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Reference Data of the Spanish Memory Binding Test in a Midlife Population from the ALFA STUDY (Alzheimer's and Family)

Nina Gramunt[a,*], Herman Buschke[b], Gonzalo Sánchez-Benavides[a,c], Richard B. Lipton[b], Jordi Peña-Casanova[d], Faustino Diéguez-Vide[e], Xavier Masramon[f], Juan D. Gispert[a], Karine Fauria[a], Jordi Camí[g,h] and José L. Molinuevo[a]

[a]*Clinical Research Program, BarcelonaBeta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Spain*
[b]*Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA*
[c]*Hospital del Mar Research Institute (IMIM), Barcelona, Spain*
[d]*Department of Behavioral Neurology, Service of Neurology, Hospital del Mar, Parc Salut Mar, Barcelona, Spain*
[e]*General Linguistics Department, University of Barcelona, Barcelona, Spain*
[f]*SAIL Statistics, Barcelona, Spain*
[g]*Pasqual Maragall Foundation, Barcelona, Spain*
[h]*Universitat Pompeu Fabra, Barcelona, Spain*

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Abstract.
Background: The Memory Binding Test (MBT) is a novel test based on the learning of two lists of words, developed to detect early memory impairment suggestive of Alzheimer's disease (AD).
Objective: To present and provide reference data of the Spanish MBT in a midlife population of mainly first-degree descendants of AD patients.
Methods: 472 cognitively unimpaired subjects, aged 45 to 65 and participants of the ALFA STUDY, were included. Raw scores were transformed to scaled scores on which multivariate regression analysis was applied adjusting by age, gender, and education level. A standard linear regression was employed to derive the scaled score adjusted. Sociodemographic corrections were applied and an adjustment table was constructed.
Results: Performance was heterogeneously influenced by sociodemographic factors. Age negatively influenced free recall. Education tends to have an influence in the results showing lower performance with lower education level. Women tend to outperform men in the learning of the first list and total recall. Only a few variables were unaffected by sociodemographic factors such as those related to semantic proactive interference (SPI) and to the retention of learned material. Our results point out that some vulnerability to SPI is expectable in cognitively healthy subjects. Close to 100% of the learned material was maintained across the delay interval.
Conclusion: This study contributes with reference data for the MBT providing the necessary adjustments for sociodemographic characteristics. Our data may prove to be useful for detecting asymptomatic at-risk candidates for secondary prevention studies of AD.

Keywords: Aging, Alzheimer's disease, cognition, early diagnosis, episodic memory, neuropsychological assessment, preclinical, reference values

*Correspondence to: Nina Gramunt, BarcelonaBeta Brain Research Center, Dr. Aiguader, 88 (PRBB building), 08003 Barcelona, Spain. Tel.: +34 933160990; Fax: +34 933160996; E-mail: ngramunt@fpmaragall.org.

INTRODUCTION

There is the increasingly accepted view that the earliest symptoms of Alzheimer's disease (AD) are

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preceded by a long, up to 20 years, silent preclinical phase [1, 2]. This preclinical stage, which can be identified by the presence of specific biomarkers, is considered to be the optimal time window for performing secondary prevention studies. These studies could be conducted with asymptomatic individuals or with those with subtle evidence of cognitive decline so as to prevent or, at least delay, the onset of full-blown clinical symptoms [3, 4]. According to the proposed framework for staging preclinical AD [4], the first stage is characterized by asymptomatic β-amyloidosis that can be detected by amyloid-β (Aβ) PET imaging and low concentrations of cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$. In the second stage, neurodegeneration indicators can be shown through FDG-PET, functional and structural MRI, and high concentrations of tau/p-tau. In the third and last stage, the distinctive feature is a subtle cognitive decline insufficient to meet criteria for mild cognitive impairment (MCI).

Biomarkers of Aβ and tau are detected through procedures that are expensive, invasive, or both. Early detection could be facilitated by the development of cognitive assessment tools that may prove useful as early as possible in the course of disease. There is emerging evidence that highly sensitive methods to measure episodic memory could detect very subtle cognitive impairment in Aβ-positive individuals [4, 5]. The hallmark of AD memory impairment, referred to as "of the hippocampal type" [6], has to be assessed through paradigms based on encoding specificity. In the updated research criteria for the diagnosis of AD [7], the Free and Cued Selective Reminding Test [8] is specifically recommended as a referent. The Free and Cued Selective Reminding Test is currently one of the most used tests for inclusion criteria in clinical trials and specific cutoff scores have been delimited as predictive for the evolution to the dementia stage of AD in subjects at the prodromal stage [9].

The Memory Binding Test (MBT), initially referred to as "The Memory Capacity Test" [10], is a novel test designed to improve the detection of the presymptomatic memory changes suggestive of AD. Some studies have pointed out to an inverse relationship between amyloid deposition and performance in this test in normal aging [11, 12].

The MBT assesses controlled learning and delayed retention of two different lists of words that share the same semantic category in pairs (favoring a binding procedure), through the testing of cued, paired, and free recall. The encoding is mediated by a controlled learning process ensuring that attention is focused in the material to be learned. This warrants a correct encoding and that eventual recall failures cannot be attributable to attentional fluctuations during the acquisition. Aside from pure memory deficits, attentional control deficits are also suggested to be an early marker of cognitive decline due to AD [13, 14]. Namely, immediate memory, resistance to semantic proactive interference, associative binding, and delayed retention of learned material are assessed, all these features being specifically relevant for memory decline related to AD. Binding refers to representational elements in memory that can be recalled together in a unitized way when a specific episode or fact is retrieved and has been related to brain structures strongly associated with AD pathology, such as the medial temporal region [15], the perirhinal cortex, and the hippocampus [16], or to cortical disconnection in AD [17]. A memory binding impairment may be explained by the age-related associative deficit hypothesis [18], which could be in line with studies that report age-related differences in binding ability, specifically in working memory [19, 20]. However, it has also been suggested that a binding deficit in verbal short term memory could represent a genuine deficit of AD [21], while the visual modality appears to have promising predictive value for AD [22]. A detailed study on the MBT performance in aging could cast light on this topic. On the other hand, the vulnerability to proactive interference may have predictive utility for the progression to dementia [23], and it is considered an early cognitive feature of MCI and mild AD [24]. The effects of semantic proactive interfere (SPI), specifically assessed with the MBT, can be observed when the subject has to learn two competing lists of targets that share semantic categories leading to semantic proactive interfere [25, 26].

The delayed recall allows a retention index to be obtained. It has been suggested that an index of rapid forgetting can be a predictor of progression to dementia among elderly subjects [27, 28], especially if used jointly with learning measures [29], representing a promising tool to use in the clinical practice [30].

In terms of the performance of each subject, the MBT may be affected by sociodemographic factors, as the majority of neuropsychological tests. As such, demographic adjustments are required and these are routinely applied to most normative data in neuropsychology [31, 32]. Due to a higher demand on self-initiated processes, and their dependence on processing resources, verbal episodic memory, in particular free recall, declines with aging [33]. The age-associated episodic memory decline can begin as early as at 20 or 30 years of age and slightly declines linearly until about age 60, at which time there is a

more precipitous decline as part of normal cognitive aging [34–36]. Normative studies of different verbal memory tests do not show a uniform effect of education in the results, what can be probably related to different sample sociodemographic characteristics (for a review, see [32]). However, higher education taken as a proxy for cognitive reserve has been associated with some kind of mitigating effect for pathology burden in cognitive decline [37, 38]. The effect of gender in verbal memory performance has been consistently reported. Women tend to outperform men [39] and take special advantage from either semantic or phonological clustering during verbal memory tasks [40].

Despite having been pointed as a very promising neuropsychological approach for the detection of subtle memory loss suggestive of preclinical AD [5], none of the previous studies of the MBT [11, 12, 41] describes reference data, nor reliability or validity analysis. Therefore, a thorough characterization of the performance of cognitively healthy subjects in this test is of great interest. Test norms are essential for proper interpretation in clinical and research settings [31]. The current and increasing interest in detecting the subtlest cognitive changes secondary to AD with prevention purposes makes the direct descendants of AD patients a particularly interesting group to be studied. It has to be taken into account that they can present a differential cognitive performance with respect to the general population [42].

The aim of our work is to provide reference data for the MBT according to age, gender, and educational level in a Spanish sample of healthy and cognitively normal subjects aged 45–65 at an increased risk to develop AD by their condition of first-degree descendants of AD patients.

MATERIALS AND METHODS

Participants

With the aim of understanding the initial changes of preclinical AD and to collect information on exogenous and endogenous risk factors (our own unpublished data; Clinicaltrials.gov Identifier: NCT01835717), we set up the ALFA (from Alzheimer and Families) study for the prospective follow-up of a population of cognitively healthy offspring of AD patients. Subjects were not eligible to be included in the ALFA STUDY if any of their scores in the screening neuropsychological tests were found to be out of the defined scope of the cutoffs (*crf. infra*), or if they presented any medical condition that could interfere with cognition or with the results of the study, relevant neurological conditions or major psychiatric disorders. The 472 subjects included in the present study are a subset of the basal population of the ALFA.

All the participants of the ALFA study ($n = 2{,}743$) were administered the MBT. As explained later (see Procedure and Materials section), two alternate forms of the test were developed (A and B). The first 472 subjects that were consecutively administered the Spanish MBT A version were included in the present reference data analysis. Participant's age, gender, and education level were registered to assess their impact on the MBT performance. The education degrees were registered according to the Spanish system. For the sake of international correspondence, the International Standard Classification of Education (ISCED) (UNESCO, 2012) is presented in the results section.

Our study was approved by the corresponding Ethics Committee and conducted in accordance to the directives of the Spanish Law 14/2007, of 3 July, on Biomedical Research (Ley 14/2007 de Investigación Biomédica). All subjects accepted the study procedures by signing an informed consent form and had a close relative that agreed to participate in the functional assessment procedure of the volunteer. Close relatives also signed an informed consent form.

Procedure and materials

To ensure compliance with the ALFA study inclusion criteria, the following screening neuropsychological tests were used (the corresponding cutoff for exclusion is specified): Mini-Mental State Examination (<26) [43, 44], Memory Impairment Screen (<6) [27, 45], verbal semantic fluency (naming animals <12) [46, 47], Time Orientation of the Test Barcelona II (<68) [48], Clinical Dementia Rating Scale (>0) [49], and Goldberg Anxiety and Depression Scales [50, 51], used to screen for mood disorders. In the cases that the scores of the Goldberg Anxiety and Depression Scales were over the cutoffs defined for suspect of disorder (anxiety >3; depression >1), the rater checked whether the subject met the DSM-IV criteria for General Anxiety Disorder or Major Depressive Episode and, if this was the case, the subject was excluded from the study.

Materials and instructions to administer the MBT were provided by its author (Herman Buschke) and the Albert Einstein College of Medicine of Yeshiva University of New York. This test uses cues for controlled learning and cued recall and, to be effective, each item must be easily recognized as a member of the corresponding category. Therefore, the MBT uses well

known items that subjects can easily and accurately identify when given the category cue corresponding to each item. These words are of moderate frequency to minimize the possibility of guessing the words by chance during recall and, on the other hand, to avoid that some words could be difficult to be related to its category, given their low frequency. The Spanish version of the MBT was obtained through a translation and transcultural adaptation process according to the linguistic criteria followed in the original version. In parallel, an alternate Spanish form (MBT B) was developed and both forms were translated and adapted to Catalan following the same linguistic criteria for obtaining the Spanish MBT A explained next. Frequency was then the main variable taken into account in the selection of words for its complete objectiveness and direct relation to familiarity. The frequency of the words in Spanish was assessed according to a widely recognized dictionary of linguistic frequencies [52] and the selected words were always of medium frequency. Whenever possible, the original categories were respected but some of them had to be changed due to cultural adaptation issues or to equivalence of the frequency of the words in Spanish.

The administration procedure of the MBT is detailed next. Sixteen items, each from one of sixteen different semantic categories, are learned by reading aloud and identifying each item in an array of printed words shown in fours when its category cue is presented (e.g., "Which is the means of transport?" ... "The helicopter"). Immediately after the identification of the sixteen items of the first list (L1), memory is tested by cued recall, using the same category cues (e.g.,"Which was the means of transport?"). The second list (L2) is learned and tested in the same way as L1, using the same category cues with different items. Then the category cues are again presented, to assess binding by recall of both items together for each category cue, that is, paired recall (e.g., "Now, from both lists, which were the means of transport?"). The subject is told that the word order does not matter. Next, without any delay or interference, free recall is tested ("Tell me all the words you can remember, in any order"). Up to this point (i.e., immediate trials) the test takes about 6 minutes. Finally, delayed free recall followed by paired cued recall is tested 30 minutes later ($\pm$ 5 min.) and, in the in-between lapse of time, other cognitive tests without verbal content were administered to avoid interferences with the recall of the MBT words. The delayed recall trial takes about 3 minutes.

The MBT was administered in the context of the visit of the ALFA study where the volunteers were administered the cognitive battery test and a few questionnaires regarding sociodemographic data. The cognitive battery consisted of the following tests listed in the order of administration: Coding (W-IV), MBT immediate trials, Visual Puzzles (W-IV), Digit Span (W-IV), Matrix Reasoning (W-IV), MBT (delayed trials), and Similarities (W- IV). W-IV refers to subtests of the Spanish edition of the WAIS-IV [53].

The raters were experienced neuropsychologists and senior neuropsychology students that received specific training on the administration and data collection and quality control procedures were implemented to assure homogenization. The quality control procedures included, for junior neuropsychologists and students, no less than 3 visits as observers of the visit procedure conducted by senior neuropsychologists, and no less than another 3 visits being observed (and corrected if necessary) by a senior neuropsychologist. When skillful enough with the procedures, the rater started to conduct the visits autonomously but could be randomly observed throughout the recruitment period. All the raters were provided with guidelines and test administration procedures. Moreover, periodical newsletters were delivered not only to inform on the study progress but also to call the attention to frequent doubts or difficulties. The MBT generates several variables that are suitable for analysis. In the present manuscript, we describe the analysis of 21 variables. To facilitate their understanding and rationale, they were grouped into three main areas: Learning and Immediate Recall, Delayed Recall, and Retention. The codification and a detailed description of each of the variables are presented in Table 1.

Data analysis

Rank-based Blom transformation [54] was applied to standardize all raw scores by transforming them into normally distributed scores. This maintained the order of the data and removed skewness from variable distributions. Scores transformed using the Blom transformation have the property of having a mean of 0 and a unit standard deviation (Z score). To obtain the scaled scores (SS), with a standard deviation of 3 and a mean of 10, the Z score was multiplied by 3 and the resulting value was added to 10. Provided that scaled scores are normally distributed, it is expected that two-thirds (68.26%) of the population would obtain scores between 7 and 13. We also present the corresponding percentiles for the SS.

The transformation of the raw score to SS produced a normalized distribution on which multivariate

Table 1
Grouping, codification, and detailed description of the MBT variables analyzed

		Code	Name	Description	Source of the score	Range
LEARNING AND IMMEDIATE RECALL	Learning	CR-L1	Cued recall List 1	Words recalled after immediate cueing for L1	Sum of words of L1 ticked as recalled under this condition	0–16
		CR-L2	Cued recall List 2	Words recalled after immediate cueing for L2	Sum of words of L2 ticked under this condition	0–16
		SPI	Semantic proactive interference	Effect of L1 learning in L2 learning	CR-L2/CR-L1x100	%
		TCR	Total Cued Recall	Total of words of L1 and L2 recalled after immediate cueing	CR-L1+CR-L2	0–32
	Paired Recall Binding	PR-L1	Paired Recall List 1	Words of L1 recalled when cueing for paired recall	Sum of words of L1 ticked as recalled under this condition	0–16
		PR-L2	Paired Recall List 2	Words of L2 recalled when cueing for paired recall	Sum of words of L2 ticked as recalled under this condition	0–16
		TPR	Total Paired Recall	Total of words of L1 and L2 recalled when cueing for paired recall.	PR-L1+PR-L2	0–32
		PRP	Paired Recall Pairs	Number of instances when both items of a semantic pair are recalled when cueing for paired recall.	Sum of semantic pairs ticked as recall under this condition.	0–16
	Immediate Free Recall	FR-L1	Free Recall List 1	Words of L1 recalled during free recall of all the words	Sum of words of L1 ticked as recalled under this condition	0–16
		FR-L2	Free Recall List 2	Words of L2 recalled during free recall of all the words.	Sum of words of L2 ticked as recalled under this condition	0–16
		TFR	Total Free Recall	Sum of words of L1 and L2 ticked as recalled under the free recall condition.	FR-L1+FR-L2	0–32
		PFR	Pairs in Free Recall	Number of instances when both items of a semantic pair are recalled in the free recall condition.	Sum of semantic pairs recalled under this condition.	0–16
DELAYED RECALL	Delayed Free Recall	DFR-L1	Delayed Free Recall List 1	Words of L1 recalled during delayed free recall of all the words.	Sum of words of L1 ticked as recalled under this condition.	0–16
		DFR-L2	Delayed Free Recall List 2	Words of L2 recalled during delayed free recall of all the words.	Sum of words of L2 ticked as recalled under this condition.	0–16
		TDFR	Total Delayed Free Recall	Sum of words of L1 and L2 ticked as recalled under the free recall condition.	DFR-L1+DFR-L2	0–32
		PDFR	Pairs in Delayed Free Recall	Number of instances when both items of a semantic pair are recalled in the delayed free recall condition.	Sum of semantic pairs recalled under this condition.	0–16
	Delayed Paired Recall	DPR-L1	Delayed Paired Recall List 1	Words of L1 recalled when cueing for delayed paired recall	Sum of words of L1 ticked as recalled under this condition	0–16
		DPR-L2	Delayed Paired Recall List 2	Words of L2 recalled when cueing for delayed paired recall	Sum of words of L2 ticked as recalled under this condition	0–16
		TDPR	Total Delayed Paired Recall	Total of words of L1 and L2 recalled when cueing for delayed paired recall.	DPR-L1+DPR-L2	0–32
RETENTION	Retention Indexes	DFRR	Delayed Free Recall Rate	Delayed free recall as a proportion of immediate free recall.	TDFR/TFR x 100	%
		DPRR	Delayed Paired Recall Rate	Delayed paired recall as a proportion of immediate paired recall.	TDPR/TPR x 100	%

regression analysis was applied for each SS adjusting by age group, gender, and education level. By means of the stepwise selection method, sociodemographic adjustments were created for those variables in which either age, education, or gender explained more than the 2% of the total variance (i.e., squared partial correlation coefficient superior than 0.02) and the regression coefficients were significant ($p < 0.05$). After that, the interactions between the regression factors were evaluated.

Following the method described by Mungas and colleagues [55], a standard linear regression was employed to derive the scaled score adjusted (SSA). The corrections were made using the unstandardized regression coefficients (B). The mean age of 54 and mean education of 13 were selected to center the adjustments. The obtained value was rounded to the nearest integer. $SS_A = SS - (B_{1*}[gender]+B_{2*}[age-54]+B_{13*}[education-13])$

From these data, demographic corrections were applied when needed and an adjustment table was constructed to help the clinician make the necessary changes on the scaled scores.

The SAS statistical package, version 9.2 was used for the statistical analyses.

RESULTS

The sample consisted of 472 subjects that were tabulated per gender, age stratum, and level of education as shown in Table 2.

As a result of the type of sampling, subjects were incidentally represented in the different demographic categories. The vast majority of participants in this study were adult children of patients diagnosed with late onset AD (93.22%). Age was stratified in 5-year ranges that show a quite proportional distribution except for a little decrease in the number of participants from the older group. Education was also tabulated in four descriptive categories taking into account the last and completed academic degree. Correspondence between the Spanish and ISCED levels is shown in Table 2 footnotes. The education levels more represented are second (39.2%) and third degree studies (28.8%).

Table 3 shows the descriptive data of the screening and functional tests used as part of the exclusion criteria in order to define a threshold for cognitive and functional normality. All the subjects had a global Clinical Dementia Rating of 0.

Tables 4 and 5 show the conversion to SS and its corresponding percentile ranges for the variables of each group. For the correct use of the tables, the obtained raw score from the subject in each variable has to be localized and then checked for the corresponding SS in any of the lateral columns. For example, a score of 27 in the variable TCR corresponds to a SS of 11 corresponding to the 63rd–74th percentile range.

Table 2
Sample sociodemographic characteristics

Gender	
Male	172 (36.4%)
Female	300 (63.6%)
Age (years)	
Mean (SD)	54.0 (5.5)
95% CI	(53.5; 54.5)
Median (min/max)	54 (44/65)
Age group	
44–49 years	117 (24.8%)
50–54 years	137 (29.0%)
55–59 years	130 (27.5%)
60–65 years	88 (18.6%)
Education level[a]	
1st grade / IL 1-2	82 (17.4%)
2nd grade / IL 3-4	185 (39.2%)
3rd grade / IL 5-6	136 (28.8%)
Postgraduate / IL 7-8	69 (14.6%)
Education (years)	
Mean (SD)	13.1 (3.7)
95% CI	(12.8; 13.5)
Median (min/max)	12 (6/20)

[a]Equivalence of the education levels to the ISCED-UNESCO classification: 1st grade = ISCED levels 1-2; 2nd grade = ISCED levels 3-4; 3rd grade = ISCED levels 5-6; Postgraduate = ISCED levels 7-8. IL = ISCED Levels. In the Spanish educational system 1st grade corresponds to *EGB* or *Bachiller Elemental*; 2nd grade to *BUP, COU* or *FP*; 3rd grade to University *Diplomatura* or *Licenciatura*; and Postgraduate to *Master* or *Doctorado*.

Table 3
Descriptive data of the cognitive and functional screening tests and mood assessment

Test/Scale	Mean (SD)	Range	Maximum possible	Cutoff
MMSE	29.1 (1.0)	26–30	30	<26
MIS	7.8 (0.5)	6–9	8	<6
Verbal Fluency (Animals)	22.8 (5.1)	12–39	–	<12
Orientation Subtest – TB II	70.0 (0.0)	69–70	70	<68
Anxiety Scale (GADS) [a]	0.7 (1.3)	0–8	9	>3
Depression Scale (GADS) [a]	0.2 (0.7)	0–6	9	>1

MMSE, Mini-Mental State Examination; MIS, Memory Impairment Screen; TB II, Test Barcelona II; GADS, Goldberg Anxiety Depression Scales. [a]It does not imply a direct exclusion criterion. It is an indication to check whether DSM-IV criteria are accomplished either for General Anxiety Disorder or Major Depressive Episode which do constitute an exclusion criterion.

Table 4
Conversion to Scaled Scores for the variables related to learning and immediate recall

		Learning				Paired Cued Recall				Immediate Free Recall					
Ptle	SS	CR-L1 (0–16)	CR-L2 (0–16)	TCR (0–32)	SPI (%)	PR-L1 (0–16)	PR-L2 (0–16)	TPR (0–32)	PRP (0–16)	FR-L1 (0–16)	FR-L2 (0–16)	TFR (0–32)	PFR (0–16)	SS	Ptle
<1	2	0–7	0–2	0–13	≤17	0–6	0–3	0–12	0	0–2	0	0–5	–	2	<1
1	3	8–9	3	14–15	18–26	7	4	13	1	3	1	6	0	3	1
2	4	10	4	16	27–36	8	–	14–15	2	–	2	7	1	4	2
5–8	5	11	5	17–18	37–43	9	5	16	3	4	3	8–9	–	5	5–8
9–15	6	12	6	19–20	44–51	10	6–7	17–18	4	5	4	10	2	6	9–15
16–24	7	–	7–8	21	52–60	–	8	19	5	6	5	11–12	3	7	16–24
25–36	8	13	9	22–23	61–67	11	9	20–21	6–7	7	6	13	4	8	25–36
37–49	9	–	10	24	68–73	12	10	22–23	8	8	–	14–15	5	9	37–49
50–62	10	14	11	25–26	74–80	13	11	24	9	9	7	16	6	10	50–62
63–74	11	15	12	27	81–87	14	12	25–26	10	–	8	17–18	7	11	63–74
75–83	12	–	13	28	88–92	–	13	27	11	10	9	19–20	8	12	75–83
84–90	13	–	14	29	93–96	15	14	28	12	11	10	21	9	13	84–90
91–94	14	16	15	30	97–103	–	15	29	13	12	11	22–23	10	14	91–94
95–97	15	–	–	31	104–108	16	–	30	14	13	12	24–25	11	15	95–97
98	16	–	16	32	109–114	–	–	31	15	14	13	26	12	16	98
99	17	–	–	–	115–118	–	16	–	–	15	14	27	13	17	99
>99	18	–	–	–	≥119	–	–	32	16	16	15–16	28–32	14–16	18	>99

Ptle, Percentile; SS, Scaled Score; CR-L1, Cued Recall List 1; CR-L2, Cued Recall List 2; TCR, Total Cued Recall; SPI, Semantic Proactive Interference; PR-L1, Paired Recall List 1; PR-L2, Paired Recall List 2; TPR, Total Paired Recall; PRP, Paired Recall Pairs; FR-L1, Free Recall List 1; FR-L2, Free Recall List 2; TFR, Total Free Recall; PFR, Pairs in Free Recall.

Table 5
Conversion to Scaled Scores for the variables related to delayed recall and retention indexes

		Delayed Free Recall				Delayed Cued Recall			Retention indexes			
Ptle	SS	DFR-L1 (0–16)	DFR-L2 (0–16)	TDFR (0–32)	PDFR (0–16)	DPR-L1 (0–16)	DPR-L2 (0–16)	TDPR (0–32)	DFRR (%)	DPRR (%)	SS	Ptle
<1	2	0–2	0	0–5	0	0–6	0–3	0–13	≤61	≤81	2	<1
1	3	3	1	6	–	7	4	14	62–64	82–85	3	1
2	4	4	2	7	1	8	5	15	65–68	86–87	4	2
5–8	5	–	3	8	–	9	6	16	69–72	88–89	5	5–8
9–15	6	5	–	9–10	2	–	7	17–18	73–77	90–92	6	9–15
16–24	7	6	4	11–12	3	10	8	19	78–85	93–95	7	16–24
25–36	8	7	5	13	4	11	9	20–21	86–90	96	8	25–36
37–49	9	8	6	14–15	5	12	10	22–23	91–97	97–98	9	37–49
50–62	10	9	7	16	6	13	11	24	98–104	99–100	10	50–62
63–74	11	10	8	17–18	7	14	12	25–26	105–109	101	11	63–74
75–83	12	11	9	19–20	8	–	13	27	110–117	102–103	12	75–83
84–90	13	–	10	21–22	9	15	14	28	118–125	104–106	13	84–90
91–94	14	12	11	23–24	10–11	–	15	29	126–132	107–109	14	91–94
95–97	15	13	12	25–26	12	16	–	30	133–145	110–111	15	95–97
98	16	14	13	27–28	13	–	–	31	146–166	112–115	16	98
99	17	15	14	29	14	–	16	32	167–181	116–125	17	99
>99	18	16	15–16	30–32	15–16	–	–	–	≥182	≥126	18	>99

Ptle, Percentile; SS, Scaled Score; DFR-L1, Delayed Free Recall List 1; DFR-L2, Delayed Free Recall List 2; TDFR, Total Delayed Free Recall; PDFR, Paired Delayed Free Recall; DPR-L1, Delayed Paired Recall List 1; DPR-L2, Delayed Paired Recall List 2; TDPR, Total Delayed Paired Recall; DFRR, Delayed Free Recall Rate; DCRR, Delayed Paired Recall Rate.

Table 6 shows the multivariate regression results, indicating which of the demographic factors (namely age, gender, and education) had a significant impact on the different MBT variables studied. Interactions between the regression factors were never statistically significant. These results were subsequently used to derive appropriate corrections for these factors. Table 7 shows the adjustments to be applied in order to facilitate to the researcher or to the clinician, the final score of the subjects according to their demographic characteristics. For example, in the case of a woman aged 64 and with a first grade education, one should look in the "Women" section of the table, in the column corresponding to 60–65 years and, then, in the column

Table 6
Regression coefficients and squared partial correlation coefficients of scaled scores with *age*, gender and education

	Gender					Age					Education				
	B_1	SE	β_1	*p*-value	R^2	B_2	SE	β_2	*p*-value	R^2	B_3	SE	β_3	*p*-value	R^2
CR-L1	1.367	0.267	0.228	<0.0001	0.053						0.557	0.137	0.182	0.0001	0.034
CR-L2															
TCR	1.044	0.279	0.170	0.0002	0.029						0.503	0.143	0.162	0.0005	0.026
SPI															
PR-L1	1.185	0.275	0.194	<0.0001	0.038						0.542	0.141	0.175	0.0001	0.030
PR-L2											0.452	0.144	0.147	0.0018	0.021
TPR	0.948	0.280	0.154	0.0008	0.024						0.583	0.144	0.188	0.0001	0.034
PRP											0.478	0.144	0.155	0.0010	0.023
FR-L1	1.022	0.274	0.166	0.0002	0.029	–0.496	0.127	–0.176	0.0001	0.044	0.489	0.143	0.155	0.0007	0.024
FR-L2						–0.690	0.126	–0.245	<0.0001	0.060					
TFR	0.935	0.273	0.151	0.0007	0.024	–0.612	0.126	–0.216	<0.0001	0.063	0.517	0.143	0.165	0.0003	0.027
PFR						–0.598	0.127	–0.212	<0.0001	0.045					
DFR-L1						–0.445	0.128	–0.156	0.0006	0.037	0.559	0.144	0.178	0.0001	0.031
DFR-L2						–0.590	0.127	–0.209	<0.0001	0.060	0.570	0.142	0.183	0.0001	0.033
TDFR						–0.571	0.127	–0.201	<0.0001	0.058	0.630	0.143	0.201	<0.0001	0.040
PDFR						–0.556	0.127	–0.197	<0.0001	0.055	0.604	0.142	0.194	<0.0001	0.037
DPR-L1	1.201	0.273	0.197	<0.0001	0.040						0.586	0.140	0.190	<0.0001	0.036
DPR-L2											0.497	0.144	0.162	0.0006	0.025
TDPR	0.995	0.277	0.161	0.0004	0.027	–0.389	0.128	–0.137	0.0026	0.031	0.560	0.145	0.180	0.0001	0.031
DFRR															
DPRR															

B, unstandardized regression coefficients; β, standardized regression coefficients (to assess the magnitude of the effect); SE, standard error; R^2, squared partial correlation coefficient; CR-L1, Cued Recall List 1; CR-L2, Cued Recall List 2; TCR, Total Cued Recall; SPI, Semantic Proactive Interference; PR-L1, Paired Recall List 1; PR-L2, Paired Recall List 2; TPR, Total Paired Recall; PRP, Paired Recall Pairs; FR-L1, Free Recall List 1; FR-L2, Free Recall List 2; TFR, Total Free Recall; PFR, Pairs in Free Recall; DFR-L1, DFR-L1, Delayed Free Recall List 1; DFR-L2, Delayed Free Recall List 2; TDFR, Total Delayed Free Recall; PDFR, Paired Delayed Free Recall; DPR-L1, Delayed Paired Recall List 1; DPR-L2, Delayed Paired Recall List 2; TDPR, Total Delayed Paired Recall; DFRR, Delayed Free Recall Rate; DPRR, Delayed Paired Recall Rate.

corresponding to 1st grade to find the needed correction, if any, to be applied to the scaled score obtained for each variable. Following with our example with the variable TCR and a raw score of 27 we will have to add 1 point to the SS, resulting then in a SS of 12, corresponding to the 75–83th percentile range.

DISCUSSION

This paper describes reference data of the Memory Binding Test, a novel cognitive test to assess presymptomatic memory decline suggestive of AD, for a Spanish population aged 45 to 65 years of age with an increased risk to develop AD, as being descendants of AD patients [42, 56].

The transformation of raw data into scaled scores resulted in a normalized distribution that enabled the analysis of the effects of age, gender, and education. This allowed us to define scaled scores adjustments when needed.

Neuropsychological tests tend to show variability as a function of the sociodemographic characteristics of subjects (gender, age, and education) [31, 32]. This vulnerability to sociodemographic factors was heterogeneously patent in the variables of the MBT (Table 6). While SPI and retention indexes (DFRR and DPRR) were unaffected by sociodemographic traits, the effects of age, gender, and education were evident in the remaining variables as discussed below.

Our results show that a certain level of vulnerability to SPI is within the psychometrically normal range, independently of any sociodemographic variable. A performance between 74 to 80% of recall efficiency in List 2 with respect to the efficiency in List 1 is in the center of the distribution (Scaled Score of 10, Table 4). It is considered normal that previous learning of a list interferes in the efficiency of learning of a new list of words semantically related. In observing the normal distribution of the scores and its conversion to scaled scores, we can affirm that approximately each 20% of loss or gain of efficiency of L2 with respect to L1 represents 1 SD. Similar to experiencing a high degree of sensitivity (i.e., superior to 70%, meaning 2 SD below the mean) to SPI would be considered abnormal, experiencing a high resistance to it (i.e., superior to 110%) would be also exceptional, in this case by falling in

Table 7
Adjustments of the scaled scores by age, gender and education

Men	44–49 y			50–59 y			60–65 y			
	1st gr	2-3 gr	Postgr	1st gr	2-3 gr	Postgr	1st gr	2-3 gr	Postgr	
CR-L1	+2	+1	0	+2	+1	0	+2	+1	0	CR-L1
CR-L2	0	0	0	0	0	0	0	0	0	CR-L2
TCR	+2	+1	0	+2	+1	0	+2	+1	0	TICR
SPI	0	0	0	0	0	0	0	0	0	SPI
PR-L1	+2	+1	0	+2	+1	0	+2	+1	0	PR-L1
PR-L2	+1	0	–1	+1	0	–1	+1	0	–1	PR-L2
TPR	+2	+1	0	+2	+1	0	+2	+1	0	TPR
PRP	+1	0	–1	+1	0	–1	+1	0	–1	PRP
FR-L1	+1	0	–1	+2	+1	0	+3	+2	+1	FR-L1
FR-L2	–1	–1	–1	0	0	0	+1	+1	+1	FR-L2
TFR	+1	0	–1	+2	+1	0	+3	+2	+1	TFR
PFR	–1	–1	–1	0	0	0	+1	+1	+1	PFR
DFR-L1	0	–1	–2	+1	0	–1	+2	+1	0	DFR-L1
DFR-L2	0	–1	–2	+1	0	–1	+2	+1	0	DFR-L2
TDFR	0	–1	–2	+1	0	–1	+2	+1	0	TDFR
PDFR	0	–1	–2	+1	0	–1	+2	+1	0	PDFR
DPR-L1	+2	+1	0	+2	+1	0	+2	+1	0	DCR-L1
DPR-L2	+1	0	–1	+1	0	–1	+1	0	–1	DCR-L2
TDPR	+1	0	–1	+2	+1	0	+3	+2	+1	TDCR
DFRR	0	0	0	0	0	0	0	0	0	DFRR
DPRR	0	0	0	0	0	0	0	0	0	DCRR
Women										
	44–49 y			50–59 y			60–65 y			
	1st gr	2-3 gr	Postgr	1st gr	2-3 gr	Postgr	1st gr	2-3 gr	Postgr	
CR-L1	+1	0	–1	+1	0	–1	+1	0	–1	CR-L1
CR-L2	0	0	0	0	0	0	0	0	0	CR-L2
TCR	+1	0	–1	+1	0	–1	+1	0	–1	TICR
SPI	0	0	0	0	0	0	0	0	0	SPI
PR-L1	+1	0	–1	+1	0	–1	+1	0	–1	PR-L1
PR-L2	+1	0	–1	+1	0	–1	+1	0	–1	PR-L2
TPR	+1	0	–1	+1	0	–1	+1	0	–1	TPR
PRP	+1	0	–1	+1	0	–1	+1	0	–1	PRP
FR-L1	0	–1	–2	+1	0	–1	+2	+1	0	FR-L1
FR-L2	–1	–1	–1	0	0	0	+1	+1	+1	FR-L2
TFR	0	–1	–2	+1	0	–1	+2	+1	0	TFR
PFR	–1	–1	–1	0	0	0	+1	+1	+1	PFR
DFR-L1	0	–1	–2	+1	0	–1	+2	+1	0	DFR-L1
DFR-L2	0	–1	–2	+1	0	–1	+2	+1	0	DFR-L2
TDFR	0	–1	–2	+1	0	–1	+2	+1	0	TDFR
PDFR	0	–1	–2	+1	0	–1	+2	+1	0	PDFR
DPR–L1	+1	0	–1	+1	0	–1	+1	0	–1	DCR-L1
DPR-L2	+1	0	–1	+1	0	–1	+1	0	–1	DCR-L2
TDPR	0	–1	–2	+1	0	–1	+2	+1	0	TDCR
DFRR	0	0	0	0	0	0	0	0	0	DFRR
DPRR	0	0	0	0	0	0	0	0	0	DCRR

1st gr, ISCED levels 1-2; 2-3 gr, ISCED levels 3–6; Postgr, ISCED levels 7-8. CR-L1, Cued Recall List 1; CR-L2, Cued Recall List 2; TCR, Total Cued Recall; SPI, Semantic Proactive Interference; PR-L1, Paired Recall List 1; PR-L2, Paired Recall List 2; TPR, Total Paired Recall; PRP, Paired Recall Pairs; FR-L1, Free Recall List 1; FR-L2, Free Recall List 2; TFR, Total Free Recall; PFR, Pairs in Free Recall; DFR-L1, Delayed Free Recall List 1; DFR-L2, Delayed Free Recall List 2; TDFR, Total Delayed Free Recall; PDFR, Paired Delayed Free Recall; DPR-L1, Delayed Paired Recall List 1; DPR-L2, Delayed Paired Recall List 2; TDPR, Total Delayed Paired Recall; DFRR, Delayed Free Recall Rate; DPRR, Delayed Paired Recall Rate.

the upper-end of the normal distribution (2 SD over the mean). This poor resistance to SPI is consistent with a previous study [12], which shows that noticeable decreases in learning the second list with respect to the first one are related with higher levels of Aβ burden in cognitively normal subjects. On the other hand, it has been noted that there is an increased vulnerability to proactive interference with aging, particularly after

age 60 [57]. In fact, attentional control deficits could affect recalling processes and trigger proactive interference. The longitudinal follow-up of the subjects of the present study will be crucial to derive conclusions regarding the value of SPI as a cognitive predictor of progression to AD in middle-aged adults as it has been suggested.

With regards to the retention indexes, free (DFRR) and paired (DPRR), close to 100% of the learned material was maintained across the delay interval (Table 5). This relative indemnity in cognitively normal subjects is consistent with previous studies [58–61]. The planned longitudinal study will allow us to determine if the retention rates assessed with the MBT are more useful than other assessment procedures to predict future progression to AD in an earlier stage of the disease. The MBT is based on a procedure that allows deep information processing of the material to be learned. This is a very relevant feature to ensure that failure in effective recall is due to "genuine" memory impairment [8] and not to ineffective processing resources, which could be derived from an attentional deficit. However, attentional control is also involved during the retrieval processes. Therefore, the MBT procedure cannot ensure that diminished recall is not influenced at all by an executive attentional control. It has been described that attentional and executive dysfunctions are early affected in the preclinical AD [13]. It has been shown that cognitively healthy subjects who undergo a solid learning process do not forget what was learned regardless of their age [61, 62].

Performance in variables related to free, cued, or paired recall, either immediate or delayed, was influenced by education, resulting in lower performance with lower educational level (Tables 6, 7). It has been widely shown that education has a consistent and direct correlation with cognitive performance, even in advanced ages although, not necessarily, with the rate of cognitive decline [63]. The influence of age was particularly restricted to the variables that are dependent on free recall, which resulted in worse performance with advancing age. Provided the narrow age range considered in this study, such restricted influence should be interpreted cautiously. However, the observed and consistent tendency of decay in MBT free recall performance associated with advancing age is in agreement with previous studies on the evolution of memory with aging [33, 34]. When cueing strategies are provided, such differences tend to disappear [8, 27, 59]. However, this usual pattern did not apply to Total Delayed Paired Recall, where age adjustments were indeed needed. The variables affected by gender, women outperforming men, were always those related to the recall of List 1 (that is, to initial learning) either in free, cued, or paired recall. This has an impact in the total score resulting from the sum of recall of both lists. The only exception to this trend was in delayed free recall. Such observation is consistent with previous reports [64], including the results on standardized memory tasks [39].

Limitations and future directions

The first limitation we encounter is the scarcity of existent information about the MBT and lack of data regarding its validity and reliability, to which we plan to contribute to in the near future.

The results presented here are not from a random population sample so they cannot be strictly comparable to normative data and the inference of the results to the general population is not straightforward. If being a direct descendant of an AD sufferer is a determining factor or not in the results of the MBT would depend on the impact that family history of AD could have in the test results or, in general, in cognitive performance. There is therefore a need for further studies that address this question. We hope to contribute to this by studying the natural aging of the participants. By their nature, all reference and normative data are of limited use and restricted to subjects whose demographic characteristics are similar to those of the reference data sample. In this respect, we believe that the reference data presented here will be of interest for clinical use and research purposes when subjects share those sociodemographic characteristics and risk profile exhibited by the study participants. Only the clinician or the researcher can determine which data best apply to a specific patient and situation [31]. The longitudinal design of the ALFA study will allow follow-up assessments on a regular basis, which may permit refining the MBT data presented here. A robust norming approach would be more suitable provided norms for healthy aging were pursued. This approach intends to identify and exclude individuals who develop diagnosable cognitive impairment following baseline assessment, thus reducing the variability in the baseline reference data and resulting in a more reliable estimate of normal cognitive function in aging [65]. In fact, the major contribution of the MBT is expected to emerge with the longitudinal data. This will presumably allow determining the predictive ability of the test to capture those subjects with subtle memory impairment that can be

considered as candidates for probable preclinical AD and could be participants in prevention trials. Further studies with preclinical and clinical subjects are of outstanding relevance to validate the clinical utility of the MBT by defining its diagnostic norms.

CONCLUSIONS

This paper presents the Spanish version of the Memory Binding Test and provides reference data in a population of 45 to 65-year-old adult children of AD patients. The main novelty of the MBT is that it is a test based on associative learning, having binding as a strategy to favor an effective and coordinated process of encoding and retrieval. As the majority of neuropsychological tests, the results of the MBT varied due to sociodemographic factors. As such, the results had to be adjusted using standardized statistical methods. Due to the particularity of the sample of this study and the particular characteristics of the MBT, these results may prove to be useful for detecting asymptomatic at risk candidates for secondary prevention studies of AD.

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