Specificity of changes in cerebral blood flow in patients with frontal lobe dementia

Sergio E Starkstein, Ricardo Migliorelli, Alejandra Tesón, Liliana Sabe, Silvia Vázquez, Martin Turjanski, Robert G Robinson, Ramón Leiguarda

Abstract
Eight patients with a clinical diagnosis of probable Alzheimer’s disease, eight patients with the clinical diagnosis of frontal lobe dementia, and eight controls were examined with single photon emission tomography (SPECT) using 99mTc-HMPAO. Patients with Alzheimer’s disease and those with frontal lobe dementia met DSM-III-R criteria for mild dementia and were in the early stages of the illness. Compared with patients with Alzheimer’s disease, the group with frontal lobe dementia had significantly lower blood flow in the frontal lobes (dorsolateral and orbital), the anterior temporal cortex, and the basal ganglia. Within the frontal lobe dementia group, blood flow was significantly lower in the orbital than in the dorsal frontal cortex, and in the anterior temporal than in the dorsal temporal cortex. The present study shows the specificity of changes in regional cerebral blood flow in the diagnosis of different types of dementia, and supports the importance of orbitofrontal, anterior temporal, and basal ganglia dysfunction in the production of the psychiatric syndrome of frontal lobe dementia.

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Neary and coworkers described frontal lobe dementia as a degenerative condition characterised by changes in personality, breakdown in social conduct, disinhibition, impulsivity, unconcern, changes in eating conduct (hyperphagia), and stereotyped and perseverative behaviour.1 Disinhibited behaviour is often found among patients with neurological disorders such as closed head injuries and brain tumours,2 and may manifest itself as motor disinhibition (for example, hyperactivity, pressured speech, decreased need of sleep), intellectual disinhibition (for example, flight of ideas, grandiose delusions, paranoia), and instinctive disinhibition (for example, hypersexuality, hyperphagia).3 In some patients, disinhibited behaviour may be severe enough to fulfill DSM-III-R4 diagnostic criteria for mania, which require a distinct period of abnormally and persistently elevated, expansive, or irritable mood, and at least three of: inflated self esteem or grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for painful results.

In a consecutive series of patients admitted to a psychiatric unit with the diagnosis of mania after a brain injury (stroke, tumour, or closed head injury) we found a high frequency of lesions involving the orbitofrontal cortex, anterior temporal cortex, head of the caudate, and thalamus.4 In a recent study that included a new series of seven consecutive patients with mania after brain injury, four had lesions involving the orbitofrontal and anterior temporal cortex, and the remaining three patients had single ischaemic lesions involving the right head of the caudate and the internal capsule.5 A PET study with 18F-fluorodeoxyglucose (18FDG) showed significant hypometabolic activity in the ipsilateral anterior temporal cortex in all three patients. Taken together, these findings suggest that disinhibited behaviour in patients with brain lesions may result from (direct or indirect) damage to the orbitofrontal and anterior temporal cortices. It is possible that similar changes may underlie the psychiatric disturbances of patients with frontal lobe dementia, as recent studies have shown significantly decreased blood flow in the frontal lobe of patients with a clinical diagnosis of frontal lobe dementia.6–10 Whether these changes in cerebral blood flow pertain to the disinhibition syndrome of frontal lobe dementia, however, rather than the cognitive impairment of this disorder, and whether there are specific areas within the frontal lobes that show blood flow deficits related to the behavioural change has not, to our knowledge, been empirically examined.

For the present study we included a series of patients with mild dementia who also met stringent criteria for disinhibited behaviour (the frontal lobe dementia group). To determine the severity, location, and specificity of blood flow deficits in frontal lobe dementia we included both an age matched control group and a series of age matched patients with a similar severity of dementia but no disinhibition who met the National Institute of Neurological and Communicative Disorder and Stroke—Alzheimer’s Disease and Related Disorders Association11 criteria for probable Alzheimer’s disease. Finally, to examine the importance of ventral structures in the production of disinhibited behaviour, we compared blood flow changes in orbitofrontal vs dorsal frontal areas, and anterior temporal vs dorsal temporal areas.
Patients and methods

Frontal lobe dementia group
The frontal lobe dementia group consisted of eight patients who met the following inclusion criteria: (a) DSM-III-R diagnostic criteria for mild dementia, (b) a score >8 or more on the Gustafson and Nilsson Pick scale,12 and a score <5 on the Gustafson and Nilsson Alzheimer scale,12 (c) no CT evidence of focal brain lesions, (d) normal results on routine laboratory tests, (e) a Hachinski ischaemic score13 <5, and (f) no history of alcohol abuse or closed head injury.

Alzheimer’s disease group
The Alzheimer’s disease group consisted of eight patients who met the following inclusion criteria: (a) DSM-III-R diagnostic criteria of mild dementia, (b) a score >8 or more on the Gustafson and Nilsson Alzheimer scale,12 and a score <5 on the Gustafson and Nilsson Pick scale, (c) no CT evidence of focal brain lesions, (d) normal results on routine laboratory tests, (e) a Hachinski Ischaemic score13 <5, and (f) no history of alcohol abuse or closed head injury.

Control group
The control group comprised four normal volunteers from our Institute and four people who complained of dizziness. All had a normal brain CT; a normal neurological evaluation, and no history of psychiatric disorders.

NEUropsychiatric Examination
The neuropsychiatric evaluation consisted of the following:

Mini-mental state examination (MMSE)
The MMSE is an 11 item examination reliable and valid in assessing a limited range of cognitive functions.14

Gustafson and Nilsson rating scales for diagnosis of Alzheimer’s disease and Pick’s disease
This is a 16 item scale that scores the frequency of intellectual deficits (early amnesia, early disorientation, apraxia, aphasia, and agnosia), motor signs (increased muscular tension, myoclonic twitchings, and epileptic seizures of late onset), behavioural disorders (early loss of insight, Klüver-Bucy syndrome, early signs of disinhibition, irritability, and dysphoria), and the temporal progression of deficits (slow progression, and progressive reduction of spontaneity of speech).15 Gustafson and Nilsson showed that scores <5 on the Alzheimer’s scale and >5 on the Pick’s scale had a sensitivity and specificity of 100% for the diagnosis of pathologically established Pick’s disease. On the other hand, scores <5 on the Pick’s scale and >8 on the Alzheimer’s scale had a sensitivity and specificity of 100% for the diagnosis of pathologically established Alzheimer’s disease. Thus in the present study patients included in the Alzheimer’s group had a score ≤5 on the Pick’s scale and a score >8 on the Alzheimer’s scale, whereas patients included in the frontal lobe dementia group had a score <5 on the Alzheimer’s scale and >8 on the Pick’s scale (we decided to be more stringent on the Pick’s scale score for the frontal lobe dementia group so as to maximise the chance of including patients with severe disinhibition) (table 1).

NEUropsychological Examinations
Patients with Alzheimer’s disease and patients with frontal lobe dementia had a comprehensive neuropsychological evaluation that was carried out within two weeks of the SPECT study and included the following tasks:

Wechsler Adult Intelligence Scale—Revised (WAIS-R)
The WAIS-R is a measure of general intellectual ability.

Wisconsin Card Sorting Test
This test measures the ability to develop new concepts and shift sets, and also requires the subject to suppress a previously correct response and produce a new one.16

Controlled Word Association Test
This test examines access to semantic information with time constraint.17

Trail Making Test
This test examines visual, conceptual, and visuomotor tracking.18

Digit Span
This test examines auditory attention.19

Buschke Selective Reminding Test
This test measures verbal learning and memory during a multiple trial learning task.20

Benton Visual Retention Test
This test assesses visual perception and visual memory.21

Token Test
This test examines verbal comprehension of sentences of increasing complexity.22

Boston Naming Test
This test examines the ability to name pictured objects.23

Raven’s Progressive Matrices
This test assesses reasoning in the visual modality.24

Apraxia Subtest of the Western Aphasia Battery
This test examines the presence of ideomotor apraxia.25

Table 1 Demographic and Neuropsychiatric Findings

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Alzheimer’s group</th>
<th>Frontal lobe dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>67 (7.5)</td>
<td>70 (6.8)</td>
<td>68 (7.4)</td>
</tr>
<tr>
<td>Sex (% females)</td>
<td>50</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>Education (mean y)</td>
<td>10 (4.1)</td>
<td>10 (5.3)</td>
<td>11 (4.7)</td>
</tr>
<tr>
<td>Duration of illness (mean y)</td>
<td>2 (1.8)</td>
<td>2 (1.8)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Mini-mental state exam (mean scores)</td>
<td>29 (2.2)</td>
<td>21 (5.3)</td>
<td>21 (5.3)</td>
</tr>
<tr>
<td>Gustafson-Nilsson Alzheimer scale</td>
<td>6 (3.3)</td>
<td>3 (2.1)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Gustafson-Nilsson Pick scale</td>
<td>2.3 (1.9)</td>
<td>9.2 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

Figures in parentheses are SDs.
**Table 2** Neuropsychological findings

<table>
<thead>
<tr>
<th>Neuropsychological task</th>
<th>Alzheimer’s group</th>
<th>Frontal lobe dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buschke SRT—long term retrieval</strong></td>
<td>23.0 (13.9)</td>
<td>12.2 (11.0)</td>
</tr>
<tr>
<td><strong>Buschke SRT—short term retrieval</strong></td>
<td>28.7 (7.2)</td>
<td>28.5 (9.6)</td>
</tr>
<tr>
<td><strong>Buschke SRT—long term storage</strong></td>
<td>30.5 (15.0)</td>
<td>17.2 (15.2)</td>
</tr>
<tr>
<td><strong>Benton visual retention test</strong></td>
<td>5.7 (3.4)</td>
<td>5.8 (1.7)</td>
</tr>
<tr>
<td><strong>Token test</strong></td>
<td>19.2 (4.3)</td>
<td>21.0 (2.7)</td>
</tr>
<tr>
<td><strong>Boston naming test</strong></td>
<td>14.5 (2.9)</td>
<td>13.6 (5.7)</td>
</tr>
<tr>
<td><strong>Wisconsin card sorting test—categories</strong></td>
<td>3.1 (2.4)</td>
<td>2.3 (1.5)</td>
</tr>
<tr>
<td><strong>Wisconsin card sorting test—perseverations</strong></td>
<td>15.8 (14.1)</td>
<td>19.7 (9.8)</td>
</tr>
<tr>
<td><strong>Trail making test part A—time (s)</strong></td>
<td>85.5 (35.0)</td>
<td>70.1 (31.0)</td>
</tr>
<tr>
<td><strong>Trail making test part B—number of errors</strong></td>
<td>0.4 (1.1)</td>
<td>0.2 (0.7)</td>
</tr>
<tr>
<td><strong>Trail making test part B—time (s)</strong></td>
<td>307 (189)</td>
<td>259 (172)</td>
</tr>
<tr>
<td><strong>Trail making test part B—number of errors</strong></td>
<td>4.1 (4.1)</td>
<td>3.2 (4.3)</td>
</tr>
<tr>
<td><strong>Controlled word association test</strong></td>
<td>31.2 (5.5)</td>
<td>25.8 (8.0)</td>
</tr>
<tr>
<td><strong>Raven’s progressive matrices—percentile</strong></td>
<td>45.5 (40.9)</td>
<td>53.1 (26.5)</td>
</tr>
<tr>
<td><strong>Digit span—forward</strong></td>
<td>5.1 (0.0)</td>
<td>5.7 (0.8)</td>
</tr>
<tr>
<td><strong>Digit span—backward</strong></td>
<td>2.6 (1.4)</td>
<td>5.8 (1.1)</td>
</tr>
<tr>
<td><strong>Ideomotor—apraxia</strong></td>
<td>58.4 (2.0)</td>
<td>56.8 (6.8)</td>
</tr>
<tr>
<td><strong>Block design</strong></td>
<td>3.7 (2.6)</td>
<td>5.1 (1.4)</td>
</tr>
<tr>
<td><strong>Analogies</strong></td>
<td>107 (6.8)</td>
<td>81 (5.4)</td>
</tr>
<tr>
<td><strong>Wechsler adult intelligence scale—total IQ</strong></td>
<td>83.6 (14.6)</td>
<td>87.0 (12.8)</td>
</tr>
</tbody>
</table>

*Figures in parentheses are SDs.*
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Table 3 Measurement of regional cerebral blood flow

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Control group</th>
<th>Alzheimer's group</th>
<th>Frontal lobe dementia group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal orbital</td>
<td>81.2 (6.9)</td>
<td>76.1 (13.7)</td>
<td>58.2 (11.1)</td>
</tr>
<tr>
<td>Frontal dorsolateral</td>
<td>85.8 (4.4)</td>
<td>81.8 (7.7)</td>
<td>71.4 (9.2)</td>
</tr>
<tr>
<td>Temporal anterior</td>
<td>91.7 (4.4)</td>
<td>85.3 (5.5)</td>
<td>74.9 (5.8)</td>
</tr>
<tr>
<td>Temporal dorsal</td>
<td>90.9 (4.5)</td>
<td>79.4 (5.2)</td>
<td>78.5 (4.9)</td>
</tr>
<tr>
<td>Parietal</td>
<td>91.7 (6.7)</td>
<td>82.8 (7.0)</td>
<td>82.4 (7.3)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>93.0 (6.6)</td>
<td>91.3 (8.5)</td>
<td>80.6 (8.9)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>86.2 (6.9)</td>
<td>84.8 (7.6)</td>
<td>79.4 (5.4)</td>
</tr>
</tbody>
</table>

Figures in parentheses are SDs.

differences were found in the remaining brain areas.

To test the relative importance of orbital vs. dorsal frontal blood flow changes in the production of disinhibition, we carried out a three way ANOVA with repeated measures (factor 1: group (Alzheimer's vs. frontal lobe dementia), factor 2: region (frontal dorsal vs. frontal orbital), and factor 3: side (left vs. right)). We found a significant group effect (patients with frontal lobe dementia had an overall significantly lower blood flow in the frontal lobes) (F (1,14) = 8.95, p = 0.009), and a nearly significant group x region interaction (F (1,14) = 3.98, p = 0.06). Patients with frontal lobe dementia had significantly lower blood flow in the frontal orbital cortex than in the frontal dorsal cortex (p = 0.0002) (fig 1). On the other hand, there were no significant differences between these cortical regions in the Alzheimer's group (fig 2).

To test the relative importance of anterior vs. dorsal temporal blood flow changes in the production of disinhibition we carried out a three way ANOVA with repeated measures, in which the region factor was anterior vs. dorsal temporal blood flow. There was a significant group effect (patients with frontal lobe dementia had an overall significantly lower blood flow in the temporal lobe; F (1,14) = 8.68, p = 0.01), as well as a significant group x region interaction (F(1,14) = 11.7, p = 0.004). Whereas patients with Alzheimer's and frontal lobe dementia had a comparable blood flow in the dorsal temporal cortex

Figure 1 Top left: CT scan of a patient with frontal lobe dementia showing mild prominence of cortical sulci. Top right: SPECT scan showing frontal lobe blood flow deficits in the axial, sagittal, and coronal planes. Bottom right: three dimensional rendering of the SPECT study showing the frontal lobe perfusion defect but no posterior brain blood flow changes.
(p = 0.63), patients with frontal lobe dementia had a significantly lower blood flow in the anterior temporal cortex (p = 0.0001).

Discussion

The main finding of the present study was that patients with mild dementia and a disinhibition syndrome had significant blood flow deficits in specific brain areas. When compared with controls, these changes primarily involved the frontal and temporal lobes and the basal ganglia. When compared with patients with mild dementia but no disinhibited behaviour (the Alzheimer’s group), patients with frontal lobe dementia showed significant blood flow deficits involving primarily the orbital frontal cortex and the anterior temporal cortex.

Before further discussion, some limitations of our study should be pointed out. One important methodological problem is the lack of valid criteria for the diagnosis of frontal lobe dementia or Pick’s disease. We tried to deal with this limitation by using the Gustafson and Nilsson scale for Alzheimer and Pick’s disease. This is a clinical scale that rates symptoms of intellectual decline, disinhibition, and motor signs, and was found to be valid for the diagnosis of pathologically established Alzheimer’s and Pick’s diseases. Moreover, to include patients with the highest probability of having Alzheimer’s or Pick’s disease, we used a high cut off score on this scale. Although we used the terms frontal lobe dementia or Pick’s disease for the same group of patients, some but not all patients with frontal lobe dementia have been reported to have Pick’s disease, and not all patients with Pick’s disease have the clinical syndrome of frontal lobe dementia. Regardless of the ultimate cause, what we have tried to examine
was disinhibition, a behaviour tightly linked to both frontal lobe dementia and Pick’s disease. Thus we are showing significant differences in cerebral blood flow between mildly demented patients with and without disinhibited behaviour, regardless of the final neuropathological diagnosis. Another limitation is our uncertainty about the validity of some of these findings. We did not rescans the patients at follow up or in a different setting (for example, conducting an attention task). Thus it is possible that our present findings are only valid for one stage of the disorder and only in the environment where the patients were tested.

Neary et al described a group of patients with mild dementia and striking behavioural changes, such as unconcern, inappropriate jocularity, distractibility, loss of social awareness, loss of emotional empathy, hyperorality, and obsessiveness. They termed this entity frontal lobe dementia, emphasising the topography of pathology rather than its pathogenesis, and speculated that frontal lobe dementia may be one type of Pick’s disease. The same authors have recently reported four patients with frontal lobe dementia and motor neuron disease, all of whom showed important personality changes such as impulsivity, unconcern, breakdown in social conduct, changes in eating habits, and stereotyped and perseverative behaviour. Neuropathological examination showed extensive atrophy involving the frontal lobes, anterior temporal cortex, insula, and the anterior cingulate. Microscopical examination showed neuropathological changes consistent with progressive subcortical gliosis. Only a few studies have empirically examined the presence of changes in cerebral blood flow in patients with frontal lobe dementia. Neary et al carried out SPECT in patients with either Alzheimer’s disease, frontal lobe dementia, or progressive supranuclear palsy. Whereas they found blood flow deficits in posterior brain areas in patients with Alzheimer’s disease, patients with either frontal lobe dementia, or progressive supranuclear palsy showed significant blood flow deficits in anterior brain areas. Miller et al have recently reported frontal and anterior temporal hypoperfusion as well as relative sparing of parietal and occipital blood flow in patients with frontal lobe dementia compared with normal controls. Although Miller et al obtained quantitative information, the diagnosis of frontal lobe dementia was only established after patients showed both deficits on frontal lobe related cognitive tasks and selective hypoperfusion of the frontal lobes.

Studies with PET in patients with either frontal lobe dementia or Pick’s disease showed similar findings. Kumar et al have recently reported three patients with dementia and frontal lobe behavioural changes such as sexual disinhibition, irritability, laughing bursts, and loud speech that showed metabolic deficits bilaterally in the orbitofrontal, anterior cingulate, and temporal lobes, with relative sparing of the parietal lobes. Significant frontal lobe hypometabolism was also reported in patients with Alzheimer’s disease and agitation, inappropriate behaviour, and personality changes, and patients with histologically established Pick’s disease.

In the present study we included patients with either Alzheimer’s disease or frontal lobe dementia with mild dementia as well as an age matched control group. Our previous study of frontal lobe dementia met stringent criteria for disinhibition, and neither the presence of deficits in frontal lobe related tasks nor the pattern of SPECT abnormalities were considered as inclusion criteria. Our study fully replicates that of Neary et al in finding frontal and anterior temporal blood flow deficits in patients with frontal lobe dementia.

The question that now arises is how these findings may be explained? Perhaps the most fundamental issue is whether these decreases in regional cerebral blood flow are a cause of the disinhibition, a consequence, or are related to a third independent factor. Although we cannot fully answer this question, the fact that the decreased cerebral blood flow occurred in areas associated with disinhibited behaviour in patients with structural brain injury suggests that dysfunction of these brain areas (as shown by diminished cerebral blood flow) may lead to these behavioural changes.

Whereas the disinhibited behaviour of frontal lobe dementia may be secondary to orbitofrontal and anterior temporal pathology, other dementing disorders, such as progressive subcortical gliosis, Lewy body disease, Pick’s disease, and even Alzheimer’s disease, may show disinhibited behaviour provided there is concomitant dysfunction of these cortical regions. In 1941, Kennard et al showed that lesions of the orbitofrontal cortex that extended into the caudate nucleus invariably produced locomotor hyperactivity. King and Steikis reported that posterior orbitofrontal resections in primates produced imported hyperorality, coprophagia, pacing and circling, irritability, inappropriate facial expressions, and vocalisations, which resulted in “social disintegration”. These changes were not present in primates with frontal dorsolateral resections. Based on these findings they suggested that bilateral lesions of the orbitofrontal cortex or the anterior temporal lobe critically disrupt behaviours of social bonding. In conclusion, we have replicated previous findings of frontal lobe hypoperfusion in patients with dementia and disinhibited behaviour. The largest blood flow changes were found in the orbitofrontal and anterior temporal areas compared with dorsal frontal and dorsal temporal regions. These findings suggest that disinhibited behaviour in mildly demented patients may result from dorsal neocortical and limbic release from cortical ventral control. As beautifully expressed by Bianchi in 1922 “the higher sentiments . . ., above all, . . . disappear after mutilation of the frontal areas, whilst the primitive emotions, . . . especially . . . irrational, . . . remain, sometimes even intensive . . .”
This work was partially supported by grants from the Instituto Di Tella and the Sandlot Foundation. We thank Dr Juan Goldar for his many valuable suggestions.


34 Kertesz A, Spencer S, Fountain G. Lesions of the orbital cortex of the frontal lobe which invade the caudate nucleus produce locomotor hyperactivity. J Neurophysiol 1941; 4:512–24.
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