



Refining memory assessment of elderly people with cognitive impairment: Insights from the short-term memory binding test

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ABSTRACT

Alzheimer's disease (AD) affects temporary memory for bound features more remarkably than for individual features. Such selective impairments manifest from presymptomatic through dementia stages via titration procedures. A recent study suggested that without titration and with high memory load the binding selectivity may disappear in people at risk of AD such as those with Mild Cognitive Impairment (MCI). We compared data from two studies on temporary binding which assessed people with MCI and controls using different memory loads (2 or 3 items). Selective binding impairments were found in MCI, but relative to controls, such selectivity was contingent upon memory load (i.e., present with 2 items). Further analysis with MCI people who tested positive to neuroimaging biomarkers (i.e., hippocampal atrophy) confirmed that this specific binding impairments are a feature of prodromal AD. The temporary binding task has been recently suggested by consensus papers as a potential screening tool for AD. The results presented here inform on task properties that can maximize the reliability of this new assessment tool for the detection of memory impairments in prodromal cases of AD.

1. Introduction

Memory assessment in individuals at risk of Alzheimer's disease (AD), such as those with Mild Cognitive Impairment (MCI), has long focused on episodic memory functions (Fields, Ferman, Boeve, & Smith, 2011; Parra, Abrahams, Logie, & Della Sala, 2010; Parra et al., 2011). Examples are Paired Associates Learning (PAL) tasks (Sahakian et al., 1988), the Face Name Associative Memory Exam (FNAME) (Amariglio et al., 2012; Rentz et al., 2013), the Free and Cued Selective Reminding test (FCSRT) (Barbeau et al., 2004; Buschke, 2014; Grober, Buschke, Crystal, Bang, & Dresner, 1988; Sarazin et al., 2007), and other episodic memory tests (Ivanou et al., 2005). These tests are known to assess functions of the hippocampus which are essential to episodic memory

formation i.e., associative memory (Tulving, 2002). Tests assessing associative memory functions of the hippocampus are considered markers for AD (Auriacombe et al., 2010; Barbeau et al., 2008; Dubois et al., 2010; Rentz et al., 2013; Sarazin et al., 2007). To uphold the claim that the associative function is that selectively impaired in AD, it is necessary to demonstrate that such impairments are greater than those found when patients remember the individual items. For instance, memory for faces (Sperling et al., 2003), lists of words (Gallo, Sullivan, Daffner, Schacter, & Budson, 2004), or locations (Stehli, Chubb, & Jacob, 2003), are functions affected by AD. This makes it difficult to ascertain that holding associations between these items in memory (e.g., faces and locations, faces and names) is the hallmark of AD. This is important because item memory and associative memory dissociate

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(Chalfonte, Verfaellie, Johnson, & Reiss, 1996; Old & Naveh-Benjamin, 2008) and the form of representation claimed to be specifically affected by the hippocampal amnesia of AD is the latter. This caveat i.e., limited underlying constructs, has been recently highlighted by a recent consensus paper (Costa et al., 2017).

The Visual Short-Term Memory Binding Test (VSTMBT) was developed to investigate if the function responsible for binding features within object representations is affected by AD above and beyond that supporting single feature processing (Parra, Abrahams, Logie, Mendez, et al., 2010). The test assesses participants' memory for single features such as shapes and for combination of features such as shape-color bindings. When memory load is controlled for (i.e., via titration to keep patients' and controls' memory performance for individual features at the same level), patients with AD show memory binding deficits which are far greater than those found when memory for single features is assessed (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012; Parra et al., 2009; Parra, Abrahams, Logie, & Della Sala, 2010; Parra, Abrahams, Logie, Mendez, et al., 2010; Parra et al., 2011). Such specific increase of the cost of binding has been observed since the preclinical stages of AD. This fits well current trends in the assessment of AD which have shifted toward a new lexicon (Costa et al., 2017; Dubois et al., 2010, 2016) that encourages the detection of subtle cognitive impairments in stages prior to dementia. The VSTMBT detects such early impairments, even when other novel and traditional tests have failed (Parra, Abrahams, Logie, Mendez, et al., 2010; Parra et al., 2011).

The results form a recent study (Koppara et al., 2015) suggest that memory load may be a factor precluding the specificity of the VSTMBT (i.e., greater cost of binding in patients than in controls). Previous studies have manipulated memory load by presenting patients and controls with a different number of to-be-remembered items (Della Sala, Kozlova, Stamate, & Parra, 2018; Della Sala et al., 2012; Parra et al., 2009; Parra, Abrahams, Logie, & Della Sala, 2010; Parra, Abrahams, Logie, Mendez, et al., 2010; Parra et al., 2011). Such manipulation rested on the assumption that VSTM stores a limited number of items (Luck & Vogel, 1997; Vogel, Woodman, & Luck, 2001) and that increasing the number of items above such a limit (i.e., 4) would overload memory, rendering the task more challenging and performance poorer. Titration aimed at reducing differences at baseline (i.e., memory for single features). This led to suggesting that patients with AD present with a selective deficit of VSTMB. (Koppara et al., 2015) showed that without titration (i.e., patients and controls tested with the same visual arrays of 3 items), the selectivity of the VSTMBT holds for people with Subjective Cognitive Deficits (SCD) but not for people with MCI. Considering that memory binding is maintained to be selectively impaired in AD and that MCI is an uncertain clinical category which holds limited value to predict future risk of dementia, it is important to demonstrate the precise testing conditions with which selective impairments of VSTMB can be found. Is the specific impaired ability to binding features in VSTM that has been considered a hallmark of AD. Hence, identifying such a hallmark in MCI people might provide more reliable evidence of AD pathology as the likely underlying mechanism. To address these outstanding issues, in the present paper we present data from groups of healthy older adults and people with MCI who were assessed with the VSTMBT using arrays of 2 and 3 items and without titration. If the above-mentioned selectivity is contingent upon memory load, it would be observed only under the low memory load condition (i.e., 2 items).

2. Methods

2.1. Participants

Participants came from two separate samples of people with MCI and matched controls assessed with different versions of the VSTMBT. One sample was tested with a version of the task presenting 2 items, the other sample was assessed with a version presenting 3 items. Table 1

shows the demographic, clinical and neuropsychological variables of the participants tested with the two set sizes. All participants underwent neuropsychological assessment. People with MCI met criteria proposed by Petersen (2004). Participants were fully informed about the study and they signed an Informed Consent Form prior to participation. The study was approved by Ethics Committees from the Psychology Faculty, Complutense University of Madrid, Clinical University Hospital San Carlos from Madrid, and the University Hospital Gregorio Marañón also from Madrid.

2.2. The Visual Short-Term Memory Binding Test (VSTMBT)

The VSTMBT required participants to remember visual arrays in which two or three black shapes (Shape Only condition) or colored shapes (Shape-Color Binding Condition) were presented for 2 s (Fig. 1A). After a brief delay (1 s), a test display appeared showing the same or different items all presented in new random locations. The task was to indicate verbally whether the study and test display showed the same (50% of the trials) or different items. Different trials in the Shape Only condition presented two new shapes at test. Different trials in the Shape-Color Binding condition presented two re-arranged combinations of shape and color (i.e., two shapes swapped their colors at test). Normal perception of shape-color bindings was ensued prior to the VSTMBT. Each condition presented 32 trials in random order. Conditions were counterbalanced across participants. We calculated proportion of correct recognition (see Parra, Abrahams, Logie, & Della Sala, 2010, for a detailed description of the task). The above described VSTMBT has been used extensively in experimental studies involving different populations with AD dementia or at risk of such dementia. More clinically friendly versions of the task (i.e., shorter version on PC or flashcard versions; see Della Sala et al., 2018) have been recently developed and validated. Using these clinical versions of the test, patients with AD dementia and controls were discriminated via ROC analyses with 100% sensitivity and specificity. These versions of the test are available for use on request (contact corresponding author).

2.3. Analysis

A mixed ANOVA model was used with Group (Controls Set Size 2 vs. people with MCI Set Size 2 vs. Controls Set Size 3 vs. people with MCI Set Size 3) as the between-subjects factor and Condition (Shape Only vs. Shape-Color Binding) as the within-subjects factor. We calculated effect size and power for main effects and interactions.

3. Results

The groups were matched on age, education, and depression scores. People with MCI showed a profile compatible with the multi-domain amnesic stage. The two groups of people with MCI showed a very similar profile of cognitive impairments. Control groups from the two samples did not differ in any of the neuropsychological scores (see Table 1).

The ANOVA model revealed a main effect of Group [$F(3,100) = 24.9, p < 0.001, \eta^2 = 0.43; \beta = 1.0$], main effect of Condition [$F(1,100) = 187.14, p < 0.001, \eta^2 = 0.65; \beta = 1.0$], and a significant Group \times Condition Interaction [$F(3,100) = 6.93, p < 0.001, \eta^2 = 0.17; \beta = 0.97$] (Fig. 1B). To unfold this interaction we ran two separate Group \times Condition ANOVAs for each Set Size. For Set Size 3 the interaction was non-significant [$F(1,50) = 2.91, p = 0.094, \eta^2 = 0.05; \beta = 0.39$], because of a large drop in binding performance in controls. For Set Size 2 it was significant [$F(1,50) = 14.86, p < 0.001, \eta^2 = 0.23; \beta = 0.79$]. Post hoc analysis (Table 1) revealed that MCI people's performance on the Shape-Color Binding condition was disproportionately lower than that on the Shape Only condition, a discrepancy not observed in controls. Although these results are appealing, they may still face limitations for diagnosis

Table 1
Demographic, clinical and neuropsychological variables of subjects tested with the two set sizes.

	Set Size 2			Set Size 3			ANOVA			Post Hoc									
	Controls (n = 25)			MCI (n = 27)			Controls (n = 29)			MCI (n = 23)			F	p	SS2	SS3	Ctr	SS2 vs SS3	MCI
	Mean (SD)	Range		Mean (SD)	Range		Mean (SD)	Range		Mean (SD)	Range								
Age	74.73 (4.74)	(66.00–83.00)		75.07 (5.30)	(65.00–87.00)		72.34 (3.76)	(68.00–80.00)		75.43 (5.77)	(67.00–86.00)		2.25	0.087	1.000	0.157	0.449	1.000	1.000
Education	10.84 (5.02)	(4.00–16.00)		10.86 (5.80)	(4.00–20.00)		11.00 (5.11)	(0.00–20.00)		9.43 (2.90)	(6.00–15.00)		0.54	0.655	1.000	1.000	1.000	1.000	1.000
GDS	1.12 (1.96)	(0.00–7.00)		2.00 (2.21)	(0.00–7.00)		1.28 (2.02)	(0.00–9.00)		2.39 (1.90)	(0.00–7.00)		2.19	0.094	0.684	0.316	1.000	1.000	1.000
MMSE	27.52 (1.98)	(24.00–30.00)		23.90 (2.88)	(20.00–29.00)		28.90 (1.23)	(26.00–30.00)		25.22 (1.73)	(20.00–27.00)		33.42	*	0.001	*	0.101	0.144	0.144
Blessed Scale	0.40 (0.76)	(0.00–2.50)		3.05 (2.62)	(0.00–10.00)		1.23 (1.54)	(0.00–7.00)		3.41 (3.02)	(0.00–12.00)		11.31	*	*	0.004	0.979	1.000	1.000
TAVEC Imm Free Recall	9.61 (3.34)	(0.00–14.00)		4.50 (3.70)	(0.00–13.00)		10.52 (2.37)	(7.00–16.00)		4.52 (4.04)	(0.00–14.00)		24.25	*	*	*	1.000	1.000	1.000
TAVEC Imm Cued Recall	11.21 (2.11)	(7.00–15.00)		6.17 (3.36)	(0.00–13.00)		11.97 (2.28)	(5.00–16.00)		6.74 (3.54)	(1.00–14.00)		29.17	*	*	*	1.000	1.000	1.000
TAVEC Delayed Free Recall	10.13 (2.97)	(0.00–14.00)		4.37 (3.64)	(0.00–13.00)		11.31 (1.97)	(9.00–16.00)		4.70 (3.73)	(0.00–14.00)		35.93	*	*	*	1.000	1.000	1.000
TAVEC Delayed Cued Recall	11.00 (1.96)	(7.00–16.00)		6.73 (3.68)	(0.00–15.00)		12.17 (2.24)	(7.00–16.00)		6.13 (3.17)	(1.00–12.00)		29.57	*	*	*	0.852	1.000	1.000
TAVEC Recognition	14.58 (1.59)	(11.00–16.0)		14.07 (1.89)	(9.00–16.00)		14.76 (1.41)	(12.00–16.00)		13.74 (2.09)	(9.00–16.00)		1.83	0.146	1.000	0.239	1.000	1.000	1.000
TMT-A	58.76 (21.58)	(23.00–116.0)		95.80 (56.19)	(31.00–260.00)		55.59 (16.06)	(26.00–97.00)		116.48 (79.33)	(32.00–357.0)		9.21	*	0.038	*	1.000	0.791	0.037
TMT-B	167.64 (93.0)	(49.00–360.0)		298.93 (150.86)	(117.00–673.0)		156.34 (76.51)	(74.00–443.0)		381.23 (231.44)	(80.00–929.0)		13.69	*	0.008	*	1.000	0.297	0.037
ROF Copy	28.56 (7.39)	(8.00–36.00)		22.92 (9.20)	(6.50–36.00)		33.69 (2.88)	(25.00–36.00)		28.54 (8.10)	(2.50–36.00)		10.83	*	0.033	0.076	0.072	0.037	0.037
ROF Imm Recall	12.48 (6.72)	(2.00–29.00)		7.79 (7.06)	(0.00–30.00)		16.50 (6.00)	(6.00–28.00)		7.22 (4.97)	(0.00–17.00)		13.14	*	0.053	*	0.143	1.000	1.000
ROF Delayed Recall	11.23 (6.27)	(2.05–26.50)		7.02 (7.04)	(0.00–28.00)		16.60 (6.15)	(3.00–28.00)		6.80 (4.74)	(0.00–18.00)		15.39	*	0.105	*	0.016	1.000	1.000
Letter Fluency (FAS)	34.92 (12.12)	(13.00–61.00)		24.03 (8.47)	(11.00–42.00)		35.24 (9.53)	(14.00–54.00)		27.82 (10.01)	(11.00–51.00)		8.43	*	0.001	0.060	1.000	1.000	1.000
Semantic Fluency	61.82 (11.30)	(37.00–81.00)		48.87 (11.53)	(24.00–80.00)		59.79 (9.44)	(45.00–76.00)		43.45 (10.95)	(22.00–60.00)		15.82	*	*	*	1.000	0.463	0.463
VSTM Shape Only	0.94 (0.10)	(0.57–1.00)		0.90 (0.11)	(0.52–1.00)		0.87 (0.11)	(0.53–1.00)		0.70 (0.12)	(0.53–0.94)		22.37	*	1.000	*	0.150	*	*
VSTM Shape-Color Binding	0.86 (0.12)	(0.51–1.00)		0.68 (0.16)	(0.40–0.98)		0.70 (0.11)	(0.53–0.97)		0.58 (0.08)	(0.41–0.75)		21.01	*	*	0.003	*	*	0.018

* $p < 0.001$; Blessed Scale (Blessed, Tomlinson, & Roth, 1968); GDS: Geriatric Depression Scale (Yesavage et al., 1982); Imm: Immediate Recall; MMSE: Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975); SS2 & 3: Set Sizes 2 and 3; TAVEC: Spanish version of the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987).

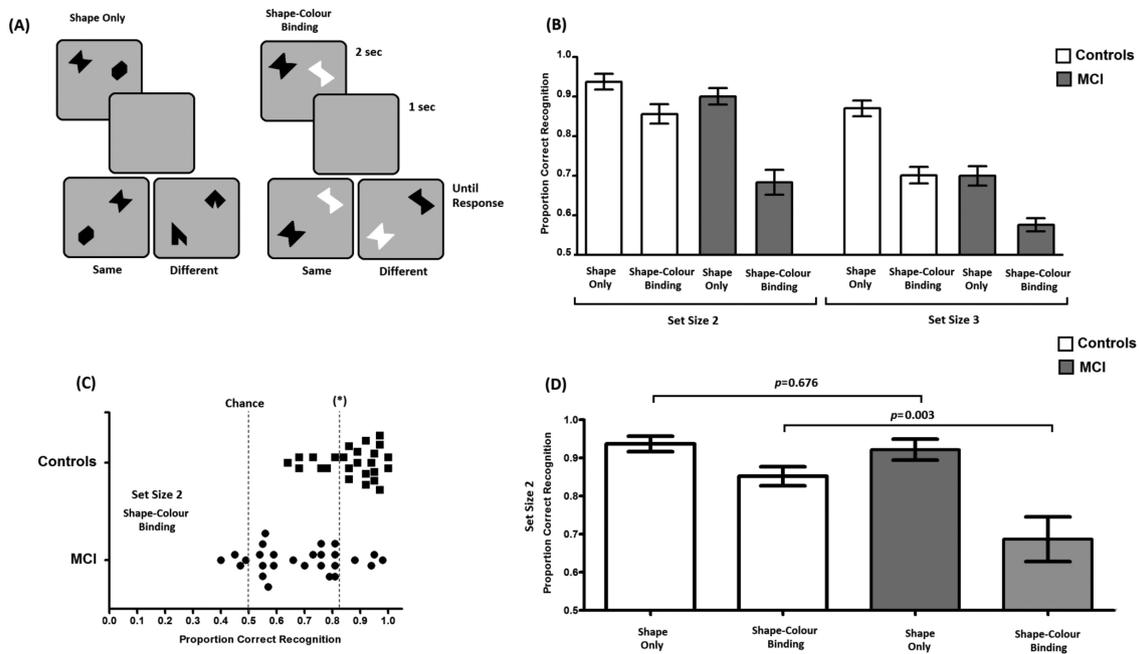


Fig. 1. (A) An example trial for each condition of the Short-Term Memory Binding Test using Set Size 2. (B) Mean data from the Short-Term Memory Binding Test (error bars = SEM). (C) Overlap between people with Mild Cognitive Impairment (MCI) and Controls in the Shape-Colour Binding condition of the Short-Term Memory Binding Test using Set Size 2. Twelve MCI people did not overlap with controls and fell below the cut-off (*) recently reported by Della Sala et al. (2017). There were 7 controls whose score were also below such a cut-off. Their neuropsychological background and that from controls above cut-off did not significantly differ (see Supplementary Table 1). (D) Mean data from the Short-Term Memory Binding Test from Controls and the 10 MCI people who had MRI evidence of hippocampal atrophy.

purposes as having MCI and VSTMB deficits may not unequivocally inform about the presence of prodromal AD. We ran further analyses using neuroimaging data to investigate if such a pattern of selective impairment holds for those who are considered biomarker positive (Dubois et al., 2010, 2016).

3.1. Additional analysis

A subsample of 17 people with MCI who were assessed with set size 2 underwent MRI scans. The volume of their hippocampus was measured and corrected for their intracranial volume. Individual hippocampal atrophy was assessed using voxel-based morphometry, as described in Olazaran et al. (2013). Hippocampal volume measurements were calculated using the freely available software FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>). We used automatic subcortical segmentation based upon the existence of an atlas containing probabilistic information on the location of structures. We followed the procedures described by Fischl et al. (2002). The accuracy of FreeSurfer results was then assessed visually for the different participants (Olazaran et al., 2013). The extracted volumes were corrected for the total Intra-cranial Volume (ICV). The cut-off to identify pathological atrophy was set at -1 SD from controls (see Supplementary Figure 1; see also Jack et al., 1997). According to these data, 10 participants with MCI show hippocampal atrophy (MTA) beyond that expected for their age (-1 SD below the control group, see Supplementary Figure 1). We ran additional analyses with the VSTMB data collected from this subsample of MCI + MTA using the model described above. These analyses revealed that 12 people with MCI showed binding deficits that did not overlap with healthy controls' score, (Fig. 1C). Among these MCI patients were those considered MCI + MTA ($n = 10$). When the ANOVA model was rerun entering solely the data from MCI + MTA, the interaction described above was replicated (Fig. 1D). The pattern shows the selectivity of binding deficits previously reported in AD samples (Group \times Condition Interaction: $F(1,33) = 13.07$, $p = 0.001$, $\eta^2 = 0.28$; $\beta = 0.94$).

4. Discussion

The present study was carried out to investigate whether and under what condition people with MCI present with the typical pattern of VSTMB impairments consistently found in patients with AD dementia. We were driven by the need of providing evidence of the task's psychometric features that can be clinically friendly as within these settings, procedures such as titration of task difficulty are unfeasible. We also sought evidence of whether VSTMB deficits in MCI are observed in those people who meet criteria for prodromal AD (i.e., significant atrophy of the hippocampus as documented by imaging biomarkers). Below we discuss the main implications of our findings.

4.1. Why dissecting memory binding impairments is important?

There are memory functions the decline of which could be detected prior to the dementia stage of AD (e.g., temporary binding abilities). These memory functions have proved both sensitive and specific to AD (Cecchini et al., 2017; Della Sala et al., 2012; Parra, Abrahams, Logie, & Della Sala, 2010). To ascertain whether they are selectively impaired, we need to refine the assessment procedures (Logie, Parra, & Della Sala, 2015). Such developments may enable us to map cognitively the continuum of AD. For instance, asymptomatic carriers of the mutation E280A-PSEN1 leading to familial AD (Parra, Abrahams, Logie, Mendez, et al., 2010) and patients with SCD (Koppara et al., 2015) tested under high memory load (3 items) showed selective memory binding impairments contrasting with a normal neuropsychological background. Without titration and with high memory load, (Koppara et al., 2015) reported that such selectivity disappeared in MCI samples. However, when memory load is low, the selectivity of binding is restored in these MCI people and mirrors that found in patients with AD dementia (Della Sala et al., 2018). Here we show, for the first time, that MCI people with evidence of hippocampal atrophy (MCI + MTA) show significant binding deficits when tested under low memory load condition. Interestingly, a subgroup of controls ($n = 7$) showed performance below a

recently reported cut-off (Della Sala et al., 2018) despite an intact neuropsychological background.

A potential account for these findings could be that under high working memory load ($n = 3$) the reliance on Medial Temporal Lobe structures such as the hippocampus increases (Doherty & Logie, 2016; Unsworth, Brewer, & Spillers, 2013), thus rendering the paradigm less specific (i.e., performance on both conditions will drop). Recent single case studies of neurological patients with hippocampal damage (Baddeley, Allen, & Vargha-Khadem, 2010; Jonin et al., 2018; Parra et al., 2015) confirmed that these patients present with preserved STMB even when memory load was higher (3 and 4) than that used with the MCI sample that underwent MRI scans ($n = 2$). However, in all cases memory load was below or within the reported capacity of working/short-term memory ($n = 4$; Cowan, 2010). Future studies with larger samples should investigate if supraspan stimulation engages hippocampal functions and if so, whether such involvement reduces the specificity of the STMBT to dissect binding deficits in samples at risk of AD.

Our results suggest that titration might not be necessary if the task demands are adjusted to and interpreted in line with the different stages of the disease. For example, strategies aimed at screening individuals at risk of AD (e.g., asymptomatic mutation carriers of APOE4 genotype or other mutations) in whom traditional memory tasks fail (Koppara et al., 2015; Parra, Abrahams, Logie, Mendez, et al., 2010), might capitalize on high memory load while those aimed at screening in more advanced prodromal stages (i.e., MCI) or at ascertaining the presence of AD, might focus on lower memory load (Della Sala et al., 2018; Della Sala et al., 2012; Parra, Abrahams, Logie, & Della Sala, 2010). It is worth noting that reducing memory load to 2 items does not undermine the need of binding (Parra, Della Sala, Logie, & Morcom, 2014). Hence, use of memory strategies, or lack thereof, should not be the factor explaining the selective binding deficits reported with this paradigm. There are other psychometric properties of the STMBT that grants reliability to this tool for the assessment of AD (Logie et al., 2015). STMB, as assessed by change detection paradigms, has proved to hold internal consistency (Logie, Brockmole, & Vandenbroucke, 2009). This seems to be a feature of tasks relying on these paradigms (Pailian & Halberda, 2015; Xu, Adam, Fang, & Vogel, 2018). Moreover, the possibility to adjust the task's demands to the severity of the disease to avoid floor and ceiling effects while retaining construct validity, is another appealing psychometric property of this novel tool. This latter feature makes the task suitable for follow up assessments. However, future studies are still needed to confirm its test-retest and inter-rater reliability.

There might factors other than age and education (see Koppara et al., 2015; Parra, Abrahams, Logie, & Della Sala, 2010) which can lead to poor performance in healthy aging populations. For instance, in this study, healthy older adults assessed with set size 3 showed a disproportionately large cost of binding compared to that reported in earlier studies (Fernández et al., 2018; Koppara et al., 2015; Parra, Abrahams, Logie, & Della Sala, 2010). To address this potential limitation a task that combines the two set sizes may be a more feasible approach. Alternatively, as recently suggested by (Della Sala et al., 2018), a version presenting binding as the only measure drawn from two set sizes could be administered easily and reliably in clinical settings. Older adults with poor VSTMB performance might be those in the very early preclinical stages of AD (see Parra, Gazes, & Stern, 2017).

4.2. The construct of memory binding in the assessment of AD

A recent review paper summarizes developments of neuropsychological approaches for the detection of preclinical AD (Rentz et al., 2013). For example, the FCSRT (Grober, Sanders, Hall, & Lipton, 2010), has shown promising results (Barbeau et al., 2004; Barbeau et al., 2008; Ivanou et al., 2005; Lemos et al., 2016; Sarazin et al., 2007). The Mnemonic Similarity Task (MST), which assesses recognition of

common items whose similarity to lures is manipulated, has also revealed promising findings Stark, Yassa, Lacy, and Stark, (2013). Mnemonic discrimination relies on pattern separation and such a construct also seems to hold marker properties for AD (Barbeau et al., 2004, 2008). Performance on such tasks holds the key to understanding memory decline along the continuum of AD (Costa et al., 2017; Sperling et al., 2011). The FCSRT and the MST tax memory functions carried out in LTM. Such functions seem to rely on the hippocampus (Bennett, Huffman, & Stark, 2015; Sarazin et al., 2010) which for long has been thought of as the earliest target of AD pathology. This view has been recently challenged (Didic et al., 2011). Papp et al. (2015) used the FCSRT and the Memory Capacity Test (MCT, recently relabelled as the Memory Binding Test–MBT–by Buschke (2014) to assess cognitively normal older adults who show evidence of brain amyloidosis ($A\beta$) and neurodegeneration. Z-scores computed over the whole sample revealed that the MCT, but not the FCSRT, detected impairment only in advanced stages. Hence, a substantial amount of brain damage needs to accumulate before deficits of LTM binding functions become apparent. However, Mowrey et al. (2016) recently investigated the predictive validity of the MBT for incident aMCI. They reported that in a longitudinal community-based study of 246 cognitively normal elderly adults aged 70+ the MBT significantly predicted incident aMCI within a time window ranging from 4 to 7 years. As suggested by Rentz et al. (2013), more work needs to be done to investigate the added value of these promising test for the preclinical detection of AD. Combining in single assessment protocols memory tests that assess the sub-hippocampal stages of AD (Didic et al., 2011, e.g., VSTMBT, see also Wolk, Signoff, & DeKosky, 2008) and those sensitive to the hippocampal stages (MBT/MCT/FCSRT, MST, CANTAB-PAL) to map decline of these functions along the AD continuum in larger longitudinal cohorts (see Costa et al., 2017), will confirm their value for screening and diagnostic purposes.

Conflict of interest

We wish to confirm that there are no known conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.archger.2019.03.025>.

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