parkinsonism</td>
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<td>12.0</td>
<td>4.2</td>
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<td>Vascular parkinsonism (MIE, SAE, MIX)</td>
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<td>3.0</td>
<td>4.2</td>
<td>8.0</td>
<td>3.1</td>
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<tr>
<td>Postencephalic parkinsonism</td>
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<td>6.3</td>
<td>1.9</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>Symptomatic (ICD, tumours, etc)</td>
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<td>0.3</td>
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<td>1.1</td>
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<tr>
<td>Toxic/drug induced parkinsonism</td>
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<td></td>
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<tr>
<td>Posttraumatic.boxer dementia</td>
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<td>0.9</td>
<td>0.3</td>
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<td>Unclassified/no lesion (“tremor”)</td>
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<td>0.9</td>
<td>1.3</td>
<td>8.0</td>
<td>3.1</td>
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Table Total

<table>
<thead>
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<tr>
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<td>202</td>
<td>143</td>
<td>110</td>
<td>380</td>
<td>260</td>
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</table>

*With SN lesion 3.0.

ICD, Jakob-Creutzfeld disease; LB, Lewy body; MIE, multi-infarct encephalopathy; MIX, Alzheimer’s disease plus vascular encephalopathy; PD, Parkinson’s disease; SAE, subcortical arteriosclerotic encephalopathy.

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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 without severe dementia, and 21 as diagnosed as probable idiopathic Parkinson's disease.

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. These were not included or mentioned in either of the British series. In our recent consecutive necropsy series of 260 parkinsonian cases, DLB accounted for almost 20% which, owing to improved neuropathological techniques and knowledge, was much higher than in previous clinicopathological series from the same hospitals and the same neuropathology department (table 2).

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

<table>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>6</td>
<td>2 (2.6)</td>
<td>5 (1.9)</td>
<td>5 (1.9)</td>
<td>7</td>
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<td>Vascular encephalopathy</td>
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<td>2.0</td>
<td>2 (0.8)</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>8</td>
<td>0.0</td>
<td>3 (1.1)</td>
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<tr>
<td>Multiple system atrophy</td>
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<td>10.0</td>
<td>3 (3.0)</td>
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<tr>
<td>Nigral atrophy (unclassified)</td>
<td>2</td>
<td>2.0</td>
<td>1 (0.4)</td>
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<td>MIX encephalopathy (AD+VaD)</td>
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<td>0.0</td>
<td>0.4</td>
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<tr>
<td>Lewy body dementia</td>
<td>6</td>
<td>0.0</td>
<td>0.4</td>
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<tr>
<td>Pick’s disease, corticobasal degeneration</td>
<td>0</td>
<td>0.0</td>
<td>0.4</td>
<td>0.4</td>
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<tr>
<td>Normal (essential tremor?)</td>
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<td>0.0</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
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<td>Others (pallido-nigral degeneration, toxic, etc)</td>
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<td>2.0</td>
<td>0.4</td>
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<tr>
<td>Postencephalitic parkinsonism</td>
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<td>4.0</td>
<td>0.4</td>
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<tr>
<td>Total</td>
<td>24</td>
<td>22.0</td>
<td>15.3</td>
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</table>

Values are % unless stated.

References


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. 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.” Some previous studies examined smoking in relation to pathological cognitive aging, but lacked cognitive data before the initiation of smoking, and used crude cognitive assessments. Among middle aged subjects, current smoking was associated with poorer cognitive performance on tasks of psychomotor speed and cognitive flexibility. Smoking has been identified as a possible risk factor for accelerated cerebral degenerative changes, cognitive decline, and dementia. 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 = 87498). The SMS1932’s Moray House test (MHT) was validated against the Stanley Binet test and includes verbal reasoning, numerical, spatial, and other items. From 1999 to 2001 we traced and retouched 530 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 (5.2) years (range 10 to 30). The ex-smokers’ mean age at starting smoking was 18.1 (5.2) years (range 7 to 28), 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(1,267) = 332.2, p < 0.001, ηp = 0.418). There was a significant, independent effect of smoking (F(2,265) = 3.3, p = 0.039, ηp = 0.041), but not of sex.
Table 1 Moray House test scores at age 11 and age 80 by smoking status

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>IQ age 11 (SD)</th>
<th>IQ age 80 (SD)</th>
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</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>101.6 (13.8)</td>
<td>100.8 (14.5)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>99.8 (15.2)</td>
<td>100.3 (14.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>98.4 (15.5)</td>
<td>94.3 (17.5)</td>
</tr>
</tbody>
</table>

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

The sex by smoking interaction was not significant ($F_{(5,132)} = 3.1, p = 0.079, \eta^2 = 0.007$). The sex by smoking interaction was not significant ($F_{(5,132)} = 1.7, p = 0.17, \eta^2 = 0.007$). Current smokers had significantly lower MHT scores at age 80 than never smokers ($p = 0.013$; mean difference = $−9.2$, 95% confidence interval (CI) $−9.4$ to $−3.1$) 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 e4 allele of the APOE gene. 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 previous results that, among middle aged participants, current smokers had reduced cognitive performance when compared with never smokers. 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 an underestimating of 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 deficiencies; neuropathological changes including acceleration of perfusional decline, cerebral atrophy, and polioaraisis and leucoaraisis (thinning of grey and white matter densities, respectively); or smoking related disease—though smoking did not explain the effect of cardiovascular disease on cognition in the Rotterdam study; nor unequivocally in the Zutphen study. 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.

Acknowledgements

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Competing interests: none declared

References

**CORRESPONDENCE**

**Neutralising antibodies to interferon β during the treatment of multiple sclerosis**

Giovannoni and colleagues are to be commended for their detailed analysis of the impact of neutralising antibodies (NAB) to interferon β (IFNβ) during the treatment of multiple sclerosis. We are in general agreement with many of their statements and conclusions, but a few points should be discussed in a wider context.

With respect to the clinical significance of neutralising antibodies to IFNβ, the authors state that “IFNβ has little if any clinical and MRI efficacy in the presence of neutralising antibodies.” We think it is appropriate to be more circumspect, as most published studies suggest that in NAB positive patients, clinical (and MRI) efficacy of interferon treatment is present when compared to placebo, and that there is some evidence that more immunogenic higher dose treatment can be more effective than less immunogenic lower dose treatment.1 Giovannoni et al appear to base their statement on the increase in T2 burden of disease in the NAB positive group in the PRISMS extension study, but they do not mention similar comparisons which, if interpreted in the same way, would indicate that the NAB positive group does better than the placebo group. For example, the relapse rate in placebo patients was 1.3/year in years one to two, whereas it was 0.81 and 0.50 in NAB positive and negative high dose patients in years three to four. We recognise that this specific comparison is fraught with difficulties owing to time trends in the relapse data, but these potential difficulties are present in all such comparisons. In a recent paper we report—in probably the largest study of neutralising antibodies in multiple sclerosis—describing 100 NAB positive patients in the European SPMS study—that high titres of neutralising antibodies do have a clinical impact, but that this impact is rather limited, and that on both clinical and MRI measures of more objective T2 lesion volume or burden of disease—that the average annualised increase in lesion volume over four years in the neutralising antibody positive (NAB+) patients is similar to the increase in the annualised lesion volume in the placebo treated patients in the first two years of the study (NAB+ 4.4% vs placebo 5.45%).2

In our opinion, these data suggest that the clinical impact of neutralising antibodies to IFNβ during the treatment of multiple sclerosis may be more limited and more transient than suggested in the editorial, and that the development of neutralising antibodies in itself does not provide justification for switching treatments or for considering (aggressive) strategies to reduce or revert the development of neutralising antibodies. Given the current rather uncertain state of knowledge concerning the impact of neutralising antibodies, we advocate that treatment decisions should be based on clinical grounds rather than on neutralising antibody titres.

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References

**Neuralntising antibodies to interferon β**

I read the editorial by Dr G Giovannoni and colleagues' with great interest. I have, however, to report a minor error concerning the list of the excipients of the Rebif reported in their table 1. In the table the authors reported the following excipients: mannitol, HSA, sodium acetate, acetic acid, sodium chloride. Actually, as you can check in the summary of product characteristics published from EMEA (www.emea.eu.int) on 29 March 1999, in the list of excipients sodium chloride is absent, whereas sodium hydroxide is present.

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Authors' reply

We would like to thank Dr Ortenzi for pointing out our transcription error in relation to the excipients of Rebif® in table 1 of our editorial.1

We agree with Polman and colleagues that recent comparisons show that the more immunogenic higher dose interferon β (IFNβ) preparations are more efficacious than the lower dose less immunogenic preparations over 24 months2 and six month3 periods of observation. However, as discussed in our editorial, the development of neutralising antibodies and their effects on the clinical efficacy of IFNβ are delayed. In the PRISMS study the effect of neutralising antibodies on clinical efficacy only became apparent after years 3–4.4 In the pivotal IFNβ-1b study an effect on relapse rate was only observed in the 19–24 and 25–30 month epochs.5 Hence we would argue that these comparative studies3 are simply too short, and in the case of the INCOMIN trial underpowered (n = 188),6 to demonstrate an effect of neutralising antibodies on clinical efficacy. It is therefore impossible to extrapolate the significant short term differences in clinical response in these studies beyond the periods of observation reported.

Because of regression to mean and the well documented tendency for the relapse rate to decrease with disease duration, it is not possible to draw any meaningful conclusions from a comparison of the relapse rate in years 1–2 and years 3–4 from the PRISMS extension study.7 In addition to the impact of neutralising antibodies on relapse rate, the PRISMS extension study clearly shows—using the more objective T2 lesion volume or burden of disease—that the average annualised increase in lesion volume over four years in the neutralising antibody positive (NAB+) patients is similar to the increase in the annualised lesion volume in the placebo treated patients in the first two years of the study (NAB+ 4.4% vs placebo 5.45%).2 Similarly, in the IFNβ-1b study8 the annualised relapse rate of NAB+ patients is identical to patients on placebo (1.08 v 1.06). In the IFNβ-1a (Avenex®) trial,9 the impact of neutralising antibodies was limited to MRI outcomes. The failure of neutralising antibodies to have an effect on disease progression and relapse rate in this study probably reflects the size and duration of follow up, as the study was terminated prematurely. It is these data from the pivotal relapsing multiple sclerosis clinical trial.
trials, and other studies on in vivo markers of IFNβ activity discussed in our editorial, that we use to support our statement that “interferon β has little if any clinical and MRI efficacy in the presence of neutralising antibodies.”

Data on the impact of neutralising antibod-
ies in secondary progressive multiple sclerosis (SPMS) trials is less clear. This is to be expected, however, as the efficacy of IFNβ on disease progression—the primary outcome measure in SPMS trials—is limited and hence it would be difficult to demonstrate a signifi-
cant impact on neutralising antibodies on the primary outcome measure when the actual ther-
apeutic intervention is only marginally e-
effective.” It would be very surprising if neutralising antibodies had a significant impact on disease progression, as none of the trials is powered to detect an effect of neutral-
ising antibodies on this outcome. For ex-
ample, in the European SPMS study, 100/360 (28%) of IFNβ-1b treated patients became NAB+ (titre > 20) over the course of the trial. In our conservative approach by applying the results from the trial,13 and assuming that NAB+ patients behave like the NAB− IFNβ-1b treated cohort, one would expect 48.9% of the 100 NAB+ patients to progress over three years, compared with 38.9% of the 260 NAB− patients. At the same level of significance (0.029) from the original study,12 it would only have a 35% chance of detecting a significant difference between NAB+ and NAB− patients (Fishier’s exact test). Compare this to a power of 80% used in the design of the original study. This power calculation is an overestimate as it ignores the therapeutic effect observed before the development of neutralising antibodies, as evidenced in this study,12 which if taken into account would seem reasonable if there are no carryover therapeutic effects of IFNβ-1b treatment from the NAB− to NAB+ phase and if the follow up in the NAB+ phase is of suffi-
cient duration to account for the delayed effects (24 to 48 months) of neutralising anti-
bodies on clinical efficacy. In this study the mean follow up in the NAB+ phase would be on average too short (less than 24 months) for one to be confident of excluding a delayed effect of neutralising antibodies on disease progression. Despite the lack of power of these subanalyses, they produce some surprising results. In the cross sectional study there was a trend towards higher disease activity in the NAB+ group in the third year, and a significant percentage T2 volume change from the underpowered and potentially flawed lon-
gitudinal analysis by limiting the longitudinal study to the former half of their statement, if true, may not be applicable to patients treated with IFNβ-1a.

In conclusion, clinicians cannot ignore the impact of neutralising antibodies, particularly in view of the evidence from other fields of medicine in which neutralising antibodies reduce or inhibit the efficacy of a wide range of biologicals, including type I interferons. Why should interferon treatment in multiple sclerosis be any different?

References

A 1908 systematic review of the laterality of hysterical hemiplegia

Since the publication of our systematic review of the laterality of functional or medically unexplained weakness and sensory distur-
bance (1965–2000)1 we have come across a study from 1908 with a similar theme.

Ernest Jones, later an eminent figure in the psychoanalytic movement, published his paper in French while working as an assistant physician at the London School of Medicine. He reported on the cumulative analysis of 277 cases of hysterical hemiplegia described by 146 authors in 164 articles published between 1880 and 1908. Most of this material is in French and German and includes cases men-
tioned in doctoral theses and books.

There was no excess of left sided hemiple-
gia compared with right in hysteria in his analysis—54% had paralysis on the right side and 46% on the left. This was contrary to the prevailing opinion of the time1 and also disa-
grees with another less systematic review of older studies (covering 100 subjects, 13 publi-
cations and 6 authors between 1885–1937).1 Jones’ conclusions—that the laterality of hysterical hemiplegia has no diagnostic value—were the same as ours. His study has not been cited for at least 40 years (and prob-
ably much longer even than that). It has been neglected, like many other negative studies before and since, but it deserves recognition on this subject.

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Psychiatric problems are the main cause of long-term memory.

The patient's behaviour showed dramatic improvement. These episodes ceased completely and the patient became cooperative. It was surprising that the EEG tracing was normal, with no focal or epileptiform features. The patient remained in the psychiatric unit for seven months during which time she developed epilepsy and a similar proportion of carbamazepine responsive neuropsychiatric symptoms after herpes simplex encephalitis. Despite the absence of any EEG abnormalities in our case, it showed a similar favourable response to carbamazepine. We feel that any patient with intermittent behavioural or psychiatric symptoms after HSE should have a therapeutic trial of carbamazepine, even in the absence of any clinical or neurophysiological evidence of seizure activity.

References

Authors’ reply
Gabre and Eshiett report an interesting case of carbamazepine responsive neuropsychiatric syndrome after herpes simplex encephalitis (HSE). Neuropsychiatric symptoms after HSE are well recognised.1 However, psychiatric disorders are also common after non-herpes virus encephalitis. Hunter and colleagues have previously implicated HSE in the delayed syndromes of violent psychoses2 and suicide.3 However, psychiatric disorders are also common after non-herpes virus encephalitis. Hunter and colleagues had emphasised the importance of considering antiepileptic antecedents, even if clinically unapparent, in the differential diagnosis of psychiatric patients.4 Long term follow up data from the National Childhood Encephalopathy study have shown more recently that 20% of the affected children developed epilepsy and a similar proportion had behavioural problems, hyperactivity or unsociable behaviour.5 Besides being a first line antiepileptic, carbamazepine is also recognised to possess considerable therapeutic value in certain psychoses and is an effective long term treatment for bipolar disorder in some cases.6 Carbamazepine responsive psychosis in particular case may not, therefore, imply that the psychiatric symptoms were epileptic in origin. However, EEG signatures of epilepsy are often absent interictally, and the presence of psychoses is known to normalise EEG changes (‘forced normalisation’) in epilepsy patients.7 In this particular case, we certainly concur with the authors’ use of carbamazepine and were delighted to learn of the favourable response.

Radiofrequency neurotomy
In reading the study by Govind and colleagues,1 in which they report the findings of an unblinded, uncontrolled, non-randomised trial of radiofrequency neurotomy for the treatment of third occipital headache, we are surprised that the authors advocate this therapy.

The last statement of the abstract is: “No other form of treatment has been validated for this common form of headache”. This implies that Govind et al believe they have validated radiofrequency neurotomy as a form of treatment for third occipital headache. Presumably they are prepared, given the apparently impressive numbers of respondents, to forego the usual practice of placebo controlled trials. We do not understand how the authors can expect this treatment to be realistically adopted in clinical practice with no attempt to validate it the way treatments are meant to be validated, through randomised, placebo controlled trials. The statement in their final paragraph that “some practitioners may be averse to implementing a treatment that requires repetition” could perhaps more appropriately be stated that “some practitioners may be averse to implementing a treatment that remains unvalidated”.

The authors state that one reason they did not do a placebo controlled study is that a previous study has already validated this technique in other patients.8 That a single trial of radiofrequency neurotomy in 24 so-called “whiplash patients” is sufficient basis for the current authors to abandon validation with traditional methods seems absurd, especially when closer inspection of that trial lays it in a less positive light.9 We do not accept an argument that it was impossible to blind these subjects. It would be entirely reasonable to see just how often a placebo procedure does indeed
“fool” the patient. Govind et al seem to have already decided that this is not possible, a convenient assumption.

Further, we are concerned that Govind et al state categorically that “among patients with whiplash injuries, third occipital headache is uncommon”. The study group from which they determine this prevalence has been reviewed elsewhere, and is wholly inappropriate for a prevalence estimate, being best described as an unusual, highly select, and heterogeneous group of subjects.1 It is of note that, in regard to validated therapies for whiplash patients, the current study would have been rejected by the criteria of the Quebec Task Force on Whiplash Associated Disorders.2 We suggest that an invasive procedure should not be advocated until it has been subjected to proper study. Fortunately, we are aware that others are undertaking a properly controlled trial of this form of therapy.

The precepts of informed consent require that participants in a randomised controlled trial be informed of all the consequences and potential complications of a procedure. We are aware that others are undertaking a procedure which has been subjected to proper study. Fortunately, we are aware that others are undertaking a properly controlled trial of this form of therapy.

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References

Authors’ reply
Our study reported an audit of outcomes for a treatment of a condition for which there is no other treatment available. It showed what proportion of patients obtained complete relief of pain, and for how long. Readers who wish to adopt this treatment for their patients can do so. If not, they should explain to their patients that they, personally, cannot offer them any treatment that is known to work, but they should not claim that there is no treatment. Our study shows that there is an option.

A placebo controlled trial would not prove that this treatment does not work. The outcomes should be the same as the benchmark established by our study, unless the operators perform the procedure poorly. A placebo controlled study could only show that all or part of the outcome is attributable to non-specific effects.

We consider this to be an unlikely outcome for we have never encountered in any of our own studies, nor in the literature, results showing that 86% of patients obtain complete relief of spinal pain following a sham procedure. Radiofrequency neurotomy has been shown to be associated with placebo responses in only a small proportion of patients, and for a limited duration.4 They claim that responses to third occipital neurotomy is only a conjecture. In principle it is worthy of testing, but in practice it cannot be tested.

In the neurological picture of the June issue (Komitjar JR, Clatterbuck RE. Cocididiomyosis of the brain, mimicking an plaque meningioma. J Neurol Neurosurg Psychiatry 2003; 74: 806) the initials of the first author were reversed; his name should read as Komitjar BJ.


The ordering of the authors in the letter by De Tiège, Laureys, Goldman, et al in the July issue (Regional cerebral glucose metabolism in akinetic catatonia and after remission. J Neurol Neurosurg Psychiatry 2003; 74: 1003–4) is incorrect, it should read as follows: X De Tiège, JC Bier, I Massat, S Laureys, F Lotstra, J Berré, J Mendlewicz, S Goldman.

In the June issue of JNNP fig 1 of the paper by Caglì S, Oktar N, Dalbasti T, et al (Failure to detect Chlamydia pneumoniae DNA in cerebral aneurysmal sac tissue with two different polymerase chain reaction methods. J Neurol Neurosurg Psychiatry 2003; 74: 756–9) was incorrect. The following figure is the correct image that should have been published.

Figure 1 C pneumoniae TETR PCR of clinical samples. Lanes 1 to 3, 5 to 7 clinical samples, Lanes 4 and 8 negative control (water). Lanes 9 and 11 positive control (C pneumoniae 4x10⁸ and 4x10⁵ CFU). Lane 10 water. Lane 12 DNA molecular weight marker (XIV, 100 bp ladder, Roche Diagnostics). (Correction to J Neurol Neurosurg Psychiatry 2003; 74: 756–9.)