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

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ABSTRACT

Objective To investigate whether specific elements of the neurological and neuropsychological evaluation are associated with anosognosia for memory impairment in subjects with neuropathologically-confirmed Alzheimer's disease.

Methods Included were subjects from the Arizona Study of Aging and Neurodegenerative Disease with clinically documented dementia and neuropathological confirmation of AD for whom anosognosia could be confirmed based on antemortem data. 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. The anosognosic and non-anosognosic groups were compared on targeted clinical, cognitive, and neuropathological findings.

Results Of 61 subjects included, 34 were diagnosed as anosognosic, and 27 non-anosognosic. 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).

Significance 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, which takes about 30 seconds to administer, may prove useful as a marker for anosognosia risk in AD.

Table of Contents:

TABLES AND FIGURES:

INTRODUCTION

In the context of Alzheimer's disease (AD), anosognosia is defined as the lack of awareness of deficits in cognitive function.(Starkstein, Jorge, Mizrahi, & Robinson, 2006) Anosognosia is a significant impediment to appropriate and timely care.(Seltzer, Vasterling, Yoder, & Thompson, 1997) *Right* hemisphere pathology has been implicated in anosognosia (Bisiach, Vallar, Perani, Papagno, & Berti, 1986) although inconsistently.(Derouesne et al., 1999) A particular role of the right *parietal* lobe in self-awareness was posited by Morris and Mograbi in the latest iteration of the cognitive awareness model of anosognosia, in which the parietal lobes function to generate the conscious experience of new memory failures.(Morris & Mograbi, 2012)

Anosognosia is not universally present in AD, even in later disease stages.(Sevush & Leve, 1993) The ability to predict which patients will develop anosognosia with AD progression would be useful in counseling patients and family members regarding legal and financial matters, among many other 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.(Fink, Green, & Bender, 1952) Unilateral extinction is seen in patients with parietal lobe injury - specifically the right parietal lobe – which creates an attentional bias towards ipsilesional stimuli.(Bisiach et al., 1986)

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.

PATIENTS AND METHODS

The research was in full compliance with the ethical rules for human experimentation stated in the Declaration of Helsinki. Subjects were enrolled in the Arizona Study of Aging and Neurodegenerative Disease (AZSAND) and the Banner Sun Health Research Institute Brain and Body Donation Program (www.brainandbodydonationprogram.org). Standardized clinical assessments included physical and neurological examinations, neuropsychiatric screening, and neuropsychological testing. Dementia was diagnosed clinically by DSM-IV criteria. A neuropathological diagnosis of AD was made on the basis of the NIA-Reagan criteria indicating "intermediate" or "high" probability that the dementia was due to AD; for this determination, any combination of Braak NFT stages III-VI and moderate or frequent CERAD neuritic plaque density was used.(Braak & Braak, 1991b)

All subjects in the AZSAND with neuropathologically-confirmed AD for whom anosognosia could be confirmed or excluded based on antemortem data were considered for inclusion. Anosognosia was defined by a discrepancy between either 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.

In our clinic, the face-hand test is performed after reflexes have been tested and before coordination is evaluated. The examiner instructs the patient as follows: "I am going to touch you either on the hands (strokes the dorsum of both hands, which are resting just above the knees) or the face (strokes both cheeks). I want you to close your eyes and tell me where I have touched you." The examiner then strokes the patient's left cheek and asks, "Where did I touch you?" The examiner then strokes the patient on both cheeks and asks, "Where did I touch you?" Finally, the examiner strokes the patient on the right cheek and the left hand and asks, "Where did I touch you?" When two points were touched, the contact was simultaneous and of equal intensity. A positive test was indicated by extinction of one stimulus when two stimuli were applied. This version of face-hand testing – in which only the initial trial is recorded – simulates that used by Bender and colleagues.(Fink et al., 1952)

Neuropsychological tests included the MMSE, WMS-R Logical Memory, Rey Auditory Verbal Learning Test, Category Fluency (animals), Controlled Oral Word Association Test (COWA), Trailmaking Tests A and B, Stroop, and Clock Drawing Test. Trailmaking is a two part pencil and paper neuropsychological test. Part A, which assesses cognitive processing speed, is scored based on the time is takes to connect 25 circled numbers in consecutive order. Part B, which assesses executive functioning, is scored based on the time to completion to connect 13 circled numbers and 13 circled letters in alternating numerical and alphabetical order (1, A, 2, B, etc.).

Neuropathological examination. The cerebrum was cut at the time of brain removal and divided into left and right halves. Slices from the right half were frozen. Slices from the left half were fixed by immersion in buffered 4% formaldehyde for 48 hours at 4 degrees C. Following cryoprotection in ethylene glycol and glycerol, selected 3 x 4 cm cerebral, cerebellar and brainstem blocks were sectioned at 40 μm thickness and stained with H & E, thioflavine S and enhanced silver methods for amyloid plaques and neurofibrillary tangles, using the Campbell-Switzer and Gallyas methods.(Braak & Braak, 1991a) These methods have been described elsewhere.(Beach et al., 2008)

Histopathological scoring was blinded to clinical and neuropathological diagnosis. Amyloid plaque and NFT density were graded and staged at standard sites in frontal, temporal, parietal, hippocampal, and entorhinal cortex, based on the aggregate impression from the stained sections. Plaque and tangle scores were assigned according to the published CERAD templates,(Mirra et al., 1991) and tangle distribution according to the original Braak protocol.(Braak & Braak, 1991b) All subjects met the NIA-Reagan neuropathological criteria for AD (“intermediate” or “high” probability). (Hyman & Trojanowski, 1997)

Data were analyzed using STATA-12 (StataCorp LP, College Station, Texas). The anosognosic and non-anosognosic groups were compared on several clinical, cognitive, and neuropathological 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. Due to the exploratory nature of this study no adjustment for multiple testing was made.

RESULTS

We identified 231 subjects with neuropathologically-confirmed AD without Parkinson's disease who expired January 2004 - April 2012. 87 were excluded due to other neuropathological diagnoses comorbid with AD (30 vascular dementia, 30 dementia with Lewy bodies, 12 hippocampal sclerosis, 8 progressive supranuclear palsy, 5 severe cerebral amyloid angiopathy, and 2 trisomy 21), and 83 because they were evaluated elsewhere, or clear documentation regarding anosognosia was lacking.

The study sample 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, as shown in Table 1.

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

Values are mean (SE; 95% CI) except for handedness, gender and FHT abnormal, which are expressed as percentages (SE; 95% CI).

p-values were determined by the Wilcoxon rank-sum test or Fisher's exact test.

Plaque and tangle data are from left hemisphere sections only.

CDR=Clinical Dementia Rating Scale, MMSE=Mini-mental State Examination, Trails B-A=Raw score on Trailmaking Test A subtracted from raw score on Trailmaking Test B, COWAT=Controlled Oral Word Association Test, total 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 frozen per laboratory protocol, and thus not examined.

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

In this cohort of patients with neuropathologically confirmed Alzheimer's disease, those who evidenced anosognosia for memory impairment were significantly more likely to have an abnormal result on face-hand testing and to exhibit frontal/executive dysfunction on neuropsychological testing. Neuropathological examination of the *left* hemisphere did not reveal differences between the groups.

These findings are in agreement with those of previous studies showing an association of anosognosia with frontal-executive dysfunction (Michon, Deweer, Pillon, Agid, & Dubois, 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. It has been proposed that hypometabolism in the parietal cortex is implicated in the inability of patients with AD to "see themselves" as others would see them (Salmon et al., 2005). Parietal lobe lesions have been associated with lack of explicit awareness of memory failure in patients with AD.(Morris & Mograbi, 2012)

Weaknesses of the study include the retrospective nature of the anosognosia diagnosis and our inability to examine the right hemisphere for group differences. Strengths of the study include the standardized evaluation protocol and the inclusion of all subjects with neuropathologically-confirmed AD and clear documentation regarding anosognosia presence.

FUTURE DIRECTIONS

If our findings regarding the FHT in AD patients with anosognosia are replicated in a prospective study, this 30-second test may prove to be useful as a clinical "quick test," a marker for anosognosia risk in AD that is positive before the patient becomes symptomatic. Our results provide further support for models of anosognosia implicating the right parietal area.(Morris & Mograbi, 2012) Future studies also should include neuropathological examination of the right cerebral hemisphere.

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