Deficits in short-term memory binding are detectable in individuals with brain amyloid deposition in the absence of overt neurodegeneration in the Alzheimer´s disease continuum.

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ABSTRACT

The short-term memory binding (STMB) test involves the ability to hold in memory the integration between surface features, such as shapes and colours. The STMB test has been used to detect Alzheimer's disease (AD) at different stages, from preclinical to dementia, showing promising results. The objective of the present study was to verify whether the STMB test could differentiate patients with distinct biomarker profiles in the AD continuum. The sample comprised 18 cognitively unimpaired (CU) participants, 30 mild cognitive impairment (MCI) and 23 AD patients. All participants underwent positron emission tomography (PET) with Pittsburgh compound-B labelled with carbon-11 ([^{11}C]PIB) assessing amyloid beta (Aβ) aggregation (A) and 18fluorine-fluorodeoxyglucose ([^{18}F]FDG)-PET assessing neurodegeneration (N) (A-N- [n = 35]); A+N- [n = 11]; A+N+ [n = 19]). Participants who were negative and positive for amyloid deposition were compared in the absence (A-N- vs. A+N-) of neurodegeneration. When compared with the RAVLT and SKT memory tests, the STMB was the only cognitive task that differentiated these groups, predicting the group outcome in logistic regression analyses. The STMB test showed to be sensitive to the signs of AD pathology and may represent a cognitive marker within the AD continuum.

Keywords: Short-term memory binding; PET; biomarkers; amyloid; mild cognitive impairment, Alzheimer's disease.

1. Introduction

The short-term memory binding (STMB) test assesses the ability to hold integrations of surface features (e.g. shape and colour) as a unique representation in memory (Luck & Vogel, 1997; Wheeler & Treisman, 2002). In a frequently used format, participants see two coloured shapes on a screen and subsequently they indicate whether there was a change between the combination of shapes and colours on a test screen. STMB has been used to identify cognitive impairment in patients in different stages of the Alzheimer´s disease (AD) continuum. The test showed high sensitivity and specificity for sporadic AD (Cecchini et al., 2020, 2017; Della Sala, Kozlova, Stamate, & Parra, 2016; Kozlova, Parra, Titova, Gantman, & Della Sala, 2020; Parra, Abrahams, Logie, Méndez, et al., 2010) and familial AD due to the presenilin-1 E280A mutation (Liang et al., 2016; Norton et al., 2020; Parra, Abrahams, Logie, Méndez, et al., 2010; Parra, Saarimäki, et al., 2015). It has also been shown to differentiate amnestic mild cognitive impairment (MCI) from controls (Cecchini et al., 2020; Koppara et al., 2015; Kozlova et al., 2020; Parra et al., 2019; Parra, Mikulan, et al., 2017; Pietto et al., 2016; Valdés Hernández et al., 2020).

In a different study evaluating carriers of the presenilin-1 E280A mutation, Parra et al. (Parra et al., 2011) found that the STMB was the only cognitive test (compared to Paired Associates Learning, Rey Figure test, verbal fluencies, trail making test and Mini-mental State Examination) that could discriminate controls from asymptomatic carriers of the mutation in analyses using receiver operating characteristic curves (ROC), with an area under de curve (AUC) equal to 0.86. In addition, the binding deficit of asymptomatic carriers of the mutation showed an equivalent deficit when compared with carriers of the same mutation in the dementia stage (controls > asymptomatic carriers = familial AD dementia) (Parra et al., 2011). These results suggest that binding deficits could be a cognitive marker of early AD that is not followed by a significant drop in performance with the progression of the disease (cognitively unimpaired > preclinical = MCI = AD), which is different of what is consistently observed with usual memory tests (cognitively unimpaired = preclinical > MCI > AD). If AD disrupts the ability to hold temporarily bound information from its early stages, the STMB test would be better used for diagnostic purposes, but not to keep track of the disease progression. Other neuropsychological tests could be less sensitive to detect preclinical AD when compared with the STMB test, but they would be better for following-up the patients.

In recent years, it has been demonstrated that the biological processes associated to sporadic AD may also be identified years before clinical diagnosis (Jack et al., 2018, 2016). This has led to the proposition in 2018 of a research framework that establishes AD as a biological construct rather than a clinical syndrome, relying on the presence of the 42-residue β- amyloid isoform ($A\beta_{42}$) (A) and phospho-tau (T) to define the diagnosis of AD based on cerebrospinal fluid (CSF) analyses or positron emission tomography (PET) imaging (Jack et al., 2018). The presence of neurodegenerative changes (N) along the course of the disease, identified by structural magnetic resonance imaging (MRI), PET with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG-PET) or total tau CSF measurements, characterizes AD with signs of neurodegeneration (Jack et al, 2018). Within such AT(N) framework, neuropsychological evaluations may be added for disease staging (Jack et al., 2018).

The neuropsychological evaluation in the preclinical stages of AD is important to document the risk of progression to dementia. Nation, Ho, Dutt, Han, and Lai (2019), for instance, showed that a decline over 12 months in neuropsychological tests increases in 2.28 times the risk for a diagnosis of dementia, even after correcting for intersubject variations in the presence and severity of AD biomarker changes. Therefore, there has been great interest in the field of neuropsychology in investigations of cognitive deficits which may be associated to Aβ and phospho-tau biomarkers, signalling the presence of preclinical AD (Hedden, Oh, Younger, & Patel, 2013; Jansen et al., 2018). In spite of the fact that tau pathology and neurodegeneration have shown to be more associated with cognitive measures than Aβ (Aschenbrenner, Gordon, Benzinger, Morris, & Hassenstab, 2018; Bejanin et al., 2017; Brier et al., 2016; Hanseeuw et al., 2019), they probably occur in a later stage of the disease. Following the amyloid cascade hypothesis, the amyloid deposition is the first sign of AD, probably triggering the other manifestations (Jack et al., 2013; Yasuno et al., 2021). Therefore, tests that significantly correlate with the amyloid burden in the brain may contribute to identify AD in its very early stages.

Different cognitive tasks have been investigated in the context of preclinical AD, especially episodic memory tasks. The Free and Cued Selective Reminding test (FCSRT) and the Rey Auditory Verbal Learning Test (RAVLT), for instance, showed to be significant predictors of disease progression when used in the preclinical stage (Grande et al., 2018; Grober, Veroff, & Lipton, 2018; Mormino et al., 2017; Schindler et al., 2017; Timmers et al., 2019). However, distinct tests may show different associations with Aβ burden in the preclinical stage of AD. The FCSRT, the Logical Memory from Wechsler Memory Scale, the Memory Capacity Test and the Face-name Association Test, for instance, have been associated with Aβ burden in the preclinical stage (Insel, Donohue, Sperling, Hansson, & Mattsson-Carlgren, 2020; Rentz et al., 2009; Rentz et al., 2011), while indices based on lists of words, such as the delayed score of the RAVLT, have not (Bilgel et al., 2018; Timmers et al., 2019, but see Bos et al., 2018)). These results could occur due to different methodologies across studies, such as sample characteristics or the technique used to measure Aβ burden or memory. For instance, Dupont et al. (2020) showed an association between Aβ burden and episodic memory in preclinical AD, but the authors used a composite score with RAVLT, Logical Memory, DSM-48 and the Rey Complex Figure Test. Therefore, the contribution of each test for this association was unclear. One other possibility relates to the characteristics of the tests, since they assess episodic memory using different methods. Tests such as the RAVLT, which uses the recall of a list of unrelated words, may be less sensitive to detect subtle memory deficits associated with amyloidosis in the preclinical stage of AD. In consistency with the latter possibility, recent metanalyses of studies with preclinical AD patients have shown only a small effect of amyloidosis on episodic memory performance (Baker et al., 2017).

In a recent study using [^{11}C]PIB-PET to measure Aβ aggregation and [^{18}F]FDG-PET to assess neurodegeneration, Squarzoni et al. (2020) compared episodic memory performance in an elderly sample divided in four groups according to the presence of Aβ burden and neurodegeneration (A-N- | A+N- | A-N+ | A+N+), including cognitively unimpaired (CU) individuals, amnestic MCI subjects and patients with dementia clinically compatible with AD. Neither the RAVLT nor the memory subscore of the Short Cognitive Performance Test (SKT) differentiated participants with and without Aβ burden in the absence

of neurodegeneration. Conversely, memory performance deficits became significant in the presence of neurodegeneration, in consistency with the view that conventional episodic memory tests may not capture the earliest manifestations of the disease.

Notwithstanding the evidence suggesting that AD affects the ability to hold bound information temporarily (Cecchini et al., 2020, 2017; Parra et al., 2009), even at preclinical or prodromal stages of the disease (Parra, Abrahams, Logie, Méndez, et al., 2010; Parra et al., 2011), only two studies have tested whether the STMB test can differentiate individuals who are positive or negative for biomarkers of AD pathology and neurodegeneration (Norton et al., 2020; Parra, Gazes, & Stern, 2017). Parra, Gazes and Stern (2017) assessed 39 CU participants and divided the sample according to high versus low STMB test performance. They showed that participants with low performance on the STMB task, who were called weak-binders, had higher Aβ burden (as assessed by CSF or [^{18}F]PIB-PET) relative to strong-binders. Norton et al. (2020) correlated the performance on the STMB test with Aβ and tau burden as assessed with [^{11}C]PIB and ^{18}Fflortaucipir PET in a sample of CU participants, asymptomatic carriers of the presenilin-1 E280A mutation and carriers of the mutation in MCI stage. The authors showed a significant correlation in the asymptomatic sample between STMB scores in the bound condition and mean cortical amyloid deposition ($r = -0.50$, $p = 0.03$), but a non-significant correlation with tau deposition on the entorhinal cortex ($r = -0.26$, $p = 0.27$) or inferior temporal lobe ($r = -0.30$, $p = 0.21$). The authors considered this a preliminary finding due to the small sample size in this correlation (n=19), and it is not clear if these results could be generalized to a sample of sporadic AD. Therefore, the objective of the present study was to verify whether STMB could differentiate patients who were considered positive or negative for the presence of Aβ burden, in the absence of overt neurodegeneration in the AD continuum.

2. Methods

2.1 Participants

The sample involved in this study was a sub-sample from Squarzoni et. al (2020) study, comprising 18 CU participants, 30 patients with amnestic MCI and 23 patients with dementia clinically compatible with mild AD (henceforth referred to as AD), who had data for the STMB test. Participants were recruited from the Neurology and Geriatric Psychiatry outpatient services of the *Hospital das Clínicas*, Medical school, University of Sao Paulo. The ethical committee of the institution approved the investigation (CAPPesq 368.037), and written informed consent was obtained from all participants or from the caregivers of patients with dementia.

CU participants had unimpaired cognition, according to age and education stratified norms, for tests in a traditional neuropsychological evaluation. The battery included neuropsychological tests for visual and verbal episodic memory, visuoconstructive function, semantic memory, attention, processing speed, language and executive functioning, described in detail in Squarzoni et al. (2020). In addition, they underwent a neurological examination and structured interview using the Structured Clinical Interview for DSM-IV (SCID-IV) for evaluation of psychiatric disorders (Del-Ben et al., 2001). Healthy controls

were recruited via announcements in the community and invitation of the relatives of AD and MCI subjects or from other studies carried out in the institution.

The MCI and AD patients performed the same neuropsychological assessment as the CU group, and all participants underwent laboratorial exams and were diagnosed in consensus meetings with neurologists, psychiatrists and neuropsychologists. The complete diagnostic procedures were previously described in detail (Coutinho et al., 2020). In short, MCI diagnosis was based on internationally accepted criteria (Albert et al., 2011; Petersen, 2011). All MCI patients were amnestic, diagnosed if they presented scores at least 1.5 standard deviation (SD) below the age norms in one memory test, or 1.0 SD below in more than one memory test. MCI patients might have deficits in other cognitive domains besides memory. In addition, MCI patients should have cognitive complaints and no impairment in functional status. AD patients were diagnosed using the National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) for probable AD (McKhann et al., 2011) and diagnosed in the dementia stage following the DSM-IV criteria (American Psychiatric Association, 2000).

For this study, as we aimed to contrast the STMB test to traditional tests of episodic memory, the following tests were included in the present analyses: the RAVLT delayed recall (Malloy-Diniz, Lasmar, Gazinelli, Fuentes, & Salgado, 2007), as a measure of long-term verbal episodic memory and the SKT memory score (Flaks, Forlenza, Pereira, Viola, & Yassuda, 2009; Lehfeld & Erzigkeit, 1997), as a measure of long-term visual episodic memory. The Mini Mental State Examination (MMSE) (Brucki, Nitrini, Caramelli, Bertolucci, & Okamoto, 2003; Folstein, Folstein, & McHugh, 1975) was used as a measure of global cognition, and the estimated intelligence quotient was obtained through the Block Design and Vocabulary tests from the third edition of the Wechsler Adults Intelligence Scale (Nascimento, 2004; Wechsler, 1997).

The exclusion criteria for all groups were: systemic disorders or medical conditions that could affect cognition; visual, auditory or motor deficits that could interfere with the neuropsychological assessment; presence of psychiatric disorders; family history of dementia with a dominant pattern of inheritance; presence of vascular pathology or lesions detected by MRI scanning.

2.2 Short-term memory binding task

The STMB test modality used in the present study was the change detection task. Participants saw a study screen with two coloured shapes and needed to memorize the combination of the shape and colour. After a 900ms interval, they were presented the test screen in which they should check if there was a change between the combination of shapes and colours. Participants should say "same" if the combinations of shapes and colours were the same or "different" if the colours had been swapped between the shapes. In the present study, only the bound (shape-colours integration) condition was used, because it is the most sensitive task to detect AD pathology (Parra, Abrahams, Logie, & Della Sala, 2010). More information and details about the task can be found in previous studies (e.g., Parra, Abrahams, Logie, Méndez, et al.,

2010). Participants completed 16 trials according to the methodological recommendations of Della Sala et al. (2016). Figure 1 presents an illustration of the STMB task used in the present study.

[INSERT FIGURE 1 HERE]

Figure 1. Short-term memory binding task: participants should detect if there was a change in shape-colours combinations between the study and test displays.

2.3 PET data acquisition

PET/CT images were acquired using a Discovery-710 PET/CT-scanner (GE-Healthcare, Milwaukee, USA), and both [^{11}C]PIB and [^{18}F]FDG-PET exams were carried out at the *Centro de Medicina Nuclear* of HC-FMUSP (LIM-43), using an on-site GMP cyclotron facility (PETtrace-880, GE-Healthcare). Details regarding radiochemical production and image acquisition procedures were described previously (Coutinho et al., 2020; Faria et al., 2019).

2.4 Quantitative indices of Aβ burden

Standardized uptake value ratios (SUVRs) of [^{11}C]PIB uptake were calculated for 34 regions-of-interest (ROIs) placed on the prefrontal, orbitofrontal, parietal, temporal, parahippocampal, anterior cingulate and posterior cingulate cortices and precuneus, normalized to whole cerebellar tracer uptake (Klunk et al., 2015) using the PMOD™ software (PMOD Technologies LLC, Zürich, Switzerland), and a composite ROI (metaROI) including all regions was used to generate [^{11}C]PIB SUVr values for each individual (Jack et al., 2019).

2.5 Classification of subjects in four biomarker categories following the recommendations of the 2018 NIA-AA Research Framework

Protocols used for visual inspection of PET datasets were described previously (Coutinho et al., 2020). In brief, [^{11}C]PIB PET datasets were rated in consensus by two nuclear medicine physicians as "positive" if there was an increase in uptake in cortical gray matter (GM) areas causing a loss of GM to white matter (WM) contrast, aided by the 3D-SSP semi-quantitative method designed for the clinical analysis of brain PET amyloid imaging (Cortex ID Suite software, GE healthcare - http://www3.gehealthcare.com/en/products/categories/advanced_visualization/applications/cortexid), with SUVr of the cortical areas normalized for the cerebellar gray matter and using a cutoff of 1.42, process described in detail elsewhere (Coutinho et al., 2020). In regard to [^{18}F]FDG-PET datasets, the two

readers scored each exam as "positive" (specifying the abnormalities as typical or non-typical of AD) or "negative".

Based on the above described individual classification of [^{11}C]PIB-PET and [^{18}F]FDG-PET datasets as “positive” or “negative”, and applying the principles of the 2018 NIA-AA (Jack et al., 2018), we classified each individual in one of the four following categories: A+N+ (Alzheimer´s pathology with neurodegeneration); A+N- (Alzheimer´s pathology without neurodegeneration); A-N- (non-pathological findings); and A-N+ (suspected non-Alzheimer pathology - SNAP). We were not able to apply the complete AT(N) classification since neither PET imaging nor CSF analyses evaluating tau pathology were performed.

2.6 Statistical analyses

The CU, MCI and AD groups were compared using one-way ANOVA, followed by a post hoc analyses using Bonferroni’s correction for multiple comparisons. For age, SKT and STMB variables, the Games-Howell correction was used due to violation of homogeneity of variances. To compare categorical variables amongst the groups, the chi-square test was performed, and 2x2 comparisons were performed to identify group differences. The Hedges’ g formula was used to calculate the effect size of differences between the CU and the other groups (MCI and AD). The Hedges’ formula is more appropriated than the usual Cohen’s d in small samples and when the sample sizes are different (Cooper, Hedges, & Valentine, 2009). To interpret the Hedges’ g effect sizes, the following criteria were used (Cohen, 1988): 0.2 = small, 0.5 medium and 0.8 large.

To test whether the STMB could identify positivity in biomarker status, we compared groups which were negative and positive for Aβ (A) deposition following the research framework for AD (Jack et al., 2018). To restrict our analyses to the AD continuum, the A-N+ (SNAP) group was dropped from these analyses. Therefore, the groups A-N-, A+N- and A+N+ were compared using ANOVA. For MMSE, SKT and STMB variables, the Games-Howell correction was used due to violation of homogeneity of variances. The Hedges’ g formula was used to calculate the effect size of differences between A-N- and the other groups.

A logistic regression model using the STMB test, RAVLT, SKT, age and education as independent variables was performed to detect classification into the A-N- and A+N- groups, as the outcome variables. These groups were chosen as outcome for the regression model because they had no statistically significant difference regarding the diagnostic (CU, MCI and AD) distributions. This is also the most relevant diagnostic pair, as the study aimed to verify whether the STMB could differentiate patients who were Aβ positive, in the absence of overt neurodegeneration in the AD continuum. The chi-square (χ^2), Nagelkerke R^2, estimate (β), standard error (SE), Wald and odds ratio values were presented.

The statistical analyses were performed using JASP v.0.14.1 (JASP Team, 2020) program, and the significance level was set at 0.05.

3. Results

The sociodemographic characteristics and cognitive performance across the clinically defined groups are presented in Table 1.

[INSERT TABLE 1 HERE]

The groups had similar age and were statistically different in educational level, the CU group being more educated than the AD, with a large effect size. The CU and MCI groups outperformed the AD group in the MMSE and SKT (CU = MCI > AD). The three groups significantly differed in the RAVLT (CU > MCI > AD). The CU group had significantly higher performance on the STMB test than the AD group, with large effect size. Although CU and MCI had statistically equivalent scores (p=0.051) in the STMB test, the effect size suggested the difference could be significant if the samples were larger.

Table 1 also indicates that the CU group had significantly lower SUVr when compared with the AD group. As expected, the CU group had more subjects rated as negative for amyloidosis, while the AD group had more patients rated as positive for amyloidosis. In the [^{18}F]FDG-PET assessment, none of the CU participants showed neurodegeneration, while around 65% of AD patients had neurodegeneration. The MCI group had [11C]PIB SUVr between the CU and AD groups, showing to be a more heterogeneous group regarding brain amyloid deposition. The biomarker-based diagnosis indicated that the CU group had significantly more people negative for both the A and N biomarkers (around 90%), while the AD group had few patients negative for both parameters (around 20%). In addition, the AD group had significantly more patients positive for amyloidosis and neurodegeneration (A+N+).

Table 2 presents the sociodemographic and cognitive characteristics of the sample divided into groups which were positive or negative for amyloid-beta (A) and neurodegeneration (N) in the AD continuum. The A-N- and A+N- groups were similar in all variables, yet the STMB was the only variable for which the difference between these groups attained a large effect size. Figure 2 (supplementary materials) presents a scatterplot with the performance on the STMB test and clinical groups distributed across the AN framework. The A+N+ group had lower estimated IQ than the A-N- group and had statistically significant worse performance on cognitive tests when compared to the other groups. In addition, comparing the A-N- and the A+N+ groups, the differences had a large effect size in the RAVLT, SKT and MMSE, while moderate effect size for IQ and the STMB test.

[INSERT TABLE 2 HERE]

The logistic regression analysis was statistically significant ($X^2 = 11.343$, $p = 0.045$), correctly classifying 86.7% of cases (A-N- vs. A+N-). Age ($p = 0.049$) and the STMB ($p = 0.022$) were significant predictors

of group classification. Older participants were 21.6% more likely to be in the A+N- group, while participants with worse STMB performance were 38% more likely to be in the same group. The regression model is presented in Table 3.

[INSERT TABLE 3 HERE]

4. Discussion

The aim of the present study was to verify whether the STMB score differs between participants with distinct A(N) profiles drawn from principles of the AT(N) framework, in a sample including CU individuals, amnestic MCI and patients with dementia clinically compatible with AD. Results indicated that in the absence of overt signs of neurodegeneration on [^{18}F]FDG-PET, patients who were positive for brain amyloid deposition on [^{11}C]PIB-PET had significantly lower STMB scores. Comparing the A-N- and A+N- groups, the effect sizes showed that the difference in performance between the biomarker-based groups was large for the STMB, but low for the visual and verbal episodic memory tests (SKT and RAVLT, respectively). Also, the regression analysis showed that the STMB test was the only cognitive variable that significantly explained the variation between these groups. Therefore, these results suggest that the STMB test may be more sensitive to uncover early cognitive deficits in the AD continuum than other neuropsychological tests commonly used in clinical settings.

The amnestic MCI group did not show significant impairment in the STMB test when compared with CU participants, in contrast with the findings of previous studies (Cecchini et al., 2020; Koppara et al., 2015; Kozlova et al., 2020; Parra et al., 2019; Valdés Hernández et al., 2020), despite a trend to significance ($p = 0.051$) and a large effect size. Conversely, the significant difference in binding performance that occurred when the CU and AD groups were compared against each other is in line with previous findings (Cecchini et al., 2020; Della Sala et al., 2016; Kozlova et al., 2020; Parra, Abrahams, Logie, & Della Sala, 2010; Parra, Abrahams, Logie, Méndez, et al., 2010).

Episodic memory deficits are considered a cognitive hallmark of AD (McKhann et al., 2011). However, distinct memory tasks may be differentially impaired at early stages of AD pathology. The fact that the effect size was large for the STMB test but small for the RAVLT and SKT tasks when the A-N- and A+N- groups were compared is consistent with the expected greater sensitivity of the STMB at early AD stages (Parra, Abrahams, Logie, Méndez, et al., 2010; Parra et al., 2011). One hypothesis to explain such differences is based on the brain areas associated with each task. The delayed recall of list learning tests, such as the RAVLT, has been shown to be related with hippocampal volume (Bonner-Jackson, Mahmoud, Miller, & Banks, 2015; Kilpatrick et al., 1997; Saury & Emanuelson, 2017; Wolk & Dickerson, 2011). The SKT memory subtest assesses visual episodic memory. The hippocampus, especially in the right hemisphere, has been related with visual memory tests (Bonner-Jackson et al., 2015; Doss, Chelune, & Naugle, 2004; Gleissner, Helmstaedter, & Elger, 1998; Jones-Gotman, 1986; Squire et al., 1992). Conversely, performance on the STMB test has been shown to rely on brain areas

other than the hippocampus. The STMB test did not show association with the hippocampal activity measured by functional MRI (Parra, Della Sala, Logie, & Morcom, 2014; Piekema et al., 2010), but with parietal and occipital lobes (Parra et al., 2014). In studies using EEG measures, the STMB was associated with the activity of a frontal-parietal-occipital network (Parra, Saarimäki, et al., 2015; Pietto et al., 2016; Smith et al., 2016). Moreover, single case studies have consistently demonstrated that STMB tests, such as the one used in this study, can be performed without an intact hippocampus (Baddeley, Allen, & Hitch, 2011; Jonin et al., 2019; Parra, Fabi, et al., 2015). Therefore, the STMB and episodic memory tests may capture different aspects of brain functioning and can be differentially sensitive to the different stages of the AD continuum (Didic et al., 2011).

The hippocampus is involved in tasks that require long-term memory, especially context-rich information and relations between different object features (Olsen, Moses, Riggs, & Ryan, 2012; Yonelinas, 2013). The STMB test used in the present study is based on a recognition paradigm, therefore, it relies on a familiarity process, which is related to extra-hippocampal areas, such as the parahippocampal region and the entorhinal cortex (Du et al., 2019; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Sadeh, Ozubko, Winocur, & Moscovitch, 2014; Turriziani, Serra, Fadda, Caltagirone, & Carlesimo, 2008). Previous studies have reported that AD pathology does not affect the hippocampus in the very early stages of the disease. The neuronal pathology (neurofibrillary tangles) first appears in the transentorhinal region, then it spreads to the entorhinal cortex and later spread for other regions, including the hippocampus (Braak & Braak, 1997; Delacourte et al., 1999; Didic et al., 2011; Tapiola et al., 2008).

Different studies have shown that atrophy in the entorhinal cortex precedes atrophy in the hippocampus. The volume of the entorhinal cortex volume was a better predictor than the hippocampal volume, in preclinical stages, for AD conversion (de Toledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2006; Dickerson et al., 2001; Killiany et al., 2002). In addition, Pennanen et al. (Pennanen et al., 2004) showed that MCI patients had more atrophy in the entorhinal cortex than in the hippocampus, while Hirni et al. (Hirni et al., 2016) showed that atrophy in entorhinal and perirhinal cortices preceded, up to 12 years, the diagnosis of dementia. Combining these pieces of evidence, tentatively, it is possible to suggest that the STMB test is sensitive to AD pathology in extra-hippocampal regions, therefore, sensitive to early signs of AD (Didic et al., 2011).

Two previous studies correlated performance on the STMB test with profiles of AD biomarkers (Norton et al., 2020; Parra, Gazes, et al., 2017). Our investigation extends the findings of Parra, Gazes and Stern (2017) in a larger sample, including CU individuals as well as patients at later stages in the AD continuum, presenting cognitive deficits and signs of neurodegeneration as assessed with [^{18}F]FDG-PET. Interestingly, in Parra et al. (2017) the brain areas showing significant Aβ increase in weak-binders included those proposed by (Didic et al., 2011) as targeted by AD in early stages affecting sub-hippocampal regions (e.g., parahippocampus, entorhinal cortex), and areas found to be binding-specific by (Parra et al., 2014) (e.g., fusiform gyrus, lateral-occipital cortex).

The results from Norton et al. (2020), in which the authors found a significant correlation between STMB and cortical amyloid deposition but not with tau deposition on the entorhinal cortex could suggest another

hypothesis to explain our results. The amyloid deposition follows a different path in the brain than the tau deposition, as it starts in basal portions of the frontal, temporal and occipital lobes (Braak & Braak, 1997) and then it spreads to the rest of the brain, following the default mode network (Palmqvist et al., 2017). As the Aβ burden disrupts brain connectivity (Drzezga et al., 2011; Wang et al., 2013), the frontal-parietal-occipital network, related with visual short-term memory (Parra, Saarimäki, et al., 2015), could be disrupted. Thus, it is possible that STMB is not related with the entorhinal cortex activity, but with occipital and parietal areas, such as the fusiform gyrus (Parra et al., 2014), and their connection with parietal and frontal areas. Other studies, using different paradigms, have shown that these areas are important to maintain visual short-term memory information (Song & Jiang, 2006; Todd & Marois, 2004; Wei, Müller, Pollmann, & Zhou, 2011). These hypotheses (highlighting either the frontal-parietal-occipital network or the entorhinal cortex), however, still need further investigation.

The present study has some limitations. The relatively small sample size limits the statistical power and the generalization of the results. With a larger sample, it would be possible to conduct further analyses specifically for the CU group, running comparisons between A-N- and A+N- groups in the absence of cognitive deficits. However, we understand that as the groups based on biomarker status (A-N-, A+N-) did not show significant differences as to the clinical diagnosis, our comparison remains valid. In addition, it is important to recognize that we did not acquire measures of pathological tau accumulation using PET or CSF. Therefore, we were not able to conduct a complete biomarker-based (AT(N)) classification of subjects along the AD continuum (Jack et al., 2018). Tau pathology has been shown to be more associated with cognitive impairments than Aβ (Aschenbrenner et al., 2018; Brier et al., 2016; Hanseeuw et al., 2019), thus such measures could provide a more complete understanding of the characteristics of the present sample and its cognitive deficits. Future studies using the STMB test with CU participants and measures of Aβ and tau could present evidence whether the binding deficits occur in the presence of Aβ alone, as it is the first sign of AD pathological change (Jack et al., 2018, 2013; Yasuno et al., 2021).

Despite the above limitations, as a merit of the study we cite that it is one of the few investigations to address the relationship between biomarkers in sporadic AD and the STMB test, which has been indicated a potentially useful test to detect preclinical AD (Fuller et al., 2019; Martínez, Trujillo, Arévalo, Ibáñez, & Cardona, 2019; Dorene M Rentz et al., 2013). Future studies should evaluate STMB performance patterns in larger CU samples, comparing participants with and without amyloidosis without tau pathology to better describe binding deficits at very early stages of AD.

5. Conclusions

The present results related the STMB test with AD biomarkers. Differently from conventional episodic memory measurements, the STMB test was able to discriminate participants with and without brain amyloid deposition in the absence of overt neurodegeneration, indicating that the STMB test may be an important cognitive marker of AD.

Disclosure statement

The authors have no actual or potential conflicts of interest.

CRediT authorship contribution statement

Mario A. Cecchini: Conceptualization, Methodology, Formal analysis, Writing - Original Draft. **Mônica S. Yassuda**: Conceptualization, Methodology, Writing - Original Draft, Supervision. **Paula Squarzoni**: Conceptualization, Investigation, Resources, Data Curation, Writing - Review & Editing. **Artur M. Coutinho**: Investigation, Data Curation, Writing - Review & Editing. **Daniele de Paula Faria**: Investigation, Data Curation, Writing - Review & Editing. **Fábio L. S. Duran**: Formal analysis, Data Curation. **Naomi A. Costa**: Formal analysis, Data Curation. **Fábio H. G. Porto**: Investigation, Data Curation, Writing - Review & Editing. **Ricardo Nitrini**: Writing - Review & Editing, Funding acquisition. **Orestes V. Forlenza**: Writing - Review & Editing, Funding acquisition. **Sônia M. D. Brucki**: Writing - Review & Editing, Funding acquisition. **Carlos A. Buchpiguel**: Writing - Review & Editing, Funding acquisition. **Mario A. Parra**: Conceptualization, Methodology, Writing - Review & Editing. **Geraldo F. Busatto**: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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