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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

Geriatric Depression Scale (Yesavage et al., 1983). Note that the healthy older adults had the long form (30 questions) of the GDS that was transformed to the short form (15 questions) to be comparable with the MCI patients, which had the short form (15 questions). Finally, an adjusted GDS score was calculated by removing 1 overlapping subjective memory complaint question (Do you feel that you have more problems with memory than most?).

2.3. Estimate of awareness of memory functioning

An index of awareness of memory functioning was assessed by calculating discrepancy scores between objective memory scores (the delayed Logical memory test of the Wechsler Memory scale) (Wechsler, 1981) and a subjective memory scores (the "general frequency of forgetting" subscale of the Memory Functioning Questionnaire) (Gilewski et al., 1990). The 18 first questions of this subscale contains items regarding everyday situations in which a person would need to use his/her memory; each item rates the frequency with which the person would rate his/her memory in terms of the kind of problems they experience on a Likert scale ranging from 1 ('major problems') to 7 ('no problem'). The scale was transformed to numbers ranging from 0 to 6. The Logical Memory IIa of the Wechsler Memory Scale-Revised is a standardized test that assesses delayed free recall of a short story, consisting of 25 units of information, approximately 20 min after it was presented. To investigate whether clinical subgroups with amyloid pathology have altered memory awareness, we computed a memory awareness measure using a normative group as reference. Thus, raw scores from objective and subjective measures were converted to z-scores for each subject, using the mean and SD from our CN individuals without Aβ pathology. A discrepancy score between the objective and subjective measures was then calculated, where a lower score indicates over-estimation of memory functioning (these individuals believe they are functioning at a higher level than their objective memory performance would suggest), 0 indicates normal awareness of memory functioning, and a higher score indicates under-estimation of memory functioning (these individuals believe they are functioning less well than their objective performance would suggest).

2.4. PiB-PET acquisition and processing

Amyloid deposition was estimated with N-methyl-[^{11}C]-2-(4-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburg Compound B, PIB), prepared as described by Mathis et al. (2002, 2003) and acquired at MGH, as previously described (Gomperts et al., 2008; Johnson et al., 2007; Rentz et al., 2010), with a Siemens/CTI ECAT HR scanner. In short, following a transmission scan, 8.5–15 mCi ^{11}C-PiB is injected intravenously as a bolus, followed by a 60-min dynamic PET scan in 3-D mode (63 image planes, 15.2 cm axial field of view, 5.6 mm transaxial resolution and 2.4 mm slice interval; 69 frames: 12 × 15 s, 57 × 60 s). PIB-PET data were processed with Statistical Parametric Mapping v8 using a protocol similar as described in Hedden et al. (2012). PiB images were realigned, and the first 8 min of data were averaged and used to normalize data to the Montreal Neurological Institute PET template and smoothed with a Guassian filter (8-mm FWHM). For each subject, PIB retention was expressed as the distribution volume ratio (DVR) at each voxel (Johnson et al., 2007; Logan et al., 1990; Price et al., 2005), applying Logan's graphical method 40–60 min interval, using gray matter cerebellum as a reference region (Mormino et al., 2014a).

Amyloid burden was estimated for each individual by extract a mean PiB value from an aggregate of cortical brain regions using the Harvard Oxford atlas that typically have elevated PiB burden in patients with AD. These regions included frontal, lateral temporal and parietal, and retrosplenial cortices. Individuals were classified as either being Aβ-positive (Aβ+) and Aβ-negative (Aβ-) using a as cutoff value of 1.20 as previously determined by our group (Mormino et al., 2014b). Subjects where not informed of their amyloid status.

2.5. Statistical methods

All assumptions of linear modeling were met in the reported analyses. A set of GLM univariate analysis of variance was performed. First, we examined the effect of clinical group (CN, MCI) and amyloid as a continuous variable on awareness of memory function (dependent variable). Age, gender, education and GDS were used as covariates. Second, awareness of memory (dependent variable) was also compared across group (CN Aβ-, CN Aβ+, MCI Aβ-, MCI Aβ+) (fixed effects), controlling for age, gender, education and GDS. Post hoc contrasts were performed adjusted for multiple comparisons using Bonferroni method to compare level of self-awareness between the groups. All data were analyzed using IBM SPSS Statistics (version 23).

3. Results

3.1. Demographics

In the whole sample, lower MMSE ($r = 0.19$, $p < 0.001$), lower GDS ($r = 0.12$, $p = 0.05$) and male gender ($t = -3.2$, $p < 0.002$) were associated with over-estimation of memory functioning. There was no effect of age and education on memory self-awareness. In the CN, increased GDS ($r = 0.18$, $p = 0.003$) and female gender ($t = -2.7$, $p < 0.007$) were associated with under-estimation of memory functioning. There was no effect of age, education and MMSE on self-awareness of memory function in the CN group. In the MCI patients, lower MMSE ($r = 0.54$, $p = 0.001$) was associated with over-estimation of memory functioning. There was no effect of age, education, and GDS on self-awareness of memory function in the MCI group.

When comparing demographic variables across the preclinical and prodromal stages of CN and MCI, CN Aβ- individuals were slightly younger than CN Aβ+ ($t = -2.7$, $df = 260$, $p = 0.007$). Both MCI groups had lower MMSE score than the CN groups (MCI Aβ- compared to CN Aβ-: $t = 3.2$, $df = 212$, $p = 0.002$; MCI Aβ- compared to CN Aβ+: $t = 2.5$, $df = 76$, $p = 0.016$; MCI Aβ+ compared to CN Aβ-: $t = 9.1$, $df = 217$, $p < 0.001$,and MCI Aβ+ compared to CN Aβ+: $t = 7.1$, $df = 81$, $p < 0.001$). In addition, MCI Aβ+ patients had lower MMSE score than MCI Aβ- patients ($t = 2.7$, $df = 33$, $p < 0.01$). MCI Aβ- patients had higher GDS score than MCI Aβ+ and both CN groups (MCI Aβ- compared to MCI Aβ+: $t = 3.6$, $df = 33$, $p < 0.001$; MCI Aβ- compared to CN Aβ-: $t = -6.4$, $df = 212$, $p < 0.001$; MCI Aβ- compared to CN Aβ+: $t = -5.1$, $df = 76$, $p < 0.001$). There were fewer females in the MCI Aβ+ group as compared to both CN groups (MCI Aβ+ compared to CN Aβ-: $\chi^2 = 4.6$, $df = 1$, $p = 0.032$; MCI Aβ+ compared to CN Aβ+: $\chi^2 = 5.0$, $df = 1$, $p = 0.025$). No significant differences in years of education and AMNART were found across the groups.

3.2. Association of memory self-awareness and amyloid pathology

A univariate analysis of variance was conducted to examine the effect of clinical group (CN, MCI) and amyloid (as a continuous variable) on self-awareness of memory function. Age, gender, education and GDS was entered as covariates. A statistically significant interaction between clinical group and amyloid was found ($F_{1,\ 289} = 11.2$, $p < 0.001$). Post hoc analysis demonstrated a significant positive correlation between memory self-awareness and amyloid in the CN group ($r = 0.2$, $p = 0.006$) such that under-estimation of memory functioning was related to increased amyloid pathology. In contrast, a significant negative correlation was found in the MCI group ($r = -0.5$, $p = 0.002$), such that over-estimation of memory functioning was related to increased amyloid pathology (Fig. 1). The Fisher r-to-z transformation demonstrated a statistically difference between the two correlation coefficients ($z = 4.01$, $p < 0.001$).

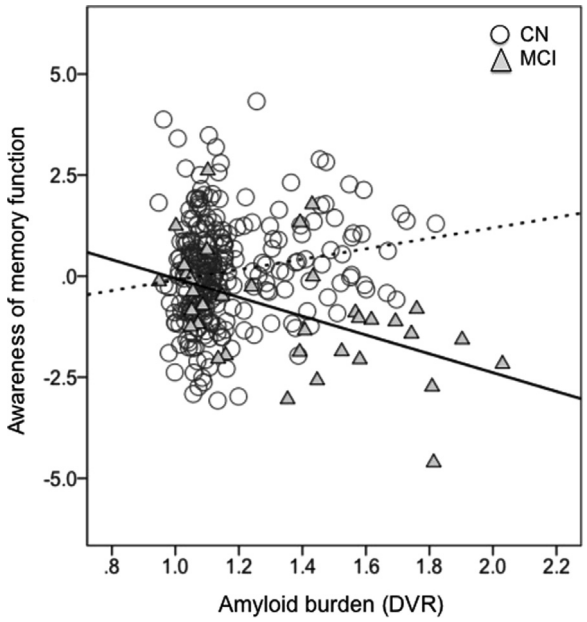

Fig. 1. Relationship between memory awareness and amyloid pathology in cognitively normal and MCI patients. CN = Cognitively normal; MCI = mild cognitive impairment; Cognitively normal individuals demonstrate a positive relationship ($r = 0.2$, $p = 0.006$) between memory awareness and amyloid pathology (dotted line), whereas MCI patients demonstrate a negative relationship ($r = -0.5$, $p = 0.002$) between memory awareness and amyloid pathology (bold line).

3.3. Comparison of memory self-awareness across Aβ groups in cognitively normal and MCI patients

To investigate the relationship between self-awareness of memory function and groups, a univariate analysis of variance with memory self-awareness as dependent variable and group (CN Aβ-, CN Aβ+, MCI Aβ-, MCI Aβ+) as fixed effect was used (Fig. 2). Age, gender, education and GDS were entered as covariates. There was a significant effect of group on memory self-awareness ($F_{3,289} = 10.4$, $p < 0.001$). Post hoc contrasts across groups revealed trend level statistically differences between CN Aβ- and CN Aβ+ ($p = 0.066$), a statistically significant difference between CN Aβ- and MCI Aβ+ ($p < 0.001$), between CN Aβ+ and MCI Aβ+ ($p < 0.001$) and between CN Aβ+ and MCI Aβ- ($p = 0.041$). Differences between CN Aβ- and MCI Aβ- ($p = 0.7$) and between MCI Aβ- and MCI Aβ+ ($p = 0.8$) were not significant. Of note, memory self-awareness for MCI Aβ- ($t = -0.9$, $p = 0.3$) was not significantly different from 0, indicating that this group had normal insight into their memory functions.

3.4. Replication of analyses using a matched CN group

To investigate that our results were not due to unequal n sizes between our groups, we performed a set of analyses with a smaller CN group, created by case-matching the sample to the MCI group based on age, gender and education. The univariate analysis (controlling for GDS) examining the effect of clinical group (CN, MCI) and amyloid (continuous) on self-awareness of memory showed a significant interaction effect between group and amyloid ($F_{1,65} = 5.38$, $p = 0.024$). Post

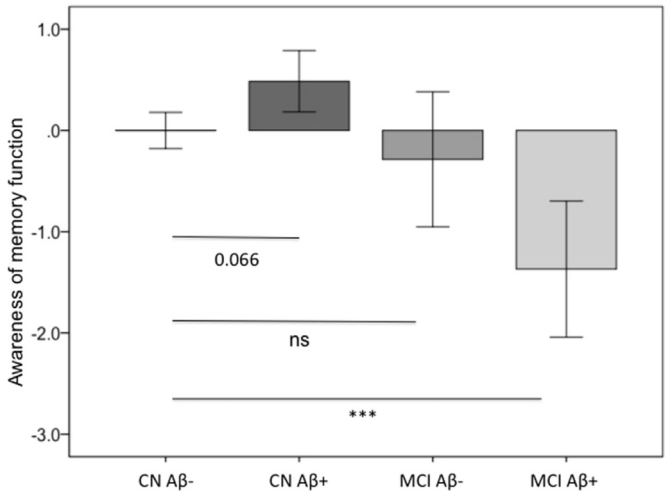

Fig. 2. Comparison of self-awareness of memory across Aβ groups in cognitively normal and MCI patients. CN = Cognitively normal; MCI = mild cognitive impairment; Aβ- = low amounts of amyloid; Aβ+ = high amount of amyloid. A PiB DVR threshold of 1.2 was used as cut-off in both groups. Cognitively normal individuals with high amounts of amyloid demonstrate increased self-awareness of memory (hypernosognosia) as compared to cognitively normal individuals without amyloid deposition. MCI patients with high amounts of amyloid demonstrate decreased self-awareness of memory (anosognosia) as compared to cognitively normal individuals without amyloid deposition. No difference in self-awareness of memory between cognitively normal individuals without amyloid burden and MCI individuals without amyloid deposition was found. Mean and 95% confidence interval. Analysis was controlled for age, gender, education and GDS. ***$p < 0.001$.

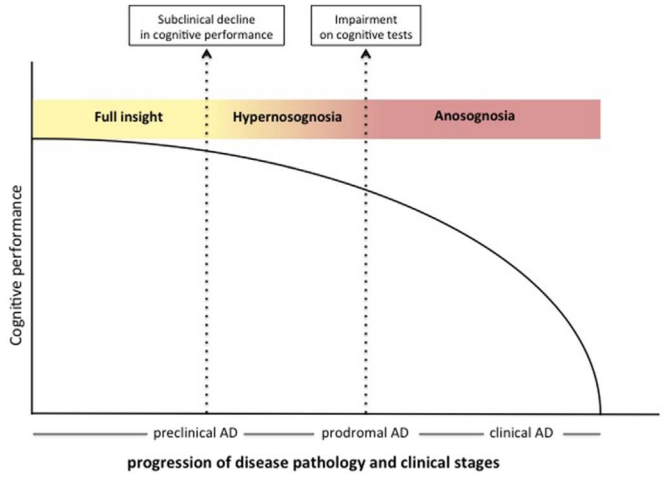

Fig. 3. A hypothetical model of awareness of memory across the preclinical and prodromal stages of AD. The model depicts cognitive performance (*y*-axis), awareness of memory function (color coded) and their relationship to disease pathology and clinical stages (*x*-axis) of Alzheimer's disease (AD). After a phase of stable cognitive performance in the presence of increasing pathology, subtle decline of cognitive performance occurs at which point the individual becomes increasingly aware of a change in memory function (hypernosognosia: orange color). Of note, hypernosognosia might be present in individuals without increased neurodegenerative pathology which might represent the "worried well" population. As pathology increases and impairment of cognitive tests is documented clinically, the individuals self-report's of memory impairment levels off and becomes less reliable (anosognosia; red color). Of note, we found that MCI patients without increased amyloid pathology had insight into their memory impairment. The model is based on cross-sectional data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hoc analysis demonstrated a positive association (although non-significant) between memory self-awareness and amyloid in the CN group ($r=0.2$, $p=0.18$) and a negative association in the MCI group ($r=-0.5$, $p=0.002$). The Fisher r-to-z transformation was statistically different between the two correlation coefficients ($z=3.1$, $p=0.002$). Similarly, the univariate analysis of variance (controlling for GDS) with memory self-awareness as dependent variable and group (CN Aβ-, CN Aβ+, MCI Aβ-, MCI Aβ+) demonstrated a significant effect of group on memory self-awareness ($F_{3,65}=8.8$, $p<0.001$). Post hoc contrasts across groups revealed a trending statistically significance differences between CN Aβ- and CN Aβ+ ($p<0.09$), a significant difference between CN Aβ- and MCI Aβ+ ($p<0.007$), and between CN Aβ+ and MCI Aβ+ ($p<0.001$) and between CN Aβ+ and MCI Aβ- ($p=0.049$). Differences between CN Aβ- and MCI Aβ- ($p=0.1$) and between MCI Aβ- and MCI Aβ+ ($p=0.35$) were not significant. Memory self-awareness for MCI Aβ- ($t=-0.67$, $p=0.51$) was not significantly different from 0, indicating that this group had insight into their memory functions.

4. Discussion

Here, we observed two states of altered self-awareness of memory across the preclinical and prodromal stages of AD. We show that CN individuals harboring amyloid pathology (CN Aß+) demonstrated heightened memory self-awareness (hypernosognosia). In contrast, MCI Aß+ patients demonstrated over-estimation of their memory functioning (anosognosia). These findings provide empirical evidence supporting the hypothesis that altered memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease are associated with amyloid pathology in brain regions that has been shown to exhibit substantial elevation of PiB retention in AD patients (Raji et al., 2008) and which, interestingly, also overlaps with brain regions that have been implicated in self-referential processing (Johnson and Ries, 2010; Northoff and Bermpohl, 2004; Northoff et al., 2006; Schmitz and Johnson, 2007). Further supporting this is our finding that MCI patients without amyloid pathology in these regions demonstrated close to full insight into their memory functions.

In an attempt to illustrate the current results we have created a hypothetical model of changes in self-awareness of memory function over the course of Alzheimer's disease (Fig. 3). In this model the level of self-awareness varies in a continuum from normal awareness of cognitive performance to anosognosia through a phase termed *hypernosognosia* in which the individual experience heightened awareness of normal memory performance (see orange area in Fig. 3). This model is similar to the cognitive model that Dalla Barba et al. (2015) recently proposed. In the model by Dalla Barba and collegues, they recognized a phase, termed *cognitive dysgnosia*, in which the individual experience awareness of normal performance as impaired. However, while the authors propose that CN individuals with *cognitive dysgnosia* may be less likely to develop Alzheimer's disease, our findings suggest that underestimation of memory functioning is linked to amyloid pathology in the CN. Our findings are consistent with previous reports in individuals with Subjective Cognitive Decline which have demonstrated that self-reports of memory impairment (but performing within normal limits on objective cognitive tasks) is linked to increased Aβ burden (Amariglio et al., 2012; Perrotin et al., 2012), metabolic dysregulation (Scheef et al., 2012) as well as decreased cerebral volume, especially hippocampal volume (Jessen et al., 2006; Palm et al., 2013; Saykin et al., 2006; Stewart et al., 2008; Striepens et al., 2010, van Norden et al., 2008; Wang et al., 2006). In addition, longitudinal studies have demonstrated that individuals with Subjective Cognitive Decline have a higher incidence of prospective Alzheimer's disease (Geerlings et al., 1999; Schmand et al., 2009; van Harten et al., 2013). However, one study found that Subjective Cognitive Decline did not predict cognitive decline in a community sample of older adults (Jorm et al., 1997). Although one caveat in the study by Jorm et al. (1997) was that the sample may have included people with cognitive impairment who were unaware of any change, again speaking for the fact that the level of self-awareness of memory function may vary across Alzheimer's disease. With this in mind, we believe that the term *hypernosognosia* (from Greek meaning hyper = over, excessive; nosos = disease; gnosis = knowledge) might better capture the perceived changes in memory that these individuals are experiencing.

Despite an increasing number of studies that have suggested that individuals with Subjective Cognitive Decline may be in the preclinical stage of Alzheimer's disease (e.g. Amariglio et al., 2015) but see also Jessen et al. (2014a), it still remains a conundrum at what stage anosognosia occurs and if, in fact, an individual's self-judgment of his/hers own cognitive abilities do change over the course of the disease as pathology increases (see red area in Fig. 3). With regard to MCI, there is evidence to show that the level of awareness do indeed vary (see Roberts et al. (2009) for a systematic review), which have implications for the use of Subjective Cognitive Decline in the setting of MCI. For instance, a recent longitudinal study by Wolfsgruber et al. (2014) studied 417 MCI patients with and without memory concerns. They found that lower memory performance and Subjective Cognitive Decline independently increased the risk of incident Alzheimer's disease. In addition, a significant interaction effect between the two was found such that Subjective Cognitive Decline was more predictive at early stages of MCI, while in more advanced stages of MCI it was not found to contribute to risk of dementia (Wolfsgruber et al., 2014), most likely reflecting the onset of anosognosia and thus reduced validity of the self-reports of memory performance. With regard to the current findings, we found that individuals with MCI do indeed vary in regard to their self-awareness of memory function, such that MCI patients with high amyloid show decreased self-awareness of memory as compared to MCI patients with low amyloid. Longitudinal studies will determine whether loss of self-awareness in these individuals may serve as a relevant predictor of progression to Alzheimer dementia, as well as investigate whether the MCI patients with insight to their memory impairment will progress, remain stable or convert back to normal after follow-up.

Interestingly, with regard to demographics, we found a gender effect such that males had significantly decreased memory awareness as compared to females across the whole sample. To investigate this further and to determine if these findings are relevant in the context of amyloid deposition and risk for AD we performed a set of univariate analysis of variance (controlling for age, education, and GDS) with memory self-awareness as dependent variable and group (CN Aβ-, CN Aβ+, MCI Aβ-, MCI Aβ+) and gender (female, male) as fixed groups. This analysis did not yield a significant interaction effect of group and gender ($F_{3,286}=1.2$, $p=0.32$). Similarly, just examining the CN and MCI groups separately did not reveal a significant interaction effect between groups Aβ- / Aβ+ and gender in the CN ($F_{1,255}=0.64$, $p=0.42$) or MCI ($F_{1,28}=1.2$, $p=0.28$). These results suggest that although there seems to be a general effect of gender on self-awareness of memory it does not seem to relate to amyloid burden or clinical group. However, future studies might examine other pathological markers such as neurodegenerative imaging markers, e.g. FDG and Tau PET, to determine whether gender might contribute to differential changes in self-awareness as individuals progress to AD dementia.

Some limitations of this work needs to be acknowledged. To date, there is no consensus on how to optimally assess anosognosia in AD, but see discussion in Starkstein (2014). Here, we use a discrepancy score between the participant's self-assessment and objective task performance, an approach that has been used in several previous publications investigating anosognosia in Alzheimer's disease (e.g. Perrotin et al. (2015)). In addition, we are aware that the accuracy of reported concerns may be affected by confounding factors, for instance mood symptoms of the participant. Further complicating the picture is that depressive symptoms could represent early Alzheimer's disease-related changes. With regard to anosognosia, previous studies have found increasing anosognosia in Alzheimer's disease to be associated with less severe depression (Starkstein, 2014), whereas studies on Subjective Cognitive Decline in preclinical Alzheimer's disease have found evidence of subthreshold symptoms of depression (Jessen et al., 2014a). To address this issue, although all of our participants were at subsyndromal levels, we controlled for depressive symptom in all our statistical models. Another limitation of this study is the fact that we had fewer MCI individuals as compared to CN. To ensure our results were not due to these unequal n sizes, we performed a set of sub-analyses using a smaller CN group matched to the MCI group using age, gender and education. Reassuringly, we found that our main results remained the same.

This is the first study to use in vivo amyloid imaging to assess the pathological substrates of altered memory self-awareness in clinically normal adults and MCI patients. Our results demonstrate “a flip” in the self-awareness of memory function that tracks with amyloid pathology across the preclinical and prodromal stages of AD. The findings of variability of awareness could have implications to the reliability of a person's complaints of memory dysfunction. Discordant subjective and objective measures may provide an important piece of information to the clinician and should be considered in the diagnostic criteria of preclinical and prodromal AD.

Authors’ contributions

Study concept and design: PV, RS, RA.
Analysis and interpretation of data: PV, RS, RA, DML, BH.
Drafting of the manuscript: PV.
Critical revision of the manuscript for important intellectual content: PV, RA, BH, KJ, JC, DML, AP-L, DR, RS.

Potential conflicts of interest

Dr. McLaren is currently a Biospective, Inc. employee; however, Biospective, Inc. did not contribute resources or have any involvement in this study. All other authors report no competing interests.

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