Memory Markers In The Continuum Of The Alzheimer's Clinical Syndrome

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Abstract

BACKGROUND: The individual and complementary value of the Visual Short-Term Memory Binding Test (VSTMBT) and the Free and Cued Selective Reminding Test (FCSRT) as markers to trace the AD continuum was investigated. It was hypothesised that the VSTMBT would be an early indicator while the FCSRT would inform on imminent progression.

METHODS: Healthy older adults (n=70) and patients with Mild Cognitive Impairment (MCI) (n=80) were recruited and followed up between 2012 and 2017. Participants with at least two assessments points entered the study. Using baseline and follow up assessments four groups were defined: Older adults how were healthy (HOA), with very mild cognitive but not functional impairment (eMCI), and with MCI who did and did not convert to dementia (MCI Converters and non-Converters). RESULTS: Only the VSTMBT predicted group membership in the very early stages (HOA vs eMCI). As the disease progressed, the FCSRT became a strong predictor excluding the VSTMB from the models. Their complementary value was high during the mid-prodromal stages and decreased in stages closer to dementia.

DISCUSSION: The study support the notion that neuropsychological assessment for AD needs to abandon the notion of one-size-fits-all. A memory toolkit for AD needs to consider tools that are early indicators such as the VSTMBT and that suggest imminent progression such as the FSCRT.

Background

Alzheimer's disease (AD) has been defined as a continuum of clinical and pathological events from normal ageing to dementia. Accordingly, the disease has been reconceptualised [1–4] and new diagnostic frameworks relying on biomarkers have been introduced [5, 6]. A motivation behind these biomarkers-based frameworks is the limitations that available neuropsychological tests have demonstrated in detecting the pre-dementia stages of such a continuum [3, 7, 8]. Memory is the cognitive function earliest and most dramatically impacted by the typical forms of AD [8–10]. However, accrued evidence suggests that neuropsychological assessment needs a paradigm shift if we are to enhance its sensitivity and specificity for the preclinical stages of the disease [8, 11–13].

Recent recommendations by the Joint Program for Neurodegenerative Diseases Working Group [9] fit well with the hypothetical model of memory decline in AD originally proposed by Didic et al. [11] (see Figure 1). The Working Group recommended two memory tests that have recently proved useful in the assessment of preclinical AD: the Visual Short-Term Memory Binding Test (VSTMBT; [14]) and the Free and Cued Selective Reminding Test (FCSRT; [15]). Both tests assess the ability to integrate information in memory. However, they tap into different memory functions.

Visual Short-Term Memory Binding (VSTMB) refers to our ability to integrate objects' features into unified representations to form and temporarily hold new identities in memory [16–18]. Typically, the VSTMBT assesses this ability by asking people to recognise changes in coloured shapes or objects occurring between two consecutive displays (i.e., study and test display of change detection tasks). To detect such changes accurately, participants do not need contextual information, rather they need to judge if the newly presented object (test display) is the same as previously presented or different.

The FCSRT, as well as other Selective Reminding Tests (SRT) such as the Memory Capacity Test (MCT, [19–21]), rely on contextual information to support both encoding and retrieval. The assumption of these tests is that if the contextual cues presented during the encoding (i.e., semantic categories) match those available during recall, they would assist the retrieval of exemplar memories linked to such categories (i.e., the encoding specificity principle [20]). Binding items (i.e., exemplars) to their context (i.e., semantic categories) effectively, should aid memory performance in the context of SRT.

The underlying construct of both these two tests is *memory binding*. However, they tax two very different binding functions. The VSTMBT assesses a form of conjunctive binding responsible for holding integrated features within object representations, whereas the FCSRT assesses a form or relational binding that supports the retention of associative memories. Before we review the evidence from AD studies endorsing the distinction between these two constructs, we will briefly discuss what Didic et al.'s [11] model implicates about these forms of binding in the AD continuum.

Didic et al. [11] suggested that AD affects medial temporal lobe (MTL) structures known to support different memory functions in a graded manner (Figure 1). Within the MTL, the disease first goes through a subhippocampal stage (Braak and Braak's stages I and II, which correspond to the asymptomatic stages) selectively impairing regions of the anterior MTL network (i.e., perirhinal and lateral entorhinal cortex, the anterior hippocampus, and the temporo-polar cortex). Damage to these regions impairs context-free memory [24, 25]. As the disease progresses to the limbic stage (i.e., Braak and Braak stages III and IV, which correspond to the mild cognitive impairment stage – MCI), pathology spreads to the posterior MTL network (i.e., parahippocampal cortex, posterior hippocampus, and posterior cingulate) which plays a critical role in context-rich memory. Hence, this model predicts that memory functions such as those assessed by the VSTMBT would be affected earlier than those assessed by SRT such as the FCSRT and the MCT. This is in line with evidence drawn from the AD literature, which we review next.

Some light on this dissociation has been shed via studies carried out in preclinical samples of carriers of mutations that inevitably lead to familial AD (i.e., E280A-PSEN1 [26, 27]). Parra et al. [27] observed VSTMB deficits in asymptomatic carriers who were about 10 years younger than the average age of onset of dementia in this familial variant. However, using the MCT to assess members of the same kindred, Romero –Vanegas et al. [28] found impairments only when carriers were in the MCI stages. Using another context-rich memory test memory test, the Paired Associates Learning of WMS[29]), Parra et al. [27] reported that the VSTMBT significantly outperformed it when discriminating between asymptomatic carriers and non-carrier controls. Similar results were reported by Koppara et al. [30] in patients with Subjective Cognitive Decline who presented with VSTMB impairments within an otherwise normal neuropsychological profile. We further observed that in confirmed cases of AD, both tests achieved excellent levels of classification at the individual level, even if the VSTMBT outperformed the FCSRT [31].

More recent studies that combined VSTMB tests with biomarker assessments (i.e., PET), have confirmed that such ability is affected by the very early stages of AD. For instance, Norton et al. [32] reported correlations between performance on the VSTMBT and amyloid deposits in asymptomatic carriers of the mutation E280A-PSEN1. Interestingly, when the disease progressed to the symptomatic stages, such correlations were no longer statistically reliable, likely due to a profound impairment in VSTMB (performance close to floor). The authors suggested that VSTMB impairments may effectively predict dementia in those affected by AD in the preclinical stages. The same research group [33] recently reported correlations between performance on a context-rich tests (Latin American Spanish version of the Face-Name Associative Memory Exam). Significant correlations were not observed when data from only asymptomatic carriers entered the statistical models. However, when data from asymptomatic and symptomatic carriers were lumped together, correlations between memory scores and amyloid deposits reached significance, suggesting that when it comes to context-rick memory tests, such an association becomes apparent in rather advanced pathological stages. Relying on the recently proposed biomarker framework [6], Papp et al. [34] reported evidence of impairment in the binding component of the MCT (i.e., cued recall) only between participants in Stage 0 (Aβ−/ND−) and Stage 2 (Aβ+/ND+), but not between those in Sate 0 and Stage 1 (Aβ+/ND−). Using a composite memory score which included various tests of context-rich memory, Jack et al. [10] recently reported that association between memory and brain pathology became significant at the A+T+(N)− indicating rather advanced disease stages. Cecchini et al. [35] recently reported that deficits in VSTMB are detectable in individuals with brain amyloid deposition in the absence of overt neurodegeneration (N aspect of the A/T/N framework, [6]) in the AD continuum. Taken together the available literature suggests that evidence drawn from recent studies which included the VSTMBT, SRT, and AD biomarkers lends support to Didic et al.'s [11] hypothetical model. Although encouraging, this evidence presents us with an important challenge, which is addressed by the current study.

Traditionally, studies that have investigated the predictive value of neuropsychological tests to anticipate who among those at risk of AD will eventually develop dementia have conducted retrospective analyses comparing baseline performance of patients with MCI who did and did not convert to dementia in the follow up period. Given the evidence summarised above, such prediction models are bound to be informative solely for neuropsychological tests sensitive to the advanced stages of the AD continuum (i.e., MCI). A function that has started to decline years before people become aware of any cognitive impairments or develop initial symptoms of dementia, is expected to have declined dramatically by the time they reach the MCI stage. At this point in time, separating MCI who will and will not develop dementia in 2 or 3 years may be problematic for such tests but may still be possible for tests that assess functions sensitive to such stages (i.e., prodromal) of the disease process. Parra et al. [36] recently suggested that the VSTMBT may need to be titrated to the targeted population (e.g., preclinical or prodromal) by adjusting memory load (i.e., 2 or 3 items) in order to achieve best classification power. Similarly, it has been suggested that future studies using biomarkers will need to rely on adjusted normative data in order to ascertain who the true control participants are [37]. In a conference paper, Parra et al. [38]

reported that older adults who are completely asymptomatic but show poor VSTMB abilities have significantly more accumulation of amyloid deposits in the brain than those whose binding abilities are spared.

We posit that both the VSTMBT and the FCRST will be able to correctly classify most of the older adults at different stages of the continuum of the AD clinical syndrome, but that their discrimination power would differ according to the stage of the disease. We predict that the VSTMBT will be able to discriminate between older adults who are asymptomatic and those who are in the very early stages of cognitive decline more effectively than the FCSRT (H1). On the contrary, the FCSRT will discriminate more accurately than the VSTMBT between older adults with MCI who converted and who did not convert to dementia in follow up assessments (H2).

Methods

Participants

We recruited participants self-reporting as being healthy who were either members of the Psychology Volunteer Panel at the University of Edinburgh or relatives of patients with dementia from the Scottish Dementia Clinical Research Network interest register (SDCRN, currently Neuroprogressive and Dementia Network - NDN) who volunteered for the study. We also received referrals from old age psychiatrists based at the NHS Lothian and NHS Forth Valley who regularly see older adults complaining about their cognitive abilities. Recruitment and follow up assessments ran between 2012 and 2017. To be eligible for the study, participants had to be over 55 year old and native English speakers. MCI patients had to have an available relative or a caregiver and demonstrate capacity to consent to the study. All the participants needed to be free from any neurological or psychiatry disease that would interfere with their cognitive functions, and had normal or corrected to normal vision. Participants with scores greater than 4 in the Hachinski Ischemia Scale [39] and 5 in the brief Geriatric Depression Scale (GDS, [40]) were not included in the final sample. Also, participants who met criteria for AD dementia at baselined were not eligible. All participants were provided with an Information Sheet describing the longitudinal nature of the study and the assessments involved. They were told that their cognitive and functional abilities would be assessed, that it was possible to detect impairments of which they were not aware, that should this happen, their GPs would be contacted with their consent. After they read the PIS, they signed a consent form prior to participating in the study. The study was approved by the NHS Multi-Site Research Ethics Committee (reference number 06/MRE07/40) and was given approval by local NHS R&D offices. In addition to the above criteria, only participants who had completed at least two assessment points including baseline were entered into the analyses here reported. The final sample consisted of 150 participants. Of these, 70 self-reported as healthy and 80 were referred by consultant old age psychiatrists as patients meeting criteria for MCI.

Sample design and rationale

Power calculation was performed which incorporated (1) pilot data obtained from 23 MCI patients and 30 controls as well as from 14 mild AD patients all assessed with the STM binding task proposed here. In addition a wide search of the literature was performed to obtain three main variables: (1) average follow-up period within which changes could be observed using sensitive cognitive tasks (3 years, [41]), (2) MCI to AD conversion rate (median = per annum 12%, 37.65% for a 3-year study), (3) attrition (14% for a 3-year follow up study). The results showed that for a desired power of 80%, a medium effect size (Cohen d = 0.5) and alpha set at 0.05, 80 MCI patients and 40 controls at baseline we would allow us to reach the study end-point with a number of converters which will permit reliable comparisons (>= 20).

Baseline data were used to define groups by applying classical MCI criteria [42–44]. We relied on tests for which valid norms had been previously published (see section on Neuropsychological Assessment). Participants were allocated to the Healthy Older Adults Group (HOA) if they performed within 1.5SD of the norms (we applied the MCI criteria relying on the Neuropsychological Tests described below) and showed normal Instrumental Activities of Daily Living (IADL, [45]). Participants entered the early Mild Cognitive Impairment Group (eMCI) if they performed below 1.5SD from the norms on any of the tests applied but had intact IADL (see [46]). Older adults who performed below 1.5SD from the norms of any test and showed mild impairments in IADL at baseline were classified as MCI [44]. The final clinical status of MCI patients was updated in November 2018 by discussing these with the referring consultants who accessed the NHS records. Those whose records confirmed the diagnosis of dementia were grouped

within the converter Group (MCI Converter), while those whose records still reflected the diagnosis of MCI entered the non-Converter Group (MCI non-Converter).

Although for the purposes of this study we did not follow the classical classification of MCI subtypes, we did apply such criteria to baseline data. Figure 2 shows the groups split after applying criteria to (1) identify MCI subtypes and (2) conform the core groups for this study. We observed a 35.2% conversion rate among MCI patients (considering eMCI and MCI) who, as Figure 1 shows, were predominantly multi-domain amnestic MCI (maMCI). This is in line with the literature [4, 47, 48]. None of the non-amnestic MCI patients developed AD dementia in the course of the study, which also seems to agree with the abovementioned literature.

In order to test our first hypothesis (H1) we compared the HOA and eMCI groups (H1: Discrimination between cognitively unimpaired and older adults with very early cognitive impairment). We were interested in identifying individuals who may be displaying early signs of cognitive impairments, among the older adults who had not sought medical advice or were worried about their cognitive abilities independently of their cognitive status. We anticipated that for those displaying cognitive impairments, such impairments would be sufficiently mild as not to cause concern nor to interfere with their IADL. To test our second hypothesis (H2: Discriminate between older adults with MCI who did and did not convert to dementia in the follow up period) we requested an updated diagnosis from the referring consultants as described above. This allowed us to retrospectively define two groups, MCI Converter and MCI non-Converter. The demographic, clinical, and cognitive characteristics of these groups are presented in Table 1.

Assessments

A battery of neuropsychological tests was administered to all participants. The battery consisted of a combination of traditional neuropsychological tests commonly used to assess dementia [49, 50] and more novel tasks, including the VSTMBT and the FCSRT. Baseline and follow up assessments were carried out a year apart.

Neuropsychological Assessment

The Addenbrooke's Cognitive Examination Revised (ACE-R) was used as a Global Cognitive screening test [51]. Memory tests included the Hopkins Verbal Learning Test Immediate Total and Delayed Recall; [52]) and visual memory (Rey-Osterrieth Complex Figure Immediate and Delayed Recall [53]). Assessment of attention/executive functions (TMT-A and TMT-B [54]), praxis (Rey-Osterrieth Complex Figure Copy [53]), and language/executive functions (Phonological - FAS - Fluency [55]). Speed of processing was assessed with the Digit to Symbol Substitution Test [56]. Premorbid function was assessed with TOPF [57]. We also administered the Instrumental Activities of Daily Living (IADL) Scale [45].

Experimental Tasks

The FCSRT test began with participants examining a card containing names of objects (Grober et al., 1988). Each card showed four names, each belonging to a unique semantic category. For instance,
$banana' wodbeanexamp \leq ofa \rightarrow$ - be - rememberedobjectwiththesemanticcueofFruit'. Each participant learned 16 names of objects, distributed in four printed flashcards presented one at the time with four names of objects on each card. Immediate Free Recall was assessed by asking participants to retrieve the 16 names of objects spontaneously. Cued recall was subsequently assessed with the aid of the semantic cue for those items not recalled under free recall. This procedure was repeated 3 times, with a 20 second interference (counting backward). The final Immediate Free Recall score is the sum of objects recalled from the three trials, with a minimum score of zero and maximum 48. The final total recall score is the sum of free recall and cued recall from all three trials, with a minimum score of 0 and maximum 48. We did not assess Delayed Recall in this protocol.

The VSTMB test consisted of three conditions. First, a perceptual binding task was given, as a screening test aimed at ruling out perceptual binding deficits of colour and shape [14]. Each trial began by presenting participants with two arrays of items on a computer screen (see [14] for a full description of the items psychophysics properties including perceptual impact of number of sides, colour luminance, screen dimensions relative to foveal vision). The task was to decide if the two arrays, one on the lower half of the screen and the other on the top half, presented the same or different coloured shapes. Ten trials were included in this screening. A cut-off score of 80% was used to decide who would progress to the memory binding test [14]. All the participants who entered the study met such a criterion. We then presented the two memory conditions. The memory assessment was based on a change detection paradigm. The task comprised two conditions, Shape Only and Shape-Colour Binding. In the Shape Only

condition, the study array consisted of three black shapes presented for 2000 milliseconds. This was followed by a retention period (blank screen) for 1000 milliseconds. Finally, a test array was presented, with three shapes in different locations to the study array. At this point, participants were required to respond *same' or* different'. In 50% of the trials the shapes in the study and test array were the same while in the rest of the trials two shapes not presented at study, appeared in the test display. A similar procedure was followed in the Shape-Colour Binding condition. The to-be-remembered items were combinations of shape and colour. Participants were required to decide if the specific colour and shape combination in the test array was the same presented in the study array. There were 32 trials in each condition. The final score was percentage of correct recognition. While there are currently no reported studies that have investigated the psychometric properties of the VSTMB test per se, the change detection paradigm, upon which the test is based, has demonstrated to hold internal consistency (Logie et al., 2009). For the present analyses we focused on performance on the Shape-Colour Binding condition of the VSTMBT which achieved the best classification power in AD studies [14, 27, 31]. As for the FCSRT, we chose Immediate Free Recall as this proved to be the most sensitive score to detect AD [58, 59].

Statistical Analysis

To compare groups we used tests of mean differences (t-Tests, MANOVA/ MANCOVA). We also used stepwise linear regression models to investigate the individual and complementary value of the VSTMBT and the FCRST to predict group membership. To test H1 we compared HOA, eMCI and MCI non-Converter groups. To test our second hypothesis (H2) we compared eMCI, MCI non-Converter and MCI Converter groups. We also ran contrasts across groups to explore whether and to what extent the classification power of these memory tests varies as a function of the diseases continuum. The rationale was that by comparing HOA vs eMCI vs MCI non-Converter we would be able to explore the transition from normal to pathological ageing. We kept such eMCI participants separate from those who entered the study as MCI patients referred by clinicians. Hence, by comparing eMCI vs MCI non-Converter vs MCI Converter, we would have the opportunity to map the outcomes from these memory markers to the disease continuum and in so doing test the hypotheses set out for this study. We were also interested in the complementary value of these tests (VSTMBT and FCSRT). We defined complementary value as the ability of these tests to account for larger between-group variance (i.e., adjusted R^2 from regression model) when used jointly than individually.

Results

General neuropsychological findings

Summaries of the descriptive and inferential statistics for the demographic variables, general cognitive and functional scales, and the neuropsychological and experimental tasks are presented in Table 1 and 2, respectively. Of note, HOA and eMCI participants did differ on a number of neuropsychological tasks, but as anticipated, IADL were preserved. eMCI participants and MCI non-Converter patients significantly differed on most neuropsychological tasks, confirming that the former group still was in the very early stages of the disease continuum. MCI non-Converter and Converter significantly differed from HOA on all the neuropsychological tasks. However, as MCI patients progressed along the disease continuum (i.e., MCI non-Converter and Converter), discrepancy on neuropsychological scores became less apparent. Although this study focused on novel neuropsychological tests, some well stablished standardised tests showed excellent abilities to discriminate between individuals in the early stages (HVLT in HOA vs eMCI). Regarding the experimental tasks, the ability of FCSRT and VSTMT to predict group membership showed differences throughout the disease continuum, with opposite patterns of sensitivity at its extremes (preclinical: VSTMBT > FCSRT, advanced prodromal: FCSRT > VSTMBT), and varying levels of complementary throughout its the intermediate stages (see Figure 2).

Table 1

Descriptive statistics for the demographic variables, general cognitive and functional scales, and the neuropsychological and experimental tasks abilities to predict group membership (HOA: Healthy older adults, aMCI: amnestic MCI, maMCI: multi-domain amnestic MCI, naMCI: non-amnestic MCI; see text for description).

	HOA (n=42)		eMCI (n=31)		MCI non-Converter (n=39)		MCI Converter (n=38)	
	M (SD)	Range	M (SD)	Range	M (SD)	Range	M (SD)	Range
Age	73.50 (5.37)	62.00-86.00	75.71 (7.17)	61.00-90.00	75.33 (6.57)	64.00-88.00	77.08 (8.24)	58.00-97.00
Education	16.19 (4.14)	10.00-33.00	14.87 (3.52)	10.00-23.00	12.21 (3.61)	9.00-25.00	13.82 (4.20)	9.00-25.00
Total ACE-R	96.12 (3.44)	87.00-100.00	92.58 (5.61)	80.00-100.00	81.74 (7.64)	66.00-97.00	76.21 (9.45)	54.00-91.00
TOPF	63.58 (6.50)	34.00-70.00	60.16 (10.07)	32.00-69.00	49.55 (14.46)	18.00-69.00	52.23 (11.70)	31.00-69.00
IADL	7.64 (0.81)	5.00-8.00	7.33 (1.23)	5.00-8.00	6.39 (1.89)	1.00-8.00	5.93 (1.54)	3.00-8.00
HVLT Delayed	9.45 (1.47)	7.00-12.00	5.65 (3.72)	0.00-12.00	3.68 (3.94)	0.00-17.00	1.76 (2.41)	0.00-9.00
HVLT Total	27.26 (4.01)	17.00-36.00	22.71 (6.24)	11.00-35.00	15.45 (5.23)	6.00-26.00	13.63 (4.04)	6.00-23.00
HVLT Recognition	11.43 (0.78)	9.00-12.00	9.81 (2.12)	4.00-12.00	7.94 (2.71)	0.00-12.00	7.66 (2.91)	1.00-12.00
Rey Figure (Copy)	34.46 (1.93)	29.00-36.00	27.87 (11.69)	0.00-36.00	28.77 (8.21)	0.00-36.00	28.06 (9.86)	0.00-36.00
Rey Figure (Immediate Recall)	19.79 (7.67)	8.00-34.00	15.03 (9.16)	0.00-32.00	10.53 (7.61)	0.00-27.00	7.36 (6.12)	0.00-24.00
Rey Figure (Delayed Recall)	19.50 (7.26)	7.00-34.00	14.95 (9.38)	0.00-34.00	10.49 (7.88)	0.00-26.00	5.71 (5.91)	0.00-21.00
TMT-A	43.29 (9.96)	22.00-59.00	50.97 (19.38)	25.00-103.00	66.00 (27.64)	29.00-159.00	78.35 (41.55)	35.00-252.00
TMT-B	84.95 (27.63)	34.00-163.00	107.45 (39.79)	44.00-203.00	179.53 (101.07)	72.00-547.00	196.67 (90.87)	76.00-465.00
Letter Fluency (FAS)	50.81 (14.42)	18.00-81.00	49.52 (12.00)	19.00-81.00	31.57 (14.20)	14.00-67.00	34.29 (16.58)	6.00-74.00
Digit-Symbol	61.64 (13.43)	36.00-83.00	54.61 (13.22)	29.00-91.00	39.74 (12.52)	14.00-62.00	34.35 (12.29)	4.00-53.00
VSTMBT (Recognition)	0.75 (0.09)	0.59-0.97	0.68 (0.08)	0.53-0.78	0.64 (0.07)	0.47-0.78	0.62 (0.10)	0.41-0.81
FCSRT (Free Recall)	27.43 (6.17)	14.00-40.00	24.26 (7.83)	12.00-38.00	15.05 (7.90)	3.00-35.00	10.47 (6.58)	1.00-24.00

ACE-R: Addenbrooke's Cognitive Examination Revised, FCSRT: Free and Cued Selective Reminding Test, HVLT: Hopkins Verbal Learning Test, IADL: Instrumental Activities of Daily Living, TOPF: Test of Premorbid Functions, TMT-A: Trials Making Test Part A and B (TMT-B), VSTMBT: Visual Short-Term Memory Binding Test.

Table 2

Inferential statistics with the demographic variables, general cognitive and functional scales, and the neuropsychological and experimental tasks (HOA: Healthy older adults, aMCI: amnestic MCI, maMCI: multi-domain amnestic MCI, naMCI: non-amnestic MCI; see text for description).

	HOA vs eMCI		HOA vs non-Converter		HOA vs Converter		eMCI vs Non-Converter		eMCI vs Converter		Non-Converter vs Converter	
	(t)	p-value	(t)	p-value	(t)	p-value	(t)	p-value	(t)	p-value	(t)	p-value
Age	-1.51	0.140	-1.38	0.170	-2.28	0.030	0.23	0.820	-0.73	0.470	-1.03	0.310
Education	1.43	0.160	4.60	<0.001	2.54	0.01	3.10	<0.001	1.11	0.270	-1.80	0.080
Total ACE-R	3.11	<0.001	10.77	<0.001	12.27	<0.001	6.60	<0.001	8.92	<0.001	2.83	0.010
TOPF	1.64	0.110	5.48	<0.001	4.85	<0.001	3.58	<0.001	2.86	0.010	-0.83	0.410
IADL	0.95	0.350	3.40	<0.001	5.07	<0.001	1.76	0.09	3.03	<0.001	1.04	0.300
HVLT Delayed	5.40	<0.001	8.42	<0.001	17.02	<0.001	2.11	0.04	5.02	<0.001	2.53	0.010
HVLT Total	3.56	<0.001	11.24	<0.001	15.13	<0.001	5.26	<0.001	7.00	<0.001	1.69	0.090
HVLT Recognition	4.04	<0.001	7.25	<0.001	7.73	<0.001	3.07	<0.001	3.44	<0.001	0.43	0.670
Rey Figure (Copy)	3.11	<0.001	4.22	<0.001	3.84	<0.001	-0.38	0.71	-0.07	0.940	0.34	0.730
Rey Figure (Immediate Recall)	2.40	0.020	5.42	<0.001	7.94	<0.001	2.25	0.03	3.98	<0.001	1.99	0.050
Rey Figure (Delayed Recall)	2.31	0.020	5.19	<0.001	9.07	<0.001	2.09	0.04	4.68	<0.001	2.89	0.010
TMT-A	-2.02	0.050	-4.79	<0.001	-4.81	<0.001	-2.56	0.01	-3.45	<0.001	-1.50	0.140
TMT-B	-2.85	0.010	-5.58	<0.001	-6.82	<0.001	-4.03	<0.001	-5.14	<0.001	-0.75	0.460
Letter Fluency (FAS)	0.41	0.690	5.96	<0.001	4.64	<0.001	5.56	<0.001	4.20	<0.001	-0.75	0.460
Digit-Symbol	2.22	0.030	7.52	<0.001	9.14	<0.001	4.79	<0.001	6.40	<0.001	1.84	0.070
VSTMBT (Recognition)	3.49	<0.001	5.78	<0.001	5.92	<0.001	2.12	0.040	2.71	0.010	1.11	0.270
FCSRT (Free Recall)	1.93	0.060	7.89	<0.001	11.73	<0.001	4.86	<0.001	7.83	<0.001	2.71	0.010

ACE-R: Addenbrooke's Cognitive Examination Revised, FCSRT: Free and Cued Selective Reminding Test, HVLT: Hopkins Verbal Learning Test, IADL: Instrumental Activities of Daily Living, TOPF: Test of Premorbid Functions, TMT-A: Trials Making Test Part A and B (TMT-B), VSTMBT: Visual Short-Term Memory Binding Test.

Transition from normal to pathological ageing

To predict group membership in the very early stages of cognitive decline, we focused on data (FSCRT and VSTMB) from HOA, eMCI and MCI non-Converter. To test H1, we first relied on tests of mean differences (MANOVA/MANCOVA or t-Tests) and later used stepwise linear regression models (see Table 3). Both tests displayed excellent abilities to discriminate between HOA, eMCI and MCI non-Converter (HOA > eMCI/MCI non-Converter). The VSTMB outperformed the FCSRT only in the preclinical stages (HOA > eMCI).

Exploring the prodromal stages

To explore the more advanced prodromal stages of the disease, we focused on data from eMCI, MCI non-Converter and MCI Converter. The same analytical approach was followed (see Table 3). Relative to the FCSRT, the VSTMB proved less effective in discriminating eMCI from MCI non-Converter, eMCI from MCI Converter, and MCI non-Converter from MCI Converter. In fact, regression models showed that the VSTMB was excluded as a predictor from all the above contrasts, which only retained the FCSRT. The MONOVA/MONCOVA analyses confirmed that such a limited predictive value of the VSTMBT relative to the FCSRT is explained by its reduced ability to differentiate between groups as soon as patients moved into the prodromal stages of the disease, point at which the FCSRT becomes more sensitive. These findings too support our H1 and H2.

Exploring the individual and complementary value of the VSTMBT and FCSRT

As reported above, the VSTMBT proved a good predictor of group membership in the early preclinical stages. As soon as the levels of cognitive impairment met criteria for the prodromal stages of the continuum, the FCSRT outperformed the VSTMBT. As Table 3 and Figure 3 show, the complementary value of these tasks varied as the level of cognitive impairment progressed. It was low at the extremes of the stages of the continuum here explored and higher in the medium stages. The individual and combined predictive value of both tests to discriminate between stages closer to dementia (MCI non-Converter and MCI Converter) was rather low.

Table 3
Results from MANOVA/MANCOVA and Regression analyses investigating the individual and complementary value of the VSTMBT and FCSRT (HOA: Healthy older adults, aMCI: amnestic MCI, maMCI: multi-domain amnestic MCI, naMCI: non-amnestic MCI; see text for description).

	HOA vs eMCI				**HOA vs Non-Converter (!)**				**HOA vs Converter ($!)**			
	MANOVA		**Regression (14%, p=0.001)**		**MANCOVA**		**Regression (57%, p<0.001)**		**MANCOVA**		**Regression (65%,p<0.001)**	
	F	**p**	t	**p**	F	**P**	t	**P**	F	**p**	t	**p**
VSTMB (% Recognition)	12.19	0.001	-3.49	0.001	20.26	<0.001	-5.32	<0.001	22.20	<0.001	**-2.98**	**<0.001**
FCSRT (Free Recall)	4.39	0.040	**-1.86**	**0.067**	41.54	<0.001	-3.11	0.003	94.20	<0.001	-8.39	0.004
	eMCI vs Non-Converter (!)				**eMCI vs Converter**				**Non-Converter vs Converter**			
	MANCOVA		**Regression (30.8%, p<0.001)**		**MANOVA**		**Regression (44.4%, p<0.001)**		**MANOVA**		**Regression (6.1%, p=0.025)**	
	F	**p**	t	**p**	F	**P**	t	**P**	F	**p**	t	p
VSTMB (% Recognition)	2.27	0.137	**-0.93**	**0.354**	7.13	0.010	**-0.84**	**0.403**	1.20	0.277	**-0.45**	**0.651**
FCSRT (Free Recall)	16.20	<0.001	-4.02	<0.001	49.78	<0.001	-7.06	<0.001	5.24	0.025	-2.29	0.025
$: Adjusting for Age, !: Adjusting for Education, Bold: Excluded from model												

Discussion

The present longitudinal study was set out to investigate the hypotheses that two memory markers for AD recently recommended by consensus [9] differently predict dementia throughout its continuum. Based on previous evidence we predicted that the VSTMBT would be able to discriminate between older adults who are asymptomatic and those who are in the very early stages of cognitive decline more effectively than the FCSRT (H1). However, the FCSRT would discriminate between older adults in the prodromal stages (MCI) who later convert versus those who do not convert to dementia more accurately than the VSTMBT (H2). Our results supported both hypotheses and have some implications for our understanding of neuropsychological assessment to track the transition from normal to pathological ageing and to monitor progression through the prodromal stages towards conversion to dementia.

Before discussing these implications, it is worth considering some observations drawn from the background neuropsychological assessment. HOA and eMCI participants differed on a number of neuropsychological tasks, yet eMCI participants were not seeking professional help. As patients with MCI progressed along the disease continuum (i.e., MCI non-Converter and Converter), discrepancies in the neuropsychological scores decreased. Hence, standard neuropsychological tests used in our study appear to be effective for detecting impairments but less so for differentiating risk phenotypes. These shortcomings of off-the-shelf neuropsychological tests have been acknowledged previously [8, 60–63] and called for new tests to better phenotype dementia and detect risk profiles [8, 60]. Notwithstanding such limitations, the ability of some neuropsychological tests used in our assessment battery to detect very early cognitive impairments, particularly of memory, is also worth highlighting.

The HVLT revealed significant memory differences along the disease continuum, particularly between groups informing the very early stages. Lonie et al. [64] had previously demonstrated that the Delayed Recall component of the HVLT can discriminate between MCI converters and non-converters over a 4-year follow up period as accurately as the Visuospatial Paired Associates (PAL) Task from CANTAB [65]. Regarding the experimental tasks, the FCSRT and VSTMT showed differential abilities to predict group membership along the disease continuum. Opposite patterns of sensitivity were observed at the extreme ends of the continuum here explored (preclinical: VSTMBT > FCSRT; advanced prodromal: FCSRT > VSTMBT), and varying levels of complementary throughout its intermediate stages. These findings lend support to the two hypotheses investigated in this study and suggest that these recently recommended tests [9, 13, 31, 66] shall form part of new memory toolkits to assess and monitor AD.

To investigate the individual and complementary values of the two experimental tasks in informing about the transition from normal to pathological ageing we focused on data from HOA, eMCI and MCI non-Converter. We predicted that the VSTMB should outperform the FCSRT in the earlier stages because it would be able to detect gradually increasing levels of impairments whereas the function assessed by the FCSRT would still be preserved. Didic et al. [11] proposed a hypothesis that is very much in line with this prediction (see Figure 1). The authors argued that in the early preclinical stages of AD when the hippocampus is still unimpaired, context-free memory tests, which seemingly rely on structures of the Anterior Medial Temporal Lobe network (i.e., entorhinal, perirhinal cortices), would stand a better chance to identify impairments than context-rich memory task, which are reliant on the integrity of hippocampus. Not much work has been done to test this hypothesis, but studies are now piling up confirming its potential validity [32, 35, 38, 67]. Tests that are sensitive to the very early preclinical stages of AD would likely reach floor levels when patients enter the symptomatic stages as such a function would have been declining for years before the disease onset (see [68, 69] for early discussions of this issue). At this point, such tests would become little informative about group membership whether such groups involve converters or non-converters MCI. This study provides the first empirical evidence supporting such a model. Tests sensitive to the symptomatic stages of the continuum (e.g., FCSRT) would take over the predicting role at this stage (MCI, [70–72]).

In the current study, we demonstrated that both tests hold excellent abilities to discriminate between HOA, eMCI and MCI non-Converter (HOA > eMCI/MCI non-Converter). The VSTMB outperformed the FCSRT only in the preclinical stages (HOA > eMCI). As the disease progressed, (i.e., eMCI/MCI non-Converter) performance on the VSTMBT became less differentiated between groups, whereas that on the FCSRT continued to effectively discriminate between them. These findings, although encouraging, raise a number of concerns for promising neuropsychological assessment aimed at the preclinical stages of AD. Logie et al. [13] suggested that a good memory marker for AD should avoid very low performance levels when the symptoms become severe. Regarding the VSTMBT, which relies on the Change Detection Paradigm, chance levels are set at 50%. This is a constraint of the method. To overcome it, Parra et al. [36] suggested strategies such as titrating the task difficulty (i.e., memory load). For instance, the authors suggested that for studies aimed at the preclinical stages of AD, a VSMTBT using set size 3 would increase changes to detect impairments (see also [26, 27, 30]). However, for the symptomatic of dementia stages, set size 2 would be preferred as 3 would pose significant challenges (see [14, 26, 27]. In the present study, we chose to use one set size (i.e., 3) for the sake of comparability of findings along the disease continuum. Furthermore, Parra et al. [36] acknowledged that titrating, at least relying on current procedures, would be an unfeasible task to be implemented in clinical settings.

The literature supporting the validity of the FCSRT to predict dementia in longitudinal cohorts of MCI patients has grown significantly over the last few fears (e.g. [70–73]). This is the first report on the use of the VSTMBT in such longitudinal cohorts. These outcomes fit the notion that, at the prodromal stages of the disease memory tests sensitive to such a stage would stand a better chance to achieve reliable predictive outcomes relative to tests that assess functions sensitive to the very early and still silent

stages of the disease (see Figure 1). Some considerations regarding these findings are warranted. First, they support the notion that the neuropsychological assessment of AD, in its new conceptualization (i.e., a continuum of clinical and pathological stages), ought to abandon the one-size-fits-all approach. Assessment protocols aimed at investigating AD related disorders (i.e., detection, prediction) need to consider this evidence. Belleville et al. [74] acknowledged that a cognitive toolkit intended to identify AD at the pre-dementia stage would need tasks that are early indicators and others that might suggest imminent progression. Second, further research is required to unveil not only "which" memory function is most sensitive to AD [11] but also the "when" in the disease continuum such memory phenotypes become apparent.

The fact that the VSTMBT detects AD related changes early (see [26, 27, 30]) and then performance drops to near or chance levels (see [32]) has pros and cons. The positive aspect of this is that we have for long needed tests that can detect the very early stages of the disease process, preferably, when people are unaware of or are very little concerned about any cognitive or functional impairment. We have learned that at this stage, the VSTMBT is taxing the early growth of amyloid in at risk individuals even before tau deposits or neurodegeneration become apparent [32, 35, 38]. Such a test would be an ideal tool for clinical trials aiming at dementia prevention as they could enhance recruitment strategies by selecting who will likely meet inclusion criteria (e.g., Aβ+).

Of note, the individual and combined predictive value of both tests to discriminate between stages closer to dementia (MCI non-Converter and MCI Converter) was rather low. That was predicted for the VSTMBT but not for the FCSRT, which performed very well in the early and middle stages of the continuum. This is an interesting finding which seems to suggest that as the VSTMBT predictive abilities decrease in the prodromal stages of the disease, the FCSRT might face similar limitations if used to predict stages closer to dementia. Therefore, the quest for the abovementioned toolkit ought to be mapped along the disease continuum including tools sensitive to the very early stages through the advanced dementia stages where cognitive assessment can still provide evidence to inform clinical practice and in so doing, ensuring patients will receive the best possible care until the end of life.

One final aspect concerns our control participants. Most participants who were allocated to the eMCI group entered the study as self-referred healthy volunteers (see Figure 2). Relative to those who met criteria for HOA, eMCI participants displayed significant differences on various standard neuropsychological assessments. This is striking, as these individuals, at the time of the study, had not sought help and a few were only mildly concerned about their cognitive abilities. There is consensus that in the new context of AD research and clinical practice (i.e., following the biological definition of AD), deciding who is a control individual is proving as challenging as deciding who is in the early stages of the disease [37]. There are two issues worth considering here. First, the source of these control volunteers and second, awareness of and stigmas against early symptoms of dementia. Volunteers entering as controls were recruited from the Psychology Volunteer Panel at the University of Edinburgh o were relatives of patients with dementia. In the case of the former source, there is awareness about the impact that such selective samples could have on the interpretation of data [75]. Older adults involved in such panels (1) regularly support research and (2) are often highly educated, thus representing a rather biased sub-sample of the relevant population. Importantly, they frequently undergo cognitive testing, which grants them additional cognitive reserves and resilience [76]. Therefore, it is not entirely surprising that these older adults overlook or underestimate the level of decline in cognitive abilities here identified. Although volunteering has been considered a protective action against cognitive decline [76], managers of volunteer panels need to be aware of these risks. In the case of the latter source of recruitment (i.e., relatives of patients with dementia), there is evidence that the burden posed by the patients' level of cognitive and behavioural problems cause caregiver stress, which in turn leads to impaired cognitive functioning [77, 78]. Therefore, volunteer panels and dyads of dementia patients, two common sources of recruitment in ageing and dementia studies, will need revised approaches if we are going to progress in the new dementia research context with more confidence and reliability. The second issue, awareness of and stigmas against early symptoms of dementia, is also relevant [79] and suggests that more work is needed to continue raising awareness about the fact that ageing is not a disease [80] and seeking help early is the best approach to mitigate the dramatic impact that departures from its normal trajectory will carry.

Limitations

There are some limitations that need to be considered when interpreting the findings here reported. The first one is the rather small sample size. However, as shown by our inferential statistics, effect sizes were rather large for the hypotheses tested. Moreover, both experimental tests used in this study have demonstrated to hold informative value to identify individual patients and not just during group comparisons. For instance the VSTMBT test had shown sensitivity and specificity value of over 77% in completely

asymptomatic individuals [27] and of 100% for patients with dementia (see Della Sala et al. [31] who reported an Area Under the Curve of 96% for the FCSRT). Nevertheless, efforts will be needed to expand such samples within diseases stages and along the continuum, and such efforts are already ongoing [81].

Another limitation is the nature of the control participants who entered this study. This is not a representative sample. Even if unpaired cognitively, it is still possible that some of these older adults were already accumulating disease pathology (see [38]). Together with the report by Parra et al. [36] this evidence suggests that some of those who entered our HOA group may still be classified as not healthy controls if the approach recommended by Bos et al. [37] is followed. This limitation is shared by many studies in the field and urgent strategies will be necessary to address this important caveat.

One final limitation of this study is that we did not have biomarkers evidence to assess the biological status of our MCI patients and hence we choose to adhere to the definition of the Alzheimer's clinical syndrome as recently recommended [1, 5, 6].

Conclusions

In the current longitudinal study, we have demonstrated that neuropsychological assessments for AD shall move away from the notion of one-size-fits-all. A memory toolkit for AD needs to be considered which contains tools that are early indicators and others that might suggest imminent progression. This study, the first one reporting on the use of the VSTMBT in longitudinal assessment of MCI, suggests that the VSTMBT may provide an early indicator for such a toolkit while the FCSRT seems to be an excellent tool to assess imminent progression.

List Of Abbreviations

A/T/N: Amyloid, Tau, Neurodegeneration Framework

ACE-R: Addenbrooke's Cognitive Examination Revised

AD: Alzheimer's disease

Aβ: Amyloid β

eMCI: early Mild Cognitive Impairment Group

FCSRT: Free and Cued Selective Reminding Test

GDS: Geriatric Depression Scale

HOA: Healthy Older Adults Group

HVLT: Hopkins Verbal Learning Test

IADL: Instrumental Activities of Daily Living

maMCI: multi-domain amnestic MCI

MANOVA/ MANCOVA: Multivariate Analysis of Variance / Covariance

MCI Converter: MCI patients who developed dementia in the follow up period

MCI non-Converter: MCI patients who did not develop dementia in the follow up period

MCI: mild cognitive impairment stage

MCT: Memory Capacity Test

MTL: medial temporal lobe

ND: Neurodegeneration

NDN: Neuroprogressive and Dementia Network

NHS: National Health Services

SDCRN: Scottish Dementia Clinical Research Network interest register

SRT: Selective Reminding Tests

TMT-A and TMT-B: Trail Making Test Parts A and B

TOPF: Test of Premorbid Functions

VSTMB: Visual Short-Term Memory Binding

VSTMBT: Visual Short-Term Memory Binding Test

Declarations

Ethics approval and consent to participate

The study was approved by the NHS Multi-Site Research Ethics Committee (reference number 06/MRE07/40) and was given approval by local NHS R&D offices (Lothian R&D: 2006/P/PSY/22 and Forth Valley: FV682)

Consent for publication

All the participants enrolled in this study signed a Consent Form after reading a Participant Information Sheet that Stated: “The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals”.

Availability of data and materials

This is the first publication emerging from this longitudinal study. The team is currently professing data to generate further publication. The data used to prepare this manuscript can be available on request.

Competing interests

There are not conflict of competing interest to declare

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Authors' contributions

MAP conceived and led the study. He also drafted the manuscript. SDS participated in discussions in the preparation of the study and actively participated in the preparation of the manuscript. CC actively participated in data collection, analysis and was involved in the preparation of the manuscript. VP: is the NHS consultant who identified suitable patients and provide clinical support. He participated in the preparation of the manuscript.

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Figures

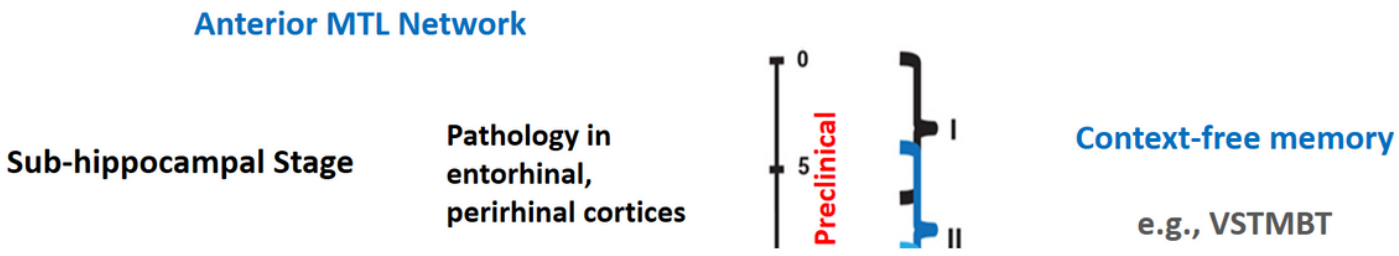
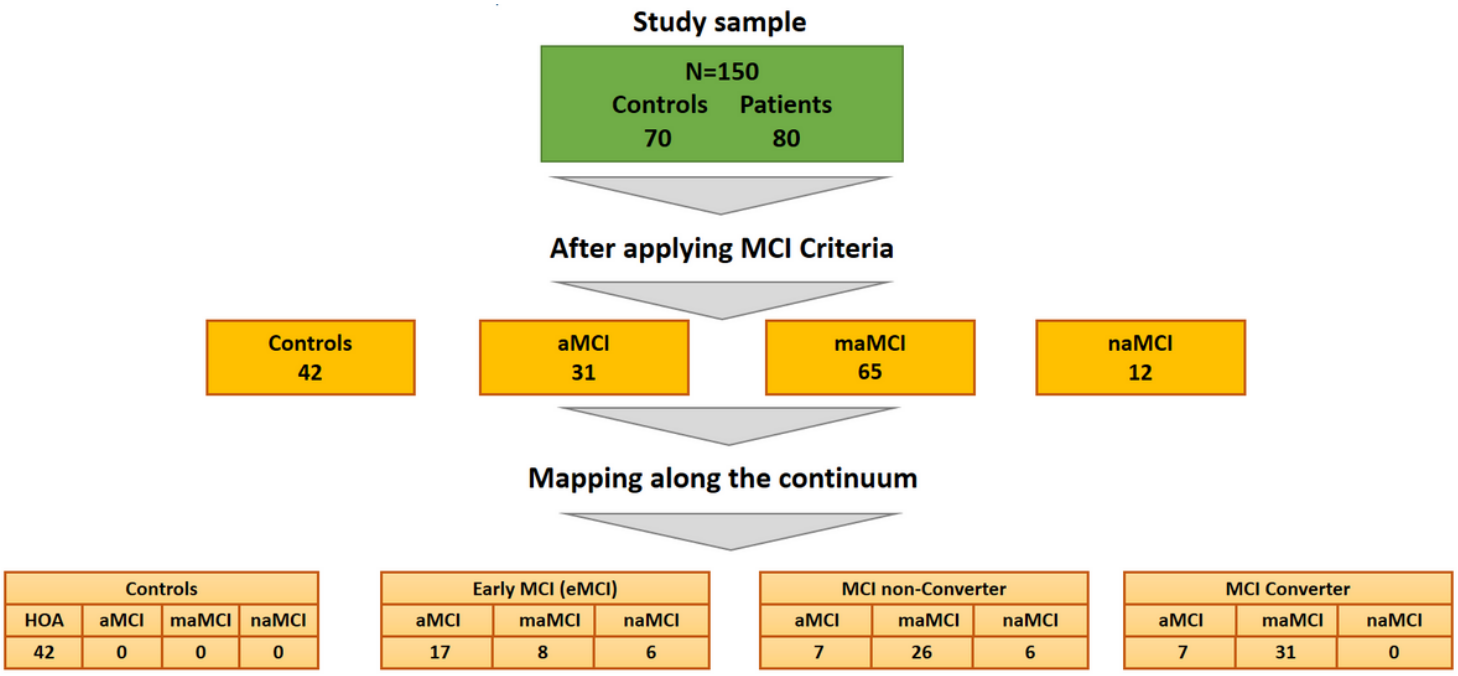


Figure 1

Diagram based on Didic et al.'s [11] model. It maps the two tests investigated here (VSTMBT and FCSRT) onto the stages of AD. It follows the rationale of the model to suggest when along the continuum, these tests would be most informative. Stage III of Braak [22, 23] corresponds to the onset of MCI (spread of pathology from the Anterior Medial Temporal Lobe – MTL- network to the posterior network). We hypothesised that the VSTMBT, as a test sensitive to the early preclinical stages, would inform who is at risk of progressing to more advanced stages (MCI), while the FCSRT would inform on risk of progressing to dementia among MCI patients.



Controls			
HOA	aMCI	maMCI	naMCI
42	0	0	0

Early MCI (eMCI)		
aMCI	maMCI	naMCI
17	8	6

MCI non-Converter		
aMCI	maMCI	naMCI
7	26	6

MCI Converter		
aMCI	maMCI	naMCI
7	31	0

Figure 2

Sample collected for the present study and its classification following criteria for MCI subtypes and those used for the present study (HOA: Healthy older adults, aMCI: amnestic MCI, maMCI: multi-domain amnestic MCI, naMCI: non-amnestic MCI; see text for description).

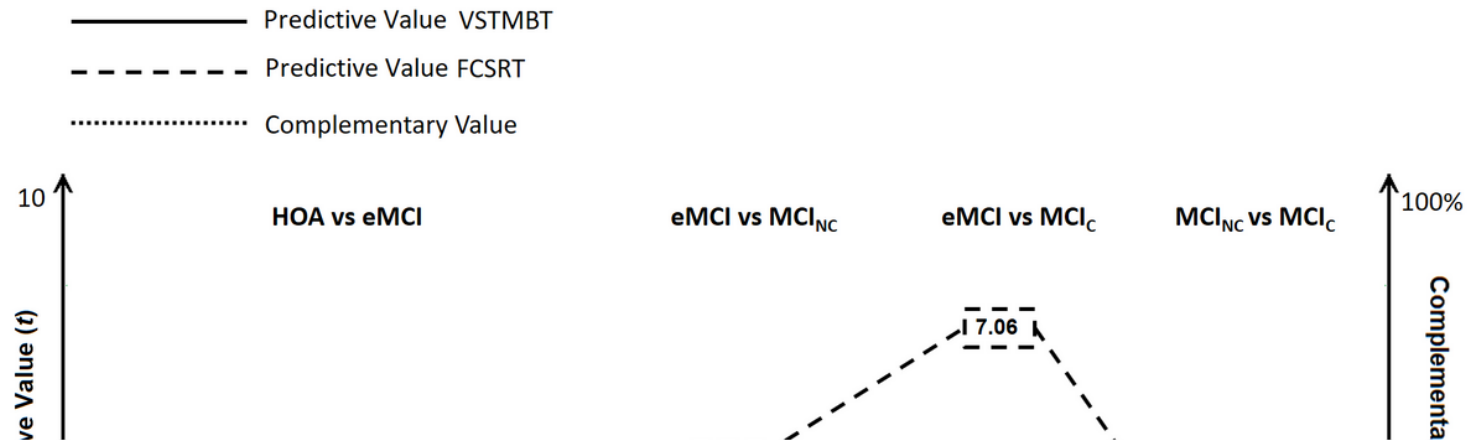


Figure 3

Diagram representing the individual and complementary value of the VSTMBT and FCSRT for the prediction of group membership along the continuum from the pre-symptomatic to prodromal stages of AD clinical syndrome.