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Cognitive and functional neuroimaging correlates for anosognosia in Mild Cognitive Impairment and Alzheimer's disease

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SUMMARY

Objectives To investigate the correlation between anosognosia and behavioural symptoms, performance on executive tests, and frontal cortex regional cerebral blood flow (rCBF) in patients with 'amnestic mild cognitive impairment' (MCI) and mild Alzheimer's disease (AD).

Methods From a prospective Memory Clinic cohort including consecutively referred patients, age 60 years or above, and with MMSE score 20 or above, 36 patients with AD and 30 with MCI were included in this study. Anosognosia was assessed using a categorical scale and discrepancy scores between patients' and relatives' reports on a 20-item Memory Questionnaire (MQ). Behavioural symptoms were assessed with Frontal Behavioural Inventory (FBI). Executive functions were examined with a range of neuropsychological tests. Tc99m-HMPAO SPECT was obtained in an unselected sample of 55 of the 66 patients, and rCBF was analysed in six cortical frontal regions.

Results Insight was equally impaired in the two patient groups. A significant correlation was found between impaired awareness and dementia severity (MMSE). Discrepancy-scores on the MQ were significantly correlated to scores on FBI and to rCBF in the right inferior frontal gyrus, but not to executive tests. The groups classified by the categorical ratings 'full', 'shallow' and 'no' awareness were not characterized by differences in behavioural symptoms, executive performance or frontal rCBF.

Conclusions Impaired awareness is associated with behavioural symptoms and may reflect functional impairment in the right inferior frontal cortex.

KEY WORDS — awareness; anosognosia; insight; Alzheimer's disease; Mild Cognitive Impairment

INTRODUCTION

Lack of insight of cognitive and functional deficits is a striking symptom among many neurological patients (McGlynn and Schacter, 1989). From clinical observations and scientific studies differences in the presentation of anosognosia have been found between patients with different disorders and between individual patients with the same disease. Anosognosia is not a unitary construct (Vasterling *et al.*, 1995; Markova and Berrios, 2001) and has different clinical manifestations (Markova and Berrios, 1995). Different terms have been used to describe the phenomenon, e.g. anosognosia, unawareness of deficits and lack of insight (McGlynn and Schacter, 1989). These concepts are used synonymously in this paper.

In Alzheimer's disease (AD) impaired awareness is a common symptom even in the earliest stages (Starkstein *et al.*, 1997a; Harwood *et al.*, 2000), and the frequency of the symptom increases with disease

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progression (Sevush, 1999). Patients with Mild Cognitive Impairment (MCI, of the amnestic type) may have impaired insight to the same degree as patients with mild AD (Vogel *et al.*, 2004).

Influential theories have suggested that the prefrontal cortex (and frontal connectivity) play an important role in anosognosia (Stuss and Benson, 1986; McGlynn and Schacter, 1989; Damasio, 1994). In some studies on cognitive deficits in AD, correlations between impaired awareness and neuropsychological tests of executive dysfunction have been found (Lopez *et al.*, 1994; Michon *et al.*, 1994; Ott *et al.*, 1996a). Further, previous studies have found frontal hypoperfusion in patients with anosognosia (Reed *et al.*, 1993; Starkstein *et al.*, 1995; Derouesne *et al.*, 1999). Some studies have found other cognitive and anatomical deficits than executive functions and frontal hypoperfusion to be associated with impaired insight in AD patients. These findings include right sided parietal/occipital dysfunction (Ott *et al.*, 1996a; Ott *et al.*, 1996b), deficits in procedural memory (Starkstein *et al.*, 1997b), and increased number of intrusions (Reed *et al.*, 1993; Dalla Barba *et al.*, 1995).

Divergent results may be due to differences in the assessment and definition of awareness (Markova and Berrios, 2001; Clare *et al.*, 2002), and different studies have used different methodological approaches. The specificity of neuropsychological tests assumed to tap frontal lobe functioning is questionable (Stuss, 1993; Kessler *et al.*, 2000), and conclusions based on cognitive measures only may be misleading. To our knowledge only two previous studies (Starkstein *et al.*, 1995; Derouesne *et al.*, 1999) have assessed both cerebral perfusion and executive performance correlates for anosognosia in AD. Since these studies found inconsistent results the cognitive and anatomical basis for impaired awareness needs further investigation.

The objective of this study was to assess if neuropsychological performance and regional cerebral blood flow (rCBF) are correlated to unawareness of cognitive deficits in patients with 'amnestic MCI' and mild AD. Specifically, we wished to address the hypothesis that anosognosia is correlated to executive functions, behavioural symptoms and regional cerebral blood flow in specific cortical frontal regions.

METHODS

Subjects

The patient group and the research program have been described previously (Vogel *et al.*, 2004). Briefly, patients were recruited from a prospective research program at the Copenhagen University Hospital Memory Clinic. The program included consecutively all newly referred patients, aged 60 years or above, with a score of 20 or above on the Mini Mental State Examination (MMSE).

A total of 105 patients completed the study program by the end of the inclusion period for this project. Thirty-six patients met the criteria for AD, and 30 met the criteria for MCI. AD was defined from the NINCDS-ADRDA criteria for probable AD (McKhann *et al.*, 1984). All AD patients had mild AD defined by the inclusion criteria of a MMSE score of 20 or above. MCI was defined by an operationalization of the Petersen *et al.* (2001) criteria. Based on a comprehensive neuropsychological test program episodic memory was the only cognitive domain with significant impairment in our MCI group. Thus, the criteria for MCI included an anterograde memory domain score on neuropsychological testing lower than -2 SD from age-corrected norms. Further, other cognitive domain scores were higher than – 2 SD. All MCI patients had normal basic ADL functions and a score on the Clinical Dementia Rating (CDR) of 0.5. Patients with a known or suspected cause for memory impairment, e.g. alcohol abuse, depression or anxiety disorder were excluded in order to include a homogenous group of patients with pure amnestic MCI due to suspected neurodegenerative disorder. Other exclusion criteria were a history of schizophrenia, more than one episode of depression, obsessive–compulsive disorder, abuse of alcohol and drugs, head trauma or severe concomitant disease which were found disabling for the study program.

A control group of healthy elderly volunteers were recruited by newspaper advertisement, and 33 persons were selected from a cohort of 50 persons to match the two patient groups for age, education and premorbid intelligence. Exclusion criteria for healthy volunteers were a history of neurological or psychiatric disease, abuse of alcohol or drugs (including use of sedatives), head trauma, a family history of mental illness in first-degree relatives or an abnormal performance on the basic assessment. The basic assessment included a physical and neurological examination (including cognitive screening-MMSE), a screening for psychiatric symptoms with the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) and a neuropsychological examination. Both patients and controls gave informed consent to participate in the study.

The clinical assessment of the patients included neurological and physical examination, laboratory screening tests, electrocardiography, cranial magnetic

resonance imaging, single photon emission computed tomography (SPECT), psychiatric evaluation and a neuropsychological examination. MMSE and CDR were performed in all patients. A diagnostic classification concerning cognitive profile, primary diagnosis and concomitant conditions was established by the multidisciplinary staff of the Memory Clinic after completion of the study program.

Assessment of awareness

Memory questionnaire. Patients and controls were given a self-rating questionnaire described by Michon *et al.* (1994). The questionnaire consists of 20 items on memory abilities. Parallel versions were filled out by the patients and the relatives independently. The patient/relative was asked to evaluate the current memory abilities of the patient as compared to 5 years ago. For each item ratings were made on a nine-point scale ranging from -4 through 0 to $+4$, giving a possible total score range of -80 to $+80$. The difference between the patient's and the relative's score was used as a measure for awareness.

Anosognosia Rating Scale. As described previously (Vogel *et al.*, 2004) the categorical four-point scale from Reed *et al.* (1993) was used. This scale has high inter-rater reliability (Reed *et al.*, 1993), and it corresponds well with the Memory Questionnaire discrepancy score (Vogel *et al.*, 2004). An experienced clinical neuropsychologist rated the level of awareness based on an overall impression after the neuropsychological assessment and an interview with the patient and caregiver. Awareness was classified into the following categories: 'Full awareness', 'shallow awareness', 'no awareness', and 'denies impairment'. For a detailed description see (Reed *et al.*, 1993). The rater was unaware of the results of other awareness assessments.

Neuropsychological battery. Neuropsychological testing of patients, including the assessment of awareness, was performed in two sessions on different days. The first session included the Danish Mental Status Test (DMST), which is a test battery with 28 subtests, the majority being modifications of internationally well-known tests. The tests are grouped in six composite cognitive domains: memory, attention, abstraction, language, visual perception and visuo-construction. (Waldemar *et al.*, 1994). Danish Adult Reading Test (DART), a Danish version of the National Adult Reading Test (Nelson and O'Connell, 1978) was used to assess the level of the premorbid intelligence. The Boston Naming Test was applied in the majority of patients. The results from the first session were the primary source for the cognitive profile.

The second session was conducted by a different neuropsychologist who was unaware of the results from the first test session. At the second visit additional testing included Category Cued Recall (Buschke *et al.*, 1997).

To assess executive functions the following tests were applied at the second test-session:

- *Stroop Test* (Stroop, 1935). Both time (seconds) and number of errors committed were noted for the congruent and the incongruent version of the test. A maximum score of 360 seconds was applied if the patients attempted to perform the test, but failed to complete the task.
- *Trail Making Test* (Reitan, 1958). Parts A and B were applied. If the patient attempted but failed to perform part B a maximum score of 500 seconds was used.
- *Wisconsin Card Sorting Test (WCST)* (Nelson, 1976). The number of obtained sets (six consecutive correct responses constitute a set) and the number of incorrect responses were used for analysis. Only very few perseveratory answers were given, and therefore not used for analysis. Some of the patients (15) failed to complete the WCST, most often because they refused to perform the test. These cases were entered as missing.
- *Design Fluency* (Regard *et al.*, 1982). Numbers of correct and perseverative answers were noted. Three minutes allowed.
- *Verbal Fluency (S-words and animals)* [applied at the first visit]. One minute allowed for each category.

To assess behavioural symptoms typically associated with lesions in the frontal lobes we applied

- *Frontal Behavioral Inventory (FBI)* (Kertesz, 1998). This questionnaire measuring behavioural changes was filled out by the neuropsychologist on basis of an interview with the caregiver.

SPECT. SPECT measures of rCBF were performed in an unselected sample of 30 AD patients and 25 patients with amnestic MCI. High resolution SPECT was obtained on two different scanners: (1) Three-slice brain dedicated Tomomatic 564 SPECT camera (Tomomatic, Hellerup, Denmark) with a HR collimator ($n = 27$) and (2) three-headed IRIX SPECT camera (Phillips, Andover, MA, USA) with a LEUHR-PAR collimator ($n = 28$). Scanning procedures were slightly different with the two scanners:

(1) Tomomatic 564 Camera: with the patient in a dark and quiet room, a dose of 800–1000 MBq technetium ^{99m}Tc-d,1-hexamtehyl propylenamine oxime, HMPAO (Amersham International, London) was injected intravenously. Twenty minutes after intravenous injection of the tracer, a 27 min 3D scan was performed in a 64×64 matrix mode, and slices with a resolution (FWHM) of 9–10 mm (image plane and slice thickness) were reconstructed using filtered back projection. Three slices were obtained simultaneously in nine recordings, yielding 27 consecutive slices parallel to the orbitomeatal plane.
(2) IRIX SPECT Camera: with the patient in a quiet and dimly lit room, a dose of 800–1000 MBq ^{99m}Tc,Stabile-HMPAO (Amersham International, London) was injected intravenously. Ninety minutes after intravenous injection of the tracer, a 27 min 3D scan was performed in a 128×128 matrix mode, and 15 slices, with a resolution of (FWHM) 7×7 mm (image plane and slice thickness) were iteratively reconstructed using low pass filtering.

For analysis of the ^{99m}Tc,HMPAO/Stabile-HMPAO regional cerebral blood flow, three regions of interest (ROIs) were selected for the study: Orbitofrontal cortex, middle frontal gyrus and inferior frontal gyrus. We used the anatomical atlas of the brain by Aquilonius and Eckernäs, (Aquilonious and Eckernäs, 1980) which depicts the brain in 10 slices parallel to the canthomeatal plane, separated by $\sim$10 mm and located from 15 to 105 mm below the vertex of the atlas brain. The definition of ROIs according to the atlas has previously been described in detail (Waldemar *et al.*, 1991). In brief, the different regions were identified according to position on one or more slices from 1 to 10. Because rCBF measurements were performed using two different scanners, additional scaling of the rCBF values was necessary. In each subject we determined the rCBF deviation from the control mean of that particular scanner by the following equation:

$$\text{Deviation of patient rCBF} = \frac{ROI_{\text{patient}}/Cbl_{\text{patient}}}{\bar{x}(ROI_{\text{control}}/Cbl_{\text{control}})}$$

where $\text{ROI}_{\text{patient}}$ is the rCBF in the specific ROI and $\text{Cbl}_{\text{patient}}$ is the rCBF in cerebellum in the patient, and $\bar{x}(ROI_{\text{control}}/Cbl_{\text{control}})$ is the mean specific ROI to cerebellum ratio of the control group. Two different control groups, one for each scanner, were used two calculate the mean control ratio for the three ROIs. Using this approach we eliminated the possible deviation between the two scanners with regard to signal strength and resolution, and were able to analyse the two groups as one.

Statistical analysis

Differences between the three groups concerning demographic variables and memory ability were determined using One Way analysis of Variance (ANOVA) with pre-testing of homogeneity of variances and post hoc tests with Bonferroni corrected *t*-tests. For the Anosognosia Rating Scale differences in the proportion of patients with MCI and AD were examined using Chi square Test, and Fischer's Exact Test (two-sided) was applied when cells had expected counts less than five. In comparisons of test results for the Memory Questionnaire discrepancy score the Kruskal Wallis Test was used due to in-homogeneity in the variances, and comparisons on a group-by-group basis were performed with Bonferroni corrected *t*-tests.

To investigate correlations between awareness and cognitive results all patients were grouped. Differences in neuropsychological executive tests between the three groups as classified by the Anosognosia Rating scale were investigated with ANOVA with pre-testing of homogeneity of variances. The impact of MMSE, CCR and executive neuropsychological tests on the Memory Questionnaire discrepancy scores was investigated using stepwise linear regression analysis with plots of residuals as model control.

Differences in rCBF in the frontal regions between the three groups as classified by the Anosognosia Rating scale were investigated with ANOVA with pre-testing of homogeneity of variances. Correlations between rCBF in the six frontal regions and MMSE were assessed with Pearson correlations. Correlations between the scores from the Memory Questionnaire discrepancy scores and rCBF in frontal regions were assessed with partial correlations controlling for MMSE. Finally, to assess the impact of rCBF on anosognosia we applied a linear stepwise regression model using MMSE and rCBF in the six frontal cortical regions as independent variables. Plots of residuals were used as model control. The level of statistical significance was set at $p < 0.05$.

RESULTS

Background data and memory ratings

The demographic data and the MMSE and CDR scores are presented in Table 1 for control subjects and for patients with MCI and AD. No significant

Table 1. Demographic data and results from MMSE and CDR

	Controls ($n=33$)	MCI ($n=30$)	AD ($n=36$)
Females/Males	19/14	16/14	21/15
Age	73.4 (5.3)	74.4 (4.8)	76.4 (6.3)
Mean (SD)	range 64–84	range 66–84	range 62–87
Education	11.7 (2.9)	11.1 (2.9)	10.9 (2.8)
Mean (SD)			
DART	33.6 (9.24)	31.8 (10.7)	27.3 (12.1)
Mean (SD)			
MMSE	29.3 (0.85)	26.07 (2.06)*	24.04 (2.5)*#
Mean (SD)	range 27–30	range 22–29	range 20–30
CDR N: score	33:0	30:0.5	21:0.5 13:1.0 1:2.0 1:3.0

*Significant difference from controls ($p<0.05$).
#Significant difference from MCI patients ($p<0.05$).

effect of group was found for premorbid intelligence measured by DART (F (2,94) = 3.09, $p=0.05$), age (F (2,96) = 2.56, $p=0.08$) or education (F (2,96) = 0.68, $p=0.51$). Using Bonferroni corrected t-tests we found no significant difference between patients with MCI and AD for immediate ($p=0.53$) or delayed recall ($p=0.59$) on the Category Cued Recall test, indicating that the level of amnesia was similar in the two patient groups.

Insight ratings

The mean discrepancy score on the Memory Questionnaire was −20.6 (SD 25.2) for AD patients and −12.4 (SD 20.6) for MCI patients. Control subjects had a mean score of 3.4 (SD 12.1). Significant effect of group was found for the Memory Questionnaire difference score (χ^2 (2) = 17.32, $p<0.001$). Post hoc t-tests showed significant differences between controls and both patient groups, but no significant difference between MCI and AD patients.

On the Anosognosia Rating Scale 38.2% of AD patients had 'full insight', 38.2% had 'shallow insight' and 23.6% had 'no insight'. In the MCI patients 40% had 'full insight', 48% had 'shallow insight' and 12% 'no insight'. No differences were found between the proportion of MCI and AD patients classified in the categories 'full' ($\chi^2=0.019$, $p=0.89$), 'shallow' ($\chi^2=0.563$, $p=0.45$) and 'no insight' ($p=0.33$).

Neuropsychological test results for executive dysfunction, behavioural symptoms and awareness

As shown in Table 2, the three groups classified by the categorical ratings 'full', 'shallow' or 'no' insight did not differ in executive functioning or behavioural symptoms. This indicates that executive functions are not directly related to anosognosia.

The impact of MMSE on the Memory Questionnaire discrepancy score was identified as a dependent factor [$r^2=0.145$, F (1,58) = 9.83, $p=0.003$]. Thus, dementia severity may have an impact on anosognosia. Using stepwise linear regression with Memory Questionnaire discrepancy score as dependent variable and results from immediate and delayed recall on CCR and MMSE as independent variables, only MMSE score [$r^2=0.137$, F (1,55) = 8.75, $p=0.005$] contributed significantly to the variance in Memory Questionnaire discrepancy score. Thus, episodic memory performance was not associated with impaired awareness. When using stepwise linear regression with the neuropsychological tests listed in Table 2 and MMSE as independent variables, FBI [$r^2=0.286$, F (1,40) = 16.05, $p<0.001$] and MMSE-score [$r^2=0.389$, F (2,39) = 12.39, $p<0.001$] were the only models that contributed significantly to the variance in Memory Questionnaire discrepancy scores. This shows that executive tests are not

Table 2. Results from the neuropsychological executive tests and FBI in groups divided by Anosognosia Scale ratings (presented as means ± SD)

	Full insight $n=23$	Shallow insight $n=25$	No insight $n=11$	group-comparisons (ANOVA) p-value
Fluency (animals)	12.96 (5.46)	12.68 (3.70)	13.70 (4.69)	0.842
Fluency (S-words)	8.91 (4.58)	9.00 (2.92)	8.20 (3.08)	0.838
WCST (sets)	3.32 (1.42)	3.78 (2.18)	2.78 (1.79)	0.402
WCST (errors)	19.44 (8.02)	17.33 (10.87)	19.33 (7.91)	0.764
Design Fluency	19.09 (7.37)	14.42 (5.96)	16.20 (7.32)	0.074
Trail Making A	66.14 (33.87)	70.60 (48.75)	70.55 (42.50)	0.928
Trail Making B	226.14 (138.90)	266.12 (155.52)	267.45 (163.65)	0.616
Stroop congruent (time)	72.76 (19.97)	74.96 (19.72)	81.10 (19.80)	0.551
Stroop in-congruent (time)	224.25 (86.97)	216.60 (62.19)	208.00 (66.13)	0.842
Frontal Behavioral Inventory	7.89 (4.39)	9.09 (5.62)	13.00 (6.37)	0.087

Note: The anosognosia rating was missing in seven patients.

associated with anosognosia in AD, but that behavioural symptoms are correlated with impaired insight. Analyses of mean scores for the 24 items of the FBI showed that disorganization, aspontaneity and apathy (together with impaired insight) were the abnormal behaviours that contributed most to the total FBI scores, and that these had the highest impact on the correlation between FBI and anosognosia.

Regional cerebral blood flow and anosognosia

Correlations between results from the Memory Questionnaire discrepancy score and rCBF were analysed for six frontal regions. Memory Questionnaire discrepancy scores were significantly correlated to rCBF in the right inferior gyrus ($r = 0.39$, $p = 0.005$) and in the left inferior gyrus ($r = 0.29$, $p = 0.037$). No other significant correlations were found. No significant correlations between MMSE score and rCBF in the frontal regions were identified.

When using stepwise linear regression with rCBF in six frontal regions and MMSE as independent variables MMSE-score alone [$r^2 = 0.176$, $F(1,48) = 10.28$, $p = 0.002$], and MMSE-score combined with rCBF in right inferior gyrus [$r^2 = 0.303$, $F(2,47) = 10.20$, $p < 0.001$] were the only models which contributed significantly to the variance in Memory Questionnaire discrepancy scores. Thus, when using a statistical model, which controlled for possible interactions between rCBF in different regions, the right inferior frontal gyrus was the only region where rCBF had significant impact on results from the Memory Questionnaire discrepancy score.

Regional cerebral blood flow in six frontal regions was compared for patients with 'full', 'shallow' or 'no' insight as classified by the Anosognosia Rating Scale. No significant differences in cerebral perfusion could be identified between patients in these three groups. Thus, cerebral perfusion in frontal cortex was not related to impaired insight when awareness was assessed on a simple categorical scale.

DISCUSSION

In this study we found that anosognosia is a frequent symptom in patients with AD and 'amnestic MCI'. Both MCI and AD patients showed large individual differences in the degree of impairment of awareness. No differences between the two patient groups in the level of anosognosia could be found, confirming, as discussed in a previous report (Vogel *et al.*, 2004), that awareness may be equally impaired in 'amnestic MCI' and AD. The study demonstrated that awareness for cognitive deficits (predominantly memory) is not significantly dependent on episodic memory since performances on CCR were not associated with awareness as assessed by the Memory Questionnaire discrepancy score. In this study our primary objective was to investigate cognitive and anatomical correlates of impaired awareness in MCI and AD. Our study is important, since it is one of the first studies to investigate correlates of awareness in AD and MCI using both neuropsychological results and data from functional imaging.

A significant correlation was found between the level of insight and dementia severity (MMSE). Some previous studies have demonstrated a significant correlation between MMSE and the level of awareness (Lopez *et al.*, 1994; Migliorelli *et al.*, 1995b; Harwood *et al.*, 2000), whereas others did not find such an association (DeBettignies *et al.*, 1990; Reed *et al.*, 1993; Seltzer *et al.*, 2001). Sevush (1999) found that anosognosia correlates slightly with dementia severity in cross-sectional studies and is independent of disease progression when assessed longitudinally, while a follow-up study of 62 AD patients demonstrated progression of anosognosia (Starkstein *et al.*, 1997a). Overall, these results indicate that dementia severity and the level of awareness are associated.

The frontal lobes have been pointed out as an important localization in dominating theories on anosognosia (Stuss and Benson, 1986; McGlynn and Schacter, 1989; Damasio, 1994), but in our study executive functions and anosognosia were not significantly correlated. These results are inconsistent with previous studies where correlations between tests for executive functions and impairments in insight were found (Lopez *et al.*, 1994; Michon *et al.*, 1994; Ott *et al.*, 1996a). In some of these studies (Lopez *et al.*, 1994; Michon *et al.*, 1994) patients had lower scores on the MMSE than patients in our study. Other studies found that executive deficits in AD are not correlated to unawareness (Dalla Barba *et al.*, 1995; Seltzer *et al.*, 2001) or that cognitive deficits in general are not linked to impaired insight in AD (Starkstein *et al.*, 1995; Derouesne *et al.*, 1999). As pointed out by Starkstein *et al.* (1995), deficits in executive tasks may be independent of anosognosia, and deficits on 'frontal lobe-related tasks' may often appear later in the disease. If a causal link between executive functions and anosognosia in AD was to be assumed, executive dysfunction should be demonstrable even in the earliest phases of AD in patients with anosognosia (or in MCI patients with the same degree of unawareness). Our results do not support such a relationship between executive functioning and anosognosia.

Performances on the FBI, which assesses behavioural changes typically associated with lesions in prefrontal cortex, were significantly correlated to the Memory Questionnaire discrepancy score. Disorganization, aspontaneity and apathy were the abnormal behaviours that contributed most to the total FBI scores, and these had the highest impact on the correlation between anosognosia and FBI. Other studies have described that behavioural and psychiatric symptoms are more frequent in patients with limited awareness (Lopez *et al.*, 1994; Michon *et al.*, 1994; Migliorelli *et al.*, 1995a; Harwood *et al.*, 2000). Taken together, these findings indicate that anosognosia is more likely related to affective/behavioural disturbances than to cognitive functioning as previously suggested (Derouesne *et al.*, 1999).

Measures of executive function do not reflect frontal lobe functioning per se (Stuss, 1993; Lafleche and Albert, 1995). The specificity of executive tests as a measure of frontal lobe functioning is questionable, since studies have failed to demonstrate a correlation between cognitive test results and functional brain imaging in AD (Kessler *et al.*, 2000). Thus, conclusions suggesting a link between unawareness and frontal lobe function (or the lack of such a link) solely based on neuropsychological data may be misleading. Executive deficits may be caused by pathological changes in subcortical regions, e.g. the basal forebrain (Lafleche and Albert, 1995; Perry and Hodges, 1999) disconnecting cholinergic pathways to the frontal lobes. Further, damage to cortico-cortical pathways may cause reduced capability in simultaneous integration of multiple types of information (Lafleche and Albert, 1995; Perry and Hodges, 1999). Studies on insight investigating results from functional (or structural) brain imaging in addition to cognitive performance may be necessary to determine anatomical correlates for impaired insight in AD. Our study is one of the first studies to investigate correlates of awareness in AD and MCI using both neuropsychological results and data from functional imaging.

The right inferior gyrus was the only region with significant impact on the Memory Questionnaire discrepancy score when we controlled for possible interactions between different brain regions. This region may constitute a neurobiological substrate of awareness. In previous studies assessing correlations between anosognosia and rCBF, specific patterns of hypoperfusion were correlated to impaired insight in AD. Two previous studies found hypoperfusion in the right frontal lobe in patients with impaired awareness (Reed *et al.*, 1993; Starkstein *et al.*, 1995), whereas one study found that awareness correlated with overall frontal rCBF (Derouesne *et al.*, 1999). Another study did not find correlations between frontal perfusion and anosognosia, but found that impaired insight was correlated to right temporoparietal perfusion (Ott *et al.*, 1996b). These results strengthen the assumption that regions in right frontal lobe are of high importance for anosognosia in AD and MCI. Based on our results we assume that the right inferior frontal gyrus is the most important location for impaired awareness among the different frontal regions.

Whether different cognitive functions can be attributed to discrete regions of the prefrontal cortex is controversial. However, advances in human lesion-mapping support a crucial role of the right inferior frontal gyrus in response-inhibition (Aron *et al.*, 2003; Aron *et al.*, 2004). Thus, the right inferior frontal gyrus may have specific functions. Whether an association between response-inhibition and insight exists cannot be investigated with our data.

Methodological differences may be the main reason that results on frontal lobe perfusion and insight are inconsistent. In this study we found a significant correlation between a test-based measure of insight and rCBF in a frontal region, but using the simple categorical rating of awareness we were not able to find this correlation. The reason for the inconsistent findings for the two rating systems for anosognosia may have been that the categorical rating scale only had three categories whereas the Memory Questionnaire had a wide range of scores. In a previous article we described that a short categorical rating is very useful in everyday clinical practice, and that discrepancy scores from the Memory Questionnaire and the categorical rating were correlated (Vogel *et al.*, 2004). This study demonstrated that multi-modal assessment of insight is relevant for research purposes since different methods of awareness-assessment elicited different results. However, quantification of impairments in awareness is difficult, and even if detailed scales (parallel version of questionnaires) can be applied, no golden standard for assessing awareness exists.

Since the majority of studies on correlates for anosognosia in AD have highlighted the frontal lobe as the most important region, we specifically studied relations between prefrontal functions (on either SPECT or by executive functions) and awareness. However, metabolic deficits in other brain areas and in other cognitive domains than those assessed in this study may also be associated with impaired insight. In previous studies other correlates of anosognosia have been found including right sided parietal/occipital

dysfunction (Ott *et al.*, 1996a; Ott *et al.*, 1996b), deficits in procedural memory (Starkstein *et al.*, 1997b) and increased number of intrusions (Reed *et al.*, 1993; Dalla Barba *et al.*, 1995). Our neuropsychological test-battery was specifically designed to assess executive functions, and we therefore limited our investigation to prefrontal functions.

The MCI patients in this study all had 'amnestic MCI', and thus represent a subgroup of all MCI patients. Further, the strict neuropsychological criteria that we applied may have biased the patient group towards the more severe cases. This may have influenced why we did not find a difference in anosognosia between MCI and AD patients. Our study also carried the limitation that the SPECT-scans were performed with two different scanners. We therefore could not apply detailed analysis of possible hypometabolism using Statistical Parametric Mapping. In future studies advanced image analysis may contribute to our understanding of the relation between anosognosia, cognitive performance and rCBF in AD and amnestic MCI.

In conclusion, anosognosia, as assessed by discrepancy scores on the Memory Questionnaire, was significantly correlated to behavioral symptoms as measured by the FBI and to rCBF in the right inferior frontal gyrus. No associations between awareness and performance on executive neuropsychological tests were found. Whether the association between impaired awareness and prefrontal rCBF reflects a neurobiological substrate of awareness remains to be confirmed.

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