Relation of anosognosia to frontal lobe dysfunction in Alzheimer’s disease

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Abstract
A self-rating scale of memory functions was administered to 24 non-depressed patients with probable Alzheimer’s disease, divided into two groups according to the overall severity of dementia (mild, mini-mental state (MMS) >21; moderate, MMS between 10 and 20). These groups did not significantly differ in their self-rating of memory functions. The same questionnaire was submitted to a member of each patient’s family, who had to rate the patient’s memory. An “anosognosia score” was defined as the difference between patient’s and family’s ratings. This score was highly variable, and covered, in the two groups, the full range between complete awareness of deficits and total anosognosia. Correlations between the anosognosia score and several neuropsychological data were searched for. No significant correlation was found with either the Wechsler memory scale, the MMS, or linguistic abilities and gestures. In contrast, this score was highly correlated with the “frontal score”, defined as the sum of scores on the Wisconsin card sorting test (WCST), verbal fluency, Luria’s graphic series, and “frontal behaviours” (prehension, utilisation, imitation behaviours, inertia, indifference). Among these tests of executive functions, the highest correlation with the anosognosia score was obtained on the WCST. This suggests that anosognosia in Alzheimer’s disease is not related to the degree of cognitive deterioration but results, at least in part, from frontal dysfunction.

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Anosognosia has been noticed in various neurological disorders such as hemiplegia, hemianopia, and aphasias (see McGlynn and Schacter for a review). As it is most often associated with deficits of the left part of the body, anosognosia has been postulated to result from a specific dysfunction of the right hemisphere. It is clear, however, that different forms of unawareness of deficits must be distinguished; for example, anosognosia has also been reported for memory deficits in different kinds of patients with amnesia and dementia at different stages of their disease. At a clinical level, if patients with Alzheimer’s disease are generally aware of and anxious about their memory problems in the earliest stages of their disease (“forgetfulness phase”), they seem to progressively lose insight and to rate their memory impairment less severely as the disease progresses and memory functions deteriorate.

Few attempts have been made to investigate awareness of memory deficits in patients with dementia. Schacter et al. showed that patients with Alzheimer’s disease grossly overpredicted their performance on a verbal learning task compared with control subjects. Neary et al. found that different subgroups of patients with Alzheimer’s disease showed different levels of awareness of deficits, suggesting a considerable degree of variability of anosognosia in this disease.

Relatively little is known about anosognosia in Alzheimer’s disease, its relations with the stages of the disease, and its underlying mechanisms. Is it significantly related to memory loss (that is, do patients forget their deficits?), to an overall decline in intellectual functioning, or to a more specific cognitive disturbance?

To answer these questions, we investigated awareness of memory deficits in patients with Alzheimer’s disease by: (a) analysing self-rating of memory functioning by patients in different stages of the disease; (b) by comparing their self-ratings with ratings by relatives, the difference being indicative about patients’ awareness of deficits; and (c) by searching for relations between anosognosia and several indices of cognitive functions, such as global deterioration scores, memory performance, instrumental activities, and executive functions.

Patients and methods

PATIENTS
Twenty-four patients with probable Alzheimer’s disease, according to the NINCDS-ADRDA criteria, were included in this study. They were recruited by the memory clinic of the Hôpital de la Salpêtrière, where they were submitted to neuropsychological, neurological, and psychiatric examination before inclusion. They were divided into two subgroups as a function of the severity of their dementia, assessed with the mini-mental state (MMS) evaluation: 13 patients with mild dementia (MMS = 21 or higher) and 11 with moderate dementia (MMS <21) (table 1). All patients were normal at neurological examination and serum analyses.
(including thyroid hormones, vitamin B-12, folates, and syphilis serology (VDRL-TPHA), and the ischaemic score14 were not higher than four in any patient. Computed tomography or MRI, or both, showed mild atrophy without any further significant abnormalities or focal lesions (exclusion criterion). Depression was assessed with the Montgomery and Asberg rating scale11 (MADRS); a French version of this scale has been validated and compared with the Hamilton scale in subjects up to 69 years of age, and it was concluded that the two scales had the same sensitivity; this scale has already been used with patients with mild to moderate dementia.15 The clinical diagnosis was based, after discussion between the psychiatrist and patients’ spouse or relatives, on a psychiatric interview guided by the DSM III-R criteria. Informed consent was obtained after the nature of the procedure had been explained.

METHODS

Self-rating of memory dysfunction

All patients were given, before any neuropsychological testing, a self-rating questionnaire adapted from Squire and Zouzounis.14 Patients had to respond to 20 items that asked them to rate their memory abilities, by comparing their current ability level to “how it was five years ago”. Ratings were made on a nine-point scale from −4 through 0 to +4, so that the total scores ranged from −80 to +80. This questionnaire investigated different aspects of memory function (table 2). Scores were calculated by adding the ratings of items which respectively assessed global evaluation (two items), recall (four items), retention (four items), remote memory for personal events (three items), attention (five items), and metamemory (two items). Self-rating profiles were obtained when transformation of these subscores into percentages of the maximum possible scores. The patients were guided by a staff member who, for each item, first asked him (her) if he or she was “worse than before, the same as before or better than before”; whenever the answer was “worse” or “better”, the psychologist reminded that ±1 meant “a little bit”, ±2 “moderately” ±3 “markedly”, and ±4 meant “better (or worse) than ever”. Such a procedure was rather time consuming, but allowed us to control that all patients reasonably understood the task.

The same rating questionnaire (in which “I” was replaced by “he” or “she”) was submitted to the patients’ relatives (in most instances spouse or children living with the patient) during the same session, with a different staff member. The difference between patient’s total self-rating score and rating by the family member defined the anosognosia score. The largest was the difference, the most severe was anosognosia. Given the range of scoring, a difference of 3 points was considered as revealing severe anosognosia, whereas any score less than +5 corresponded to an awareness of deficits.

Complementary tests

All patients were submitted to a standard neuropsychological battery including: the MMS; the Wechsler memory scale with delayed testing for logical memory, visual memory, and paired associates; naming of 10 pictures of the Boston naming test, across all levels of difficulty; imitation of unimanual and binominal meaningless gestures such as interlaced rings; copy of bidimensional drawings; and block design. Scores on these last three tests were combined into a “visuospatial score”.

Executive functions were evaluated in 15 patients with the simplified version of the Wisconsin card sorting test (WCST),14 a verbal fluency test (names of animals and words beginning with “M” in one minute), and a graphic series requiring alternation between open squares and open triangles.17 Behavioural abnormalities (preoccupation, imitation, utilization behaviours, inertia, indifference) observed in patients with fronto-temporal lesions18 were also assessed separately on
five-point scales. From the performance at these tasks, a “frontal score” was defined.18

Statistical analyses
The interrelations between the anosognosia score and the performance on cognitive and memory tests, MADRS, and tests of executive functions were analysed by linear correlations. Comparisons between groups of patients were calculated by analysis of variance.

Results
SELF-RATING OF MEMORY FUNCTIONS AND SEVERITY OF DEMENTIA
The two groups of patients (table 1) differed significantly in terms of global deterioration (MMS: F [1, 22] = 46·05; p < 0·0001) and degree of memory impairment (Wechsler memory scale: F [1, 22] = 5·59; p = 0·027), but not for depression (MADRS: F [1, 22] = 0·59; p = 0·45). Despite these differences, they showed similar profiles in their self-ratings of memory functions (fig 1), with the most severe self-rating scores relating to the global evaluation of memory abilities, and the less severe relating to attention and remote memory for personal events. Patients with moderate dementia tended to give more severe ratings than patients in the other group, but the difference did not reach the statistical significance for the overall rating scores (p = 0·35) and for the subscores of global evaluation (p = 0·25), attention (p = 0·90), retention (p = 0·57), and remote memory for personal events (p = 0·47). This difference did not reach significance for the recall subscore (F [1, 22] = 3·17; p = 0·088), but was significant for the subscore for metamemory (F [1, 22] = 5·40; p = 0·029). Finally, there was no correlation between the severity of self-rating and either performance at the standard neuropsychological tests or depression.

ANOSOGNOSIA SCORES AND COGNITIVE DETERIORATION
An anosognosia score was available for 22 patients (11 in each group). These scores were highly variable among patients and covered the full range between complete anosognosia (score = +61) and “hyperognosia”—that is, overestimation of the deficits by the patients compared with family members (score = −30). The distributions of these scores did not differ between patients with mild or moderate dementia: in the two groups, three patients were fully aware of their memory deficits (anosognosia score < +5) and six patients with mild dementia and five with moderate dementia showed severe anosognosia (anosognosia score >25).

Overall self-rating scores in the two groups of patients and rating scores by their relatives were submitted to an analysis of variance with repeated measures. Patients with moderate dementia tended to rate their memory functions more severely than patients in the other group, but the difference was not significant (F [1, 20] = 0·90; p = 0·35). The same tendency was observed with ratings of relatives (F [1, 20] = 2·24; p = 0·15). The differences between ratings by patients and by relatives were of the same order, however, (17·36 points for the group with moderate dementia v 20·36 for patients in the other group; table 3).

No significant interaction was found between degree of cognitive impairment (groups) and rater (patient v relative: F [1, 20] = 0·074; p = 0·78).

No significant correlation was found between the anosognosia scores and the degree of global cognitive deterioration assessed by the MMS (r = 0·29; p = 0·19), memory impairment assessed by the Wechsler memory scale (r = 0·36; p = 0·11), linguistic abilities (r = 0·21; p = 0·44), nor the visuospatial score (imitation of gestures, copy of drawings, block design; r = 0·40; p = 0·10).

ANOSOGNOSIA AND TESTS OF EXECUTIVE FUNCTIONS
As stated earlier, 15 patients were also submitted to tests of executive functions; they were highly representative of the larger group as their mean (SD) MMS score was 20·6 (5·0) (range 13–26) and their mean (SD) Wechsler memory score was 78·5 (12·0) (range 58–99). With respect to executive functions, they displayed various degrees of impairment. On the WCST four had a normal performance and achieved four (three patients) or five (one patient) categories (normative data for age-matched controls: 4 (0·8) categories); one patient achieved three categories, and the other 10 only two or less. Verbal fluency was preserved in only three patients (normative data: 27 (5)); but was moderately to severely reduced in the others (range 19–8). In the same way three patients were normal on the graphic series (normative data: 9/10 (0·5)); the others ranged from 6 to 0/10. Finally, all patients but two showed mild to moderate behavioural abnormalities (normative data: 20/20 (0)), ranging from...
Anosognosia with patients and their relatives. The rating 20-82 (−3 to +41) of patients’ scores (mild dementia: −5 to 10; moderate dementia: −10 to 20) are within the range of normal age-matched controls (normative data: 54/60 (6)); the other scores ranged from 38/60 to 19/60. The anosognosia score was highly correlated with the frontal score (r = 0.70; p = 0.0038) (fig 2). Among tests of executive functions the highest correlation appeared with the WCST (r = 0.72; p = 0.0025).

Discussion
This study showed similar self-rating profiles in two groups of patients with Alzheimer’s disease with different degrees of cognitive deterioration (mild or moderate dementia); these profiles were characterised by relatively less severe ratings for items tapping attentional abilities and remote memory for personal events, and were close to those already described by Squire and Zouzounis for several groups of patients with memory disorders, namely patients after electroconvulsive treatment, patients with non-Korsakoff amnesic syndrome, and patients with Korsakoff syndrome. This pattern corresponds with the common observation that attentional abilities and remote memory for personal events are relatively less impaired than other domains of memory and cognition in the early stages of Alzheimer’s disease. It suggests, as a whole, that self-rating of memory deficits by these patients with Alzheimer’s disease can be considered as still fairly accurate.

Two patients had a frontal score which can be considered within the range of normal age-matched controls (normative data: 54/60 (6)); the other scores ranged from 38/60 to 19/60. The anosognosia score was highly correlated with the frontal score (r = 0.70; p = 0.0038) (fig 2). Among tests of executive functions the highest correlation appeared with the WCST (r = 0.72; p = 0.0025).

Anosognosia must therefore be considered as part of Alzheimer’s disease, together with other cognitive and behavioural disorders. Moreover, the variability of anosognosia contributes to the heterogeneity of the disease. If so, to which processes is it related? Correlational analyses showed that anosognosia was not related to the severity of dementia, memory, linguistic, or visuospatial disorders. In contrast, anosognosia scores were highly correlated with scores on tests of executive functions. These tests have been shown to be sensitive to a frontal lobe dysfunction: the WCST, lexical fluency tasks, graphic series, and the searching of behavioural disorders (utilisation and imitation behaviours). These scores are also related to frontal dysfunction in degenerative diseases of the brain. Thus this strong correlation suggests that anosognosia is related to frontal lobe dysfunction, a hypothesis which has received support from a study of PET scans which showed some parallelism between frontal hypometabolism and anosognosia.

Evidence from the domain of amnesia is consistent with this hypothesis. Numerous clinical observations have shown little awareness of (and concern for) memory deficits in patients with Korsakoff’s syndrome, who also show frontal lobe-like symptomatology. Additionally, patients with damage in the frontal regions after penetrating brain injury, or ruptured aneurysms of the anterior communicating artery, are known to be anosognosic for their memory deficits, in contrast with patients with amnesia without frontal signs, such as NA or HM, who have been reported as aware of their deficits. In the domain of dementias, several workers have argued on the basis of clinical rating scales that early loss of insight is useful in differentiating Alzheimer’s disease from Pick’s disease, with earlier loss in the latter. Interestingly, the two dementias have generally been associated.

<table>
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<th>Table 3 Rating of memory functions by patients with Alzheimer’s disease and their relatives, and anosognosia score</th>
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<tr>
<td>Mean (range) score for patients with mild dementia</td>
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<td>Patients’ rating</td>
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<td>Relatives’ rating</td>
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A score of zero means that memory functions are considered to be exactly the same as they were “five years ago”; negative scores correspond to an estimated enhancement, positive scores to an impairment. The anosognosia mean scores (differences between ratings by patients and ratings by their relatives) are similar in the two groups; they cover the full range from complete anosognosia (positive differences) to “hyperognosia” (negative differences).
with signs of frontal lobe dysfunction,\(^8\) which is typically more pronounced in early Pick's disease than in early Alzheimer's disease.

The hypothesis according to which anosognosia in patients with amnesia is linked with frontal dysfunction has found additional support from studies using questionnaire methods to assess subjective memory impairment.\(^9\) This has been studied by Squire and Zouzounis\(^14\) using the same self-rating questionnaire; they showed that patients with Korsakoff's syndrome tended to report less severe memory impairment than six other non-Korsakoff patients with amnesia. McGlynn et al.\(^10\) compared two patients, one with frontal lesions and another with restricted left temporal lesions, and also found, by using several rating questionnaires, that unawareness of memory deficits was related to frontal damage.

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