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Memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease

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ABSTRACT

While loss of insight of cognitive deficits, *anosognosia,* is a common symptom in Alzheimer's disease dementia, there is a lack of consensus regarding the presence of altered awareness of memory function in the preclinical and prodromal stages of the disease. Paradoxically, very early in the Alzheimer's disease process, individuals may experience heightened awareness of memory changes before any objective cognitive deficits can be detected, here referred to as *hypernosognosia*. In contrast, awareness of memory dysfunction shown by individuals with mild cognitive impairment (MCI) is very variable, ranging from marked concern to severe lack of insight. This study aims at improving our mechanistic understanding of how alterations in memory self-awareness are related to pathological changes in clinically normal (CN) adults and MCI patients. 297 CN and MCI patients underwent PiB-PET (Positron Emission Tomography using Pittsburgh Compound B) in vivo amyloid imaging. Amyloid burden was estimated from Alzheimer's disease vulnerable regions, including the frontal, lateral parietal and lateral temporal, and retrosplenial cortex. Memory self-awareness was assessed using discrepancy scores between subjective and objective measures of memory function. A set of univariate analysis of variance were performed to assess the relationship between self-awareness of memory and amyloid pathology. Whereas CN individuals harboring amyloid pathology demonstrated hypernosognosia, MCI patients with increased amyloid pathology demonstrated anosognosia. In contrast, MCI patients with low amounts of amyloid were observed to have normal insight into their memory functions. Altered self-awareness of memory tracks with amyloid pathology. The findings of variability of awareness may have important implications for the reliability of self-report of dysfunction across the spectrum of preclinical and prodromal Alzheimer's disease.

1. Introduction

The capability to accurately assess our own cognitive abilities is crucial for us to function effectively (Clare et al., 2010; West et al., 1996) and may be particularly important in the setting of Alzheimer's disease, when deterioration in mental capacity can threaten the most basic everyday functions (Rosen, 2011). Lack of awareness, or *anosognosia* (Babinski, 1914; McGlynn and Schacter, 1989), of memory or behavioral deficits is a common and striking symptom in Alzheimer's disease (Agnew and Morris, 1998), and has major clinical relevance since it is directly related to the reliability of a patient's complaints of dysfunction (Kalbe et al., 2005). However, the evolution of altered self-awareness of memory function across the preclinical and prodromal stages of Alzheimer's disease is not fully understood. Specifically, the pathology underpinning the differences in awareness of memory function across the Alzheimer's disease spectrum remains to be

Abbreviations: Aβ, Beta amyloid; CN, Clinically normal; MCI, Mild Cognitive Impairment; PiB, Pittsburgh Compound B; PET, Positron Emission Tomography

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elucidated.

Previous research has estimated that as many as 80% of individuals diagnosed with Alzheimer's disease at the dementia stage have some form of anosognosia (Reed et al., 1993), and the disorder has been shown to correlate with overall disease severity (Kalbe et al., 2005). In contrast, awareness of cognitive dysfunction shown by individuals with mild cognitive impairment (MCI) is very variable, ranging from clear insight and marked concern about cognitive difficulties (e.g. Kalbe et al., 2005) to severe lack of insight (e.g. Galeone et al., 2011), but see also Roberts et al., 2009. The findings of variability of awareness may have implications for the use of subjective memory complaints in the diagnostic criteria of MCI, as anosognosia may reduce the validity of the subjective experience of cognitive abilities. In fact, anosognosia is beginning to be recognized as an important clinical symptom of MCI, that may predict greater progression to Alzheimer's disease dementia (e.g. Tabert et al., 2002).

Paradoxically, very early in the Alzheimer's disease process, individuals may experience heightened awareness of subtle changes in their memory function, despite performing well on standardized memory tests. Previous studies have estimated that the prevalence of memory complaints in the non demented elderly population range between 22 to 56% (Jonker et al., 2000). Often referred to as Subjective Cognitive Decline, accumulating evidence suggests that these individuals have an increased likelihood of harboring biomarker and neuroimaging abnormalities consistent with Alzheimer's disease pathology (Amariglio et al., 2012, 2015; Palm et al., 2013; Perrotin et al., 2012; Saykin et al., 2006; Striepens et al., 2010, van der Flier et al., 2004) as well as an increased risk of prospective Alzheimer dementia (Jessen et al., 2010, 2014b), consistent with the concept of preclinical Alzheimer's disease (Sperling et al., 2011). Of note, previous studies on Subjective Cognitive Decline in preclinical Alzheimer's disease have been defined by self-reported cognitive concerns in otherwise unimpaired older adults (Jessen et al., 2014a). Whether or not Subjective Cognitive Decline should be considered a reliable precursor of Alzheimer's disease, especially in the prodromal phase of Alzheimer's disease, is a matter of controversy. Thus, in line with this, recent publications have called for studies to investigate the concurrent relationship between subjective and objective cognitive performance along the axis of Alzheimer's disease development (Dalla Barba et al., 2015; Jessen, 2014; Jessen et al., 2014a). In particular, it has been suggested that the association between awareness of memory function and pathophysiological changes across the Alzheimer's disease stages will help discriminate individuals who are likely to progress to Alzheimer's disease dementia from those whose awareness of memory is not associated with an underlying neurodegenerative pathology.

In the search for brain changes that contribute to altered awareness, as seen in Alzheimer's disease, evidence from several lines of research have demonstrated an association between anosognosia and dysfunction in frontal, temporomedial and temporoparietal regions (Prigatano, 2010; Starkstein and Power, 2010). These observations overlap with brain regions that have been implicated in self-referential processing in normal individuals (Johnson and Ries, 2010; Northoff and Bermpohl, 2004; Northoff et al., 2006; Schmitz and Johnson, 2007) and have been shown to be affected by Alzheimer's disease pathology (Buckner et al., 2008, 2009), such as amyloid beta (Aβ) (Edison et al., 2007; Engler et al., 2006; Forsberg et al., 2008; Kemppainen et al., 2006; Klunk et al., 2004; Mintun et al., 2006). To date, the relationship between amyloid pathology and memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease has not been investigated.

The aim of the current study was to investigate self-awareness of memory function across the preclinical and prodromal phase of Alzheimer's disease. Specifically, we wanted to improve our mechanistic understanding of how alterations in memory awareness are related to amyloid pathology across cognitively normal adults and MCI patients.

Table 1
Demographics of the whole sample and by groups.

	Total	Cognitively normal		Mild Cognitive Impairment	
		Aβ -	Aβ +	Aβ -	Aβ +
N	297	199	63	15	20
Age, y	73.2 (6.5)	72.5 (6.2)	74.9 (6.2)	74.9 (7.1)	73.1 (8.5)
Female, %	56.9	59.2	58.7	53.3	30.0
Education, y	15.7 (3.1)	15.5 (3.1)	16.3 (2.8)	14.7 (3.8)	16.9 (2.4)
MMSE, score 0–30	28.8 (1.4)	29.0 (1.1)	28.8 (1.0)	28.1 (1.3)	26.4 (2.1)
AMNART	120.4 (9.6)[a]	120.0 (9.6)	122.5 (8.4)[a]	117.5 (15.4)	120.1 (7.7)
GDS, score 0–14	1.2 (1.4)	1.1 (1.2)	1.0 (1.2)	3.4 (2.9)	0.8 (1.2)
Subjective, score 1–7	5.1 (1.0)	5.3 (0.9)	4.9 (0.9)	4.2 (0.9)	4.3 (0.8)
Objective, score 0–25	12.7 (4.3)	13.5 (3.5)	13.9 (3.0)	8.4 (5.5)	4.9 (4.6)

All values (except gender) represent means ± standard deviation. Abbreviations: Aβ- = amyloid negative; Aβ + = amyloid positive; AMNART = American National Adult Reading Test; GDS = Geriatric Depression Scale; MMSE = Mini Mental State Examination; y = years.

[a] Missing data for one person.

2. Material and methods

2.1. Design

This was a cross-sectional study comparing awareness of memory functioning in cognitively normal older adults with and without amyloid deposition and individuals with MCI with and without amyloid deposition. IRB approval was granted by the Partners Human Research Committee at the BWH and MGH (Boston, MA). Informed written consent was obtained from every subject prior to experimental procedures.

2.2. Subjects

A total of 297 English speaking participants, 262 CN (mean age 73.1 ranging between 60–90; 59.2% where women) and 35 patients with MCI (mean age 73.9 ranging between 53.5 to 84.8; 40% were women) participated in the study (Table 1).

The healthy older adults were enrolled in the Harvard Aging Brain Study at the Massachusetts General Hospital (Dagley et al., 2015). Participants were defined as cognitively normal if they had a mini-state mental exam (MMSE) (Folstein et al., 1975) score of 27–30 (inclusive with educational adjustment), and a global Clinical Dementia Rating (CDR) (Morris, 1993) score of 0.

The MCI patients were enrolled in an investigator-initiated study at the Center for Alzheimer Research and Treatment and the Massachusetts General Hospital. All patients met criteria for amnestic MCI (single or multiple domain) (Petersen, 2004), with an MMSE score of 24–30 (inclusive), a CDR global score of 0.5 (with memory box score of 0.5 or higher), essentially preserved instrumental ADL (as determined by a clinician) and no evidence of dementia. Of note, subjects with non-amnestic MCI were not eligible to participate in this study.

Exclusion criteria for all subjects were a history of neurologic or major psychiatric disorder, history of head trauma with loss of consciousness, contra-indications for MRI, use of medications that affect cognitive function, severe cardiovascular disease, alcohol or substance abuse, or known cerebrovascular disease (as determined by a the Modified Hachinski Ischemic score of 4 and higher (Rosen et al., 1980)) and/or presence of cortical infarct, or multiple lacunes, extensive leukoariosis on structural MRI. All subjects performed the