Abnormal Face-hand Testing is Associated with Anosognosia in Patients with Neuropathologically-confirmed Alzheimer's disease

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Abstract

We investigated elements of the neurological and neuropsychological evaluation that might be associated with anosognosia for memory impairment in subjects with Alzheimer's disease. Anosognosia was defined by a discrepancy between 1) the patient's self-report and results of testing, and/or 2) the patient's self-report and the caregiver's report regarding memory impairment. A total of 61 subjects were included, 34 with anosognosia and 27 without anosognosia. The anosognosic group performed worse on two tests of frontal systems function - letter fluency (COWAT) (p=0.010) and a score derived from the Trailmaking test (Trailmaking B time – Trailmaking A time) (p=0.015). In addition, significantly more anosognosic subjects (92%) had abnormal results on face-hand testing (double simultaneous stimulation) compared to non-anosognosic subjects (62% abnormal; p=0.018). In this study of patients with moderate Alzheimer's disease (mean CDR=2), the anosognosic group showed significantly greater impairment on tests of frontal/executive function. In addition, this group had a significantly higher rate of abnormal face-hand testing, consistent with right parietal pathology. The FHT may prove useful as a marker for anosognosia risk in AD.

Introduction

Anosognosia refers to lack of insight into deficits or disease states, and in the context of Alzheimer's disease (AD), unawareness of deficits in cognitive function or activities of daily living. Anosognosia can be a significant impediment to appropriate and timely care (Seltzer et al., 1997). Frontal systems and right temporoparietal pathology have been implicated in anosognosia (Bisiach et al., 1986).

Anosognosia is not universally present in AD (Sevush & Leve, 1993). The ability to predict which patients will develop anosognosia with AD progression would be useful in counseling patients and family members about future behavioral, financial, and legal issues.

The face-hand test (double simultaneous stimulation) was investigated in the early 1950s by Bender and colleagues, who noted extinction of the hand stimulus on the initial trial in more than 90% of patients with "organic mental syndromes," including AD (Bender, et al., 1951). Unilateral extinction is seen in patients with parietal lobe injury - specifically the right parietal lobe – which creates an attentional bias towards ipsilesional stimuli. De Haan et al., 2012). This is of potential interest in AD, a disease involving significant parietal hypoperfusion and hypometabolism at particular disease stages (Jacobs et al., 2012; Pakrasi et al., 2005).

We report an association of abnormal face-hand testing (extinction on double simultaneous stimulation) with anosognosia for memory impairment in subjects with AD. Alzheimer pathology in the right parietal lobe likely accounts for the abnormal test, and also likely contributes to this form of anosognosia. This finding may be of interest to clinicians as a rapid screening tool for anosognosia risk, and to researchers exploring the mechanism underlying anosognosia for memory impairment in AD.

Methods

All subjects with a clinicopathological diagnosis of AD for whom anosognosia could be confirmed or excluded based on antemortem data were considered for inclusion. All subjects met the NIA-Reagan neuropathological criteria for AD (Hyman & Trojanowski, 1997). Anosognosia was defined by a discrepancy between 1) the patient's self-report of no memory impairment and abnormal results on memory testing, and/or 2) the patient's self-report of no memory impairment and the caregiver's endorsement of memory impairment.

The face-hand test assesses detection of simultaneous stimulation. A positive test was indicated by extinction of one stimulus when two stimuli were applied.

Neuropsychological evaluation included the MMSE, WMS-R Logical Memory, Rey Auditory Verbal Learning Test, Category Fluency (animals), Controlled Oral Word Association Test (CFL), Trailmaking Tests A and B, Stroop, and Clock Drawing Test.

Data were analyzed using STATA-12 (StataCorp LP, College Station, Texas). The anosognosic and non-anosognosic groups were compared on variables. To compare continuous variables between the groups, the Wilcoxon rank-sum test was used. To compare binary variables, the Fisher's exact test was used.

Results

The study group comprised 61 subjects with neuropathologically-confirmed AD with unambiguous documentation regarding anosognosia: 34 with anosognosia and 27 without. All subjects had a Clinical Dementia Rating Scale score of ≥ 1. The groups were not different in age, gender, education, or duration of illness, as shown in Table 1.

On the MMSE, the group difference was marginally significant (p=0.059), with the anosognosia group having a slightly lower mean score. The groups were significantly different on two tests of frontal systems function: letter fluency (COWAT) (p=0.010) and a score derived from the Trailmaking test (Trailmaking B time – Trailmaking A time) (p=0.015). This was taken as a proxy for the "split" in Trailmaking A and B scores that can signify frontal/executive dysfunction (Ashendorf et al., 2008).

Analysis of neuropathological data from the *left* hemisphere revealed no association between anosognosia and regional or total measures of plaque, plaque density, or tangles. Right hemisphere tissue was not examined.

Table 1: Group Comparisons: demographic, clinical, and neuropathological variables

	Anosognosia (n=34)	No Anosognosia (n=27)	*p*-value
Age	90 (1.6; 86-93)	89 (1.6; 86-93)	0.260
Handedness (% RH)	91% RH, 6% LH, 3% A	93% RH, 7% A	0.891
Years of education	14 (0.5; 13-15)	15 (0.9; 13-17)	0.232
Global CDR	2.24 (.127) 1.98-2.50	2.04 (.136) 1.76-2.32	0.272
Duration of Illness	8.12 (.786) 6.5-9.7	8.16 (.923) 6.25-10.1	0.987
Gender	50% F (0.09; 32-68)	41% F (0.10; 21-61)	0.475
Face-hand Test abnormal	91% (0.05; 81-100)	67% (0.09; 48-86)	0.018*
MMSE	18 (1.5; 15-21)	19 (1.1; 17-22)	0.059
Trails B – A	148 (18; 109-187)	135 (21; 92-178)	0.015*
COWAT	20 (2.3; 15-25)	29 (2.6; 23-35)	0.010*
Tangles-total	11 (0.6; 10-13)	11 (0.8; 12-15)	0.517
Plaque-total	13 (0.4; 12-14)	14 (0.5; 12-15)	0.620
Plaque density	2.9 (0.06; 2.7-3.0)	2.8 (0.54; 2.6-3.0)	0.914

A significant difference was found between the groups on face-hand testing (FHT). Of anosognosic subjects, 92% had an abnormal test result, and of non-anosognosic subjects, 62% had an abnormal test result (p=0.018). The FHT result was not predicted by age (p=0.892), duration of illness (p=0.484), or CDR score (p=0.106).

Discussion and Conclusions

In this cohort of patients with Alzheimer's disease, those with anosognosia for memory impairment were significantly more likely to have abnormal results on face-hand testing and exhibit frontal/executive dysfunction on neuropsychological testing. Neuropathological examination of the *left* hemisphere revealed no differences between groups.

These findings are in agreement with those of previous studies showing an association of anosognosia with frontal-executive dysfunction (Michon et al., 1994). The neuropathological data provide indirect evidence in support of the primacy of *right* hemisphere pathology in the genesis of anosognosia (Bisiach et al., 1986). More direct evidence implicating the right parietal area was provided by the specific protocol used here for face-hand testing. Parietal lobe lesions have been associated with lack of explicit awareness of memory failure in patients with AD (Morris & Mograbi, 2012).

The FHT is a 30-second test that may prove to be useful as a marker for anosognosia risk in AD that is positive before the patient becomes symptomatic. Future study also should include neuropathological examination of the right cerebral hemisphere.

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