Regional cerebral glucose metabolism in akinetic catatonia and after remission

K I Kalibbaum published in 1874 the first recorded description of catatonia. Akinetic catatonia is now defined as a neuropsychiatric syndrome principally characterised by akinesis, mutism, stupor, and catalepsy. 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+ tomograph. A first PET (PET1) using $[^18F]$-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, logorrhea, and disinhibition characterised by uncontrollable 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 cortex (Brodmann area 10) as shown in table 1. PET2 was conducted after akinetic catatonia remission, it was used for an exclusive masking analysis of PET1 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).

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 parietal 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

<table>
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<tr>
<th>Table 1</th>
<th>Results of SPM analysis of PET1 and 2</th>
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<tr>
<td><strong>PET</strong></td>
<td><strong>Hypometabolism</strong></td>
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<tr>
<td></td>
<td><strong>Cluster level</strong></td>
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<tr>
<td></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>1</td>
<td>0.001</td>
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<td>&lt;0.001</td>
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<td>&lt;0.001</td>
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<td></td>
<td>0.008</td>
</tr>
<tr>
<td>2</td>
<td>&lt;0.001</td>
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<td></td>
<td>&lt;0.001</td>
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*After small spherical volume correction (radius 20 mm).
the occurrence of episodic spontaneous stereotyped movements and the prolonged maintenance of posture (catatopy). 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 neuromuscular 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 akinetic 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 characterizes 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 the self. Dissociation of the left lateral parietal cortex is the metabolic hallmark of the normal resting state. Decreased density of GABA-A receptors in the left region which persists after clinical remission participated in the left sensorimotor cortex in akinetic catatonia: investigation of in vivo benzodiazepine receptor binding. J Neurol Neurosurg Psychiatry 1999; 67:445–50.

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 cortical origins of mirth. Some reports on pathological laughter have implicated the hypothalamus, brain stem, and temporal lobe.1

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 studies1 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.3

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 lobe. Long term video/EEG monitoring with scalp electrodes done before this invasive monitoring showed lateralizing lateralization 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 amobarbital test revealed the dominance of language and memory in the left hemisphere.

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 A2–A4) (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.
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 order with 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. The melody which produced mirth in this patient, the melody which might not necessarily have reflected the representation of mirth and laughter in the normal brain, no mirth was seen during the stimulation with higher intensity and longer duration. The electric stimulation elicited mirth and laughter are represented. In this patient, the temporal lobe is involved in memory function. As far as the area, suggesting a close relation between mirth and memory function. Thus this particular area (A4–A12) producing mirth on stimulation can be judged to reflect normal function in this patient.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Incidence of different types of Parkinsonism in necropsy series (percentages)</th>
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</thead>
<tbody>
<tr>
<td>Idiopathic Parkinson’s disease (Brainstem LB disease)</td>
<td>61.4</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>2</td>
</tr>
<tr>
<td>Lewy body disease (total)</td>
<td>12</td>
</tr>
<tr>
<td>Other degenerative parkinsonism</td>
<td>1.5</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>3.0</td>
</tr>
<tr>
<td>Pick disease, corticobasal degeneration</td>
<td>—</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>—</td>
</tr>
<tr>
<td>Secondary parkinsonism</td>
<td>17.0</td>
</tr>
<tr>
<td>Vascular parkinsonism (MIE, SAE, MIX)</td>
<td>5.5</td>
</tr>
<tr>
<td>Corticobasal degeneration, Pick</td>
<td>—</td>
</tr>
<tr>
<td>Posttraumatic</td>
<td>3.5</td>
</tr>
<tr>
<td>Unidentified/no lesion (‘tremor’)</td>
<td>22.8</td>
</tr>
</tbody>
</table>

*With SN lesion 3.0.

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

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 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 only a close relation between the clinical criteria of Parkinson’s disease and memory function, in which the rate of false positive diagnosis ranged between 22–24%4–7 and 15–18%8–11. 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 parkinsonism syndromes 71.4%—for example, for multisystem atrophy (MSA), 85.7%, and for progressive supranuclear palsy (PSP), 80%.7–7

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%.4–7 (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 clinical and pathological diagnoses in this cohort was much better than in previous series1 (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...
in movement disorders over a 12 year period from 1990 to the end of 2001—gave the in movement disorders over a 12 year period from 1990 to the end of 2001—gave the

| Pathology                          | Hughes et al<sup>6</sup> (n=100) | Rajput et al<sup>5</sup> (n=41) | Jellinger (1971–88)<sup>3</sup> (n=380) | Jellinger (1989–2001)<sup>4</sup> (n=260) | Hughes et al<sup>6</sup> (n=143)
|-----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------
| Alzheimer’s disease               | 6                               | 2.0                             | 2.6                             | 5                               | 1.9                             | 7
| Vascular encephalopathy          | 0                               | 2.0                             | 3.5                             | 2                               | 0.8                             | 0
| 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                             | 0
| M0X encephalopathy (AD+VaE)       | 0                               | 0.0                             | 0.0                             | 0                               | 0.4                             | 0
| Lewy body dementia               | 5                               | 0.0                             | 3.6                             | 12                              | 3.6                             | 8
| Pick’s disease, corticobasal degeneration | 0                      | 0.0                             | 0.2                             | 0                               | 0.8                             | 0
| Normal (essential tremor?)        | 1                               | 0.0                             | 0.3                             | 2                               | 0.8                             | 0
| Others (pallido-nigral degeneration, toxic, etc) | 0                       | 2.0                             | 0.3                             | 0                               | 0.4                             | 0
| Postencephalic parkinsonism       | 0                               | 4.0                             | 0.1                             | 0                               | 0.4                             | 0
| Total                             | 24                              | 22.0                            | 15.3                            | 30                              | 11.5                            | 15.2

Values are % unless stated.

AD, Alzheimer’s disease; VaE, vascular encephalopathy.

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

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 cerebrovascular 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 = 67 498). 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 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 of 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 3. MHT scores at age 11 had a large effect on scores at age 80 (F<sub>MS</sub> = 332.2, p < 0.001, η<sup>2</sup> = 0.418). There was a significant, independent effect of smoking (F<sub>MS</sub> = 3.5, p = 0.039, η<sup>2</sup> = 0.041), but not of sex.
the is similar in size to other contributors, such as Smoking affects cognitive change detrimentally from age 11 to age 80, with an effect that is similar in size to other contributors, such as Smokers. Current smokers had significantly lower MHT scores at age 80 than never smokers ($p = 0.013$; mean difference $= -9.4$ to $-5.0$, $95\%$ CI $-5.2$ to $-9.0$). 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 Smokers. Current smokers had significantly lower MHT scores at age 80 than never smokers ($p = 0.013$; mean difference $= -9.4$ to $-5.0$, $95\%$ CI $-5.2$ to $-9.0$). These group comparisons remained similar in effect size and significance after entering years of full time education to the model.

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>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>104.6 (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.

($F_{1,74} = 3.1$, $p = 0.079$, $\eta^2 = 0.007$). The sex by smoking interaction was not significant ($F_{1,74} = 1.7$, $p = 0.17$, $\eta^2 = 0.007$). Current smokers had significantly lower MHT scores at age 80 than never smokers ($p = 0.013$; mean difference $= -9.4$ to $-5.0$, $95\%$ CI $-5.2$ to $-9.0$). These group comparisons remained similar in effect size and significance after entering years of full time education to the model.

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 leukoaraiosis and leukoaraiosis (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 evidence to smoking on cognitive aging.

Competing interests: none declared

References

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