Design and validation of the One-Week Memory Battery for assessing episodic memory and accelerated long-term forgetting in cognitively unimpaired subjects

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ABSTRACT

Objective: Subtle decline in memory is thought to arise in the preclinical phase of Alzheimer's disease (AD). However, detecting these initial cognitive difficulties cross-sectionally has been challenging and the exact nature of the decline is still debated. Accelerated Long-term Forgetting (ALF) has been recently suggested as one of the earliest and most sensitive indicators of memory dysfunction in subjects at risk of developing AD. The objective of this study was to design and validate the One-Week Memory Battery (1WMB) for assessing episodic memory and ALF in cognitively unimpaired individuals.

Methods: The 1WMB is unique in that it assesses multimodal memory and measures recall at both short-delay (20 minutes) and at long-term (1 week). Forty-five cognitively unimpaired subjects were assessed with 1WMB and standardized neuropsychological tests. Subjective Cognitive Decline (SCD), levels of anxiety and depression, and cognitive reserve were also measured.

Results: The tests of 1WMB showed a high internal consistency and concurrent validity was observed with standard tests of episodic memory and executive functions. The analysis revealed a greater loss of information at 1 week compared to short-term forgetting (20 minutes). Performance in the 1WMB was affected by age and educational level, but was not associated with levels of anxiety and depression. Unlike standard tests, performance in the 1WMB correlated with measures of SCD.

Conclusion: ourfindings indicate that the 1WMB has good psychometric properties and future studies are needed to explore its potential usefulness to assess cognitively unimpaired subjects at increased risk of developing AD.

KEY POINTS

- **Question:** Can we validate the One-Week Memory Battery (1WMB) as a comprehensiveassessment to explore accelerated long-term forgetting (ALF)?
- **Findings:** The 1WMB has good psychometric properties. Performance was not associated with levels of anxiety and depression while it was correlated with measures of Subjective Cognitive Decline (SCD).
- **Importance:**The identification and monitoring of the first cognitive manifestations within the Alzheimer's continuum is critical for developing secondary prevention trials and allowing earlier interventions.
- **Next steps:** Further research will determine whether the 1WMB will be a useful tool for the early detection of subtle cognitive dysfunction within the Alzheimer's continuum.

1. INTRODUCTION

Alzheimer's disease (AD)is currently conceptualized as a continuum that starts with a preclinical phasebeginning years and even decades before the emergence of the clinical syndrome of dementia(Jack et al., 2018; Jack & Holtzman, 2013).Subtle cognitive decline is thoughtto begin in this asymptomatic phaseand has been proposed as a predictive measure offuture clinical stages(Sperling et al., 2011).

Episodic memory has been suggested to be the earliest cognitive domain to be typically affected in the Alzheimer's continuum(Hedden, Oh, Younger, & Patel, 2013; Morris et al., 2009).Although longitudinal studies have generally found evidence of memory decline in preclinical AD samples(Lim et al., 2014; Small, Mobly, Laukka, Jones, & Bäckman, 2003; Soldan et al., 2016), cross-sectional studies have frequently failed to detect the initial signs of memory difficulties at this stage(Aizenstein et al., 2008; Mormino et al., 2009; Storandt, Mintun, Head, & Morris, 2009).On the other hand, there is no consensus to date regarding the characterization of episodic memory difficulties in preclinical AD(Chételat et al., 2011).

In this context, a concept that is gaining attention is theacceleratedlong-term forgetting(ALF).ALF refers to the rapid or abnormal loss of information that occurs in the long-term (i.e.,daysto weeks) despite normal acquisition or initial consolidation(Butler, Gilboa, & Miller, 2019). ALF may go undetected in the clinical setting, with standardized memory tests typically testing delays of up to 30-minutes. Recent studies of ALFhave suggested that it could be one of the first detectable cognitive changes that occur in the asymptomatic phase of AD(Wearn et al., 2020; Weston et al., 2018; Zimmermann & Butler, 2018).In the last years, our group has been

working on the applicability of ALF measures for the early detection of subtle learning and memory dysfunction in cognitively unimpaired individuals at increased risk of developing AD, including preclinical AD(Tort-Merino et al., 2017), APOE ε4 carriers(Tort-Merino et al., 2021a) and subjectivecognitive decline (SCD) samples(Tort-Merino et al., 2021b). However, research is still scarce and the design of reliable tests for measuring ALFis needed to assess its role in the early detection of AD. The development of new, more sensitive neuropsychological tests assessing different aspects ofmemory iscritical forbetter understanding the nature of the earliest cognitive difficulties in preclinical AD.

The aim of this study wasto design and validate the One-Week Memory Battery (1WMB). The 1WMB has been specifically designed to explore subtle memory difficulties in the earliest stages of the Alzheimer's continuum. This battery is innovative in that it includes different modalities of episodic memory (i.e., verbal and visual memory, associative-learning)from an ecological approach, and it assesses not only short-term recall but also accelerated long-term forgetting at one week. In this first-stage of the battery development, we describe the tests included and its performance in a sample of cognitively healthy adults. Internal consistency and reliability are described. The relationships between the 1WMB and SCD measures are also explored.

2. MATERIAL AND METHODS

2.1. Participants

Forty-five cognitively unimpaired participants, recruited from several City Council centers for older adultswere included in this study. The Ethics Committee of Hospital

Clínic de Barcelona approved the study and all participants provided signed informed consent in accordance with the Declaration of Helsinki.Inclusion criteria were: 1) Age ≥ 55, 2) Mini-Mental State Examination (MMSE) score ≥26, 3) Cognitive performance within the normal range (cutoff 1.5 SD below the normative mean) for all tests of an exhaustive neuropsychological battery (see below), and 4) Clinical Dementia Rating Scale (CDR) score of 0. In addition, the following exclusion criteria were applied: 1) presence of severe visual disturbances, 2) diagnosis of a neurological disease, 3) serious or unstable medical conditions that may affect cognition, 4) diagnosis of a major psychiatric disorder including schizophrenia, major depression or substance abuse, and 5) previous medical visits due to memory complains.

Transparency and Openness: We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study. This study was not preregistered. All data is available from corresponding author on reasonable request.

2.2. Neuropsychological battery and psychological assessment

All participants underwent a comprehensive neuropsychological batteryexamining all cognitive domains. Battery consisted of the MMSE(Folstein, Folstein, & McHugh, 1975) and Memory Alteration Test (M@T; Rami, Molinuevo, Sanchez-Valle, Bosch, & Villar, 2007) as screening tests. Episodic verbal memory was evaluated with the Free and Cued Selective Reminding Test (FCSRT). The FCSRT is a verbal associative memory test, consisting on pairing a word with a semantic category to improve encoding and retrieval. A total of 16 words are presented with a semantic clue and free and cued recall is evaluated within 3 learning trials. After a 30 min delay, Free and cued delayed recall is assessed. The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub,

2001) was used for assessing language and semantic memory was studied through a category fluency test(Goodglass & Kaplan, 1983). Praxis was determined by the constructive praxis subtest from the CERAD battery(Morris et al., 1989). Visual perception was assessed by the incomplete letters subtest of the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991). Frontal functions were evaluated by Trail Making Test parts A and B(R Reitan, 1994).Furthermore, we measured the anxiety and depression levels by the Hospital Anxiety and Depression Scale (HADS;Zigmond & Snaith, 1983), and SCD was evaluated using the validated Subjective Cognitive Decline Questionnaire (SCD-Q; Rami et al., 2014).The SCD-Q includes 24 items assessing the perceived subjective decline in several cognitive functions, such as memory, language, and executive functions in the last two years. It contains two forms: form I, named MyCog, which is answered by the participant; and form II, TheirCog, which includes the same questions and is answered by an informant. Finally,since cognitive reserve has been suggested to have an effect on cognitive performance in aging and cognitive impairment (Stern, 2009), we administered the cognitive reserve questionnaire(Rami et al., 2011) in order to explore possible relationships between this construct and the 1WMB scores. Premorbid intelligence was defined with the Spanish Word Accentuation Test (TAP; Gomar et al., 2011).Tests were completed in two separate days separated by one week, each session lasting approximately 90 minutes. Participants were not warned that they will be asked to recall the previously learned information at the one-week session.

2.3. The One-Week Memory Battery (1WMB)

The 1WMB includes four different tests assessing different types of episodic memory (see Fig. 1). Total administration time of the whole battery was approximately 50 minutes.Preliminary pilot studies in independent samples were carried out in order to avoid floor and ceiling effects in the different tests of the 1WMB.The principal characteristics of the tests included in the 1WMB are shown in Table 1.

2.3.1. The Doll's House – Visuospatial Binding Memory

The Doll's House is a visuospatial memory test through object-location binding. First, the 20 stimuli were showed to participants on a single sheet of paper for 20 seconds to familiarize them with the household objects. Next, the neuropsychologist read the test instructions to the participant, asking them to retain both the stimuli and their location in the house (object-location binding).The Doll's House was presented in digital format using a PowerPoint presentation on a standard 15" laptop. In the learning phase, a green arrow pointing at the exact location of the upcoming stimulus was shown on screen for 1 second, followed by the stimulus presentation which was shown on screen for 5 seconds. Once the 20 stimuli were presented, participants were asked to recall what stimulus was placed in each position: an arrow appeared on screen and the subject needed to point at the correct target stimulus for the particular position indicated by that arrow.The test contained three learning trials. Recency effects were not controlled; however, in no case wasthe last stimulus of a learning trial the first to be recalled.A delayed recall trial was done twenty minutes later. Participants completed the task at their own pace without receiving any feedback. The order of appearance of targets in each trial of the learning and recall trials was randomized. One week later, participants came back to clinic for the one-week delayed recall trial,

followed by a re-learning trial and an immediate recall trial. Scoring followed a simple rule: 1 point for a correct match, 0 points for an incorrect match. The maximum possible score for a single trial was 20 points.

2.3.2. The Maze Test – 2D visuospatial navigation and memory

The participant had to complete the maze as fast as possible while simultaneously memorizing the route employed. A 15 x 13.5 cm maze was presented in print on a standard A4 sheet of paper. The learning phase included two trials, in which participants resolved the same maze two consecutive times, plus a delayed recall trial twenty minutes later. Participants completed the task at their own pace without receiving any feedback. A week later, participants came back to clinic to complete the one-week delayed recall trial. After this trial, a relearning trial was performed to investigate initial learning influence. The test scoresare their maze completion times recorded in seconds.

2.3.3. The News Test – Verbal episodic memory

The News Test is a tool to measure episodic verbal memory. It includes two texts, one text containing emotionally negative information and the other emotionally neutral information. Each text has 109 words. Both contain 17 key information units, including 2 person names, 1 location and 2 numbers.The participant have to read the textthree times trying to retain the information on it with as much detail as possible in order to be able to repeat it back using the exact same words.The first and third reads were asked to be out loud and reading time was registered in all cases. The order of text presentation (neutral or negative) was counterbalanced amongst participants and the texts were learned and assessed one after the other. An immediate free recall trial was

performed, followed by an immediate cued recall of missing information. The cued recall consisted of providing the participant a clue for each key information unit that was not freely recalled. Twenty minutes later, a free and cued delayed recall trial was performed. Participants came back to clinic for the free and cued delayed recall at one week. Scoring: 1 point for each information unit remembered. The maximum recall score possible is 17 points.Only verbatim responses were considered as correct and it was not necessary to recall the information in the correct order.

2.3.4. The Street Picture – Visual episodic memory

The Street Picture was designed to evaluate episodic visual memory through a picture with a complex scene (but not perceptually challenging).The participants have to look closely at the picture for two minutes paying attention at the people in it, their clothes, surrounding area, etc. After two minutes, the picture was removed from sight and participants were required to describe the scene with as much detail as possible. A delayed recall trial was done twenty minutes later. Finally, a week later, participants came back to clinic for the one week delayed recall. The scene has 21 prominent objects rated as “high frequency targets” and 40 objects considered “low frequency targets”. This distinction was made according to data collected in a pilot study on cognitively unimpaired elder volunteers. For example, the musicians and its instruments were high frequency targets while the balconies, plants or the people outfit were low frequency targets. Each target was worth 1 point. The maximum possible score was 61 points.

2.3.5. Overall procedure and order of administration

The different subtests from the 1WMB were administered in the following order: News test, Doll's House, Maze Test, News test (delayed recall), Doll's House (delayed recall), Maze Test (delayed recall), and Street Picture. After the Street Picture, we assessed the FCSRT, the HADS and the SCD-Q. That was followed by the delayed recall of the Street Picture and the FCSRT. Finally, we administered the remaining tests from the standard neuropsychological battery (i.e., BNT, category fluency test, constructive praxis subtest from the CERAD battery, incomplete letters subtest of the VOSP battery and Trail Making Test (forms A and B).

2.4. FCSRTone-week recall administration

In order to establish relevant comparisons with our newly developed tests, we decided to also include a long-term delayed recall trial of the FCSRT. As we did for the novel tests, a week later participants were asked to recall the words they had learned on the first testing session. The free recall was followed by a cued recall of the missing words.

2.5. Statistical analyses

Statistical analyses were performed using the SPSS (v.22.0) package for Windows. A *p*-value <0.05 was considered significant for all analyses.The sample's demographic characteristics were explored using descriptive statistics. To determine performance on the 1WMB, we calculated mean and standard deviation of the different trials, 20-min delayed recall, 1 Week delay recall and relearning for each test separately. Free (FFR) and cued (CFR) forgetting rates were calculated by comparing the 20-min recall with initial learning [e.g., 20-min FFR: 1-(20-min free recall/final free learning score)] and the one-week recall with the 20-min recall[e.g., 1-weekCFR: 1-(1-week cued recall/20-min cued recall)], where higher scores represent a greater loss of

information. Non-parametric statistics were performed. We used Wilcoxon t-tests to compare the differences between the 20-minute forgetting rate and one-week forgetting rate. Principal Components Analysis (PCA) by extracting Principal Components (PC) was used as a measure of internal consistency of the tests of 1WMB.To explore the intercorrelations between variables of the tests of 1WMB and the association between performance on the 1WMB and demographic variables we usedSpearman's correlations. Correlation analyses were performed in an exploratory way. To assess the concurrent validity of the 1WMB, Spearman's correlations coefficient was calculated between the variables of 1WMB and the standard neuropsychological tests. In addition, we created two age groups (cut-off 66 years), and two education groups (cut-off 12 years) according to the median. No post hoc comparisons between groups were analyzed because the aim of this study was to provide a descriptive profile of the variables and not to estimate differences between groups. To analyze interaction between neuropsychological measures and levels of anxiety and depression, the Spearman's correlation coefficient was calculated.

3. RESULTS

3.1. Sample characteristics

Demographical and cognitive data of the sample are shown in Table 2. All subjects scored below the cut-off value for clinically relevant anxiety and/or depression scale (i.e., HADS score ≤ 6).Age correlated significantly with theFCSRT (r=-.28; p=0.048), BNT (r=-.37; p=0.032), category fluency test (r=-.35; p=0.018), TMT-A (r=0.47, p=0.001) and TMT-B (r=0.31, p=0.040). Years of educationwere significantly correlated with the BNT (r=.45; p=0.009) and the category fluency test (r=.40; p=0.006). Gender showed no

effects on the performance of the standard neuropsychological tests.The cognitive reserve questionnaire was correlated with FCSRT (r=0.33, p=0.028), BNT (r=0.38, p=0.010), category fluency test (r=0.56, p=0.001) and TMT-B (r=-0.34, p=0.021).Significant correlations between anxiety and depression levels and TMT-B (r=0.39; p=0.012) were found.

3.2. Performance of the 1WMB

Table 3 shows the mean and standard deviation of each test of the 1WMB. Significant intercorrelations were found among the different variables of the Doll's House, Maze, News, and Street Picture tests (Fig. 2). Significant differences were observed between the 1-weekand 20-minforgetting rates in theDoll's House (t=-5.11; p=0.0001), the Maze Test (t=2.39; p=0.017), theNews Test [neutral news: FFR (t=-5.65; p=0.0001) and CFR (t=-5.51; p=0.0001); negative news: FFR (t=-5.67; p=0.0001) and CFR (t=-5.55; p=0.0001)] and the Street Picture (t=-5.43; p=0.0001), with higher forgetting rates observed at the one-week delay sessions (Fig. 3). Regarding the News test, significant differences in the 1-weekFFR were observed between the neutral and the negative news (t=-2.58; p=0.033).

3.2.1. Internal consistency and reliability

The PCA showed high internal consistency for each test of 1WMB. We determined to extract a single component (the first PC) which explained the 40.5% of the variance (Fig.4A).The contribution of each variable to the first PC ranged between 5.87-0.24 (%), being the mean variable contribution 1.44% (Fig. 4B).The 5 most reliable measures wereStreet Picture 1 week FR HF+LF (5.88%), Street Picture IFR HF+LF (5.74%), Street Picture 20 min FR HF+LF (5.55%), Doll's House 20 min FR (5.50 %) and Doll's House Trial

3 (4.47%). The 5 variables that contributed the least were Neutral news 20 min CR (0.24%), Neutral news 1 week CR (0.72%), Neutral news ICR (1.00%), Neutral news 20 min FR (1.21%) and Neutral news 1 week FR (1.44%).

3.2.2. Concurrent validity

Table 4 shows the significant correlationsthat were found between the 1WMB and standardized neuropsychological tests. Significant correlations were found among the different variables of the Doll's House, Maze, News, Street Picture, and the FCSRT, with *r* values between -0.501 and 0.596 (p<0.05).Significant correlations were also found between the tests of the 1WMB and the TMT (parts A and B), with *r* values ranging between -0.433 and 0.522 (p<0.05).

3.3. Relationshipsof the1WMB with demographics and anxiety/depression levels.

A statistically significant association was found between age and all the tests included in the battery, with *r*values between -0.525and 0.382 (p<0.05). Years of education showed significant correlations only with the neutral News Test, with *r*values between -0.213 and 0.349 (p<0.05).On average, females scored higher than males in the Doll's House (p<0.05). The correlations between the 1WMB and the demographical variables are shown in Table 5 and Supplementary Fig. 1.

No significant correlations were found between the cognitive reserve questionnaire and the different tests of the 1WMB (*r* values between -0.290 and 0.292). Regarding the levels of anxiety and depression, no significant correlations were found between the 1WMB and the HADS.

Mean and standard deviation scores adjusted for age and educational level were defined for each test of the 1WMB (Appendix).

3.4. The relationship between the 1WMB and the SCD-Q.

Significant correlations were observed between the TheirCog form of the SCD-Q and the Doll's House total (r=-0.31, p=0.048) and relearning *(*r=-0.36, p=0.024), and the Maze Test 20-min recall(r=0.38, p=0.014) (Fig.5).

3.5. Performance of the FCSRT one-week recall

The mean and standard deviation of the FCSRT 1-week performance is shown in Table 2. Significant differences were observed between the 20-min and 1-week FFR (t=-5.13, p=0.0001) and CFR (t=-5.31, p=0.0001), with higher forgetting rates observed at the 1-week sessions.Significant intercorrelations were found among the free recall and total recall variables *(*r=0.5*,* p=0.001). Significant correlations were found between the 1-week free recall(with r values between 0.3-0.4; p<0.05) and the 1-week total recall (r values between 0.3-0.5, p<0.05) and the different variables of the FCSRT. The TMT-A (*r=-0.3,* p=0.038)also correlated with the FCSRT. We found significant correlations between the 1WMB and the 1-week FCSRT(see Table 4), particularly with with the Maze Test 1-week recall (r=-0.51, p=0.016), Negative News 1-week recall (r=0.59, p=0.0001), and the Street Picture 1-week recall (r=0.45, p=0.003).No significant correlations were found between the 1-week FCSRT and any of the demographical variables, levels of anxiety and depression, the cognitive reserve questionnaire score or the SCD-Q scores.

DISCUSSION

The 1WMB is a novel, highly-demanding, and ecological battery developed to assess episodic memory in cognitively unimpaired individuals. The battery includes the evaluation of ALF as a measure that could increase the cognitive assessments'

sensitivity in subjects within the AD continuum. In the psychometric analysis, the 1WMB showed a high internal consistency and convergent validity with widely used standardized tests for the assessment of episodic memory and executive functions. Also, we found that several learning, short-term recall and relearning outcomes from the 1WMB were associated with informant-reported SCD measures.

The identification of subtle cognitive difficulties in cognitively unimpaired individuals at increased risk of developing AD has been,and still is, a challenge. Since SCD has been suggested to increase the risk of cognitive decline(Jessen et al., 2014), we explored the relationships between the 1WMB and the SCD-Q. The SCD-Q has showed to be a specific and sensitive tool for detecting SCD within the preclinical stage of the Alzheimer's continuum(Valech et al., 2015, 2018). We observed significant correlations between the informant´s report of the SCD-Q and 1) the total learning and relearning scores from the Doll's House and 2) the 20-min recall score from the Maze test. Some longitudinal studies have found that informants' assessments of SCD are a better predictor of subsequent decline in cognitively healthy elderly than self-reported SCD(Carr, Gray, Baty, & Morris, 2001; Rabin et al., 2012). Furthermore, it was interesting to found that the strongest correlations were observedwiththe language and executive items of the SCD-Q. This is in line with a previous study showing a higher specificity of language and executive complaints in preclinical AD(Valech et al., 2018). Here, it is important to note that we did not find any associations between the ALF outcomes of the 1WMB and measures of subjective cognitive decline in the present sample.

On the other hand, no associations were found between the SCD-Q and the standard neuropsychological tests' scores. In this regard, it has been shown to be very challenging to detect subtle cognitive changes along the preclinical phase of the Alzheimer's continuum with standard cognitive measures due to the requirement of high sensitivity and robustness against within subject variability(Bouwman et al., 2007). Indeed, standard neuropsychological tests have been designed to detect objective cognitive impairment, namely MCI or dementia. Thus, most studies using a cross-sectional design have failed to find a relationship between cognitive performance on standard neuropsychological tests and biomarker evidence of AD (Aizenstein et al., 2008; Mormino et al., 2009; Villemagne et al., 2011). However, some recent studies have found that using highly demanding cognitive measures it is possible to find subtle cognitive changes in otherwise cognitively healthy populations (Rentz et al., 2011; Papp et al., 2015; Tort-Merino et al., 2017, 2019). Therefore, it seems mandatory to develop more sensitive cognitive measures. The 1WMB was designed to identify subtle difficulties in the earliest stages of the Alzheimer's continuum. The associations observed between the 1WMB and the SCD-Q could suggest a potential sensitivity of the 1WMB for detecting subtle cognitive dysfunction.

One of the main objectives of the 1WMB is to assessALFin cognitively unimpaired individuals at increased risk of developing AD. Based on previous research from the Ancient Farming Equipment paradigm(Laine & Salmelin, 2010), our group evaluated a highly demanding learning and long-term memory test called the Ancient Farming Equipment Test (AFE-T). In a previous study, the AFE-T showedlong-term forgetting differences between controls and cognitively unimpaired individuals within the Alzheimer's continuum(Tort-Merino et al., 2017).ALF has also been found in

asymptomatic subjects with autosomal dominant Alzheimer´s disease, with the severity of ALF increasing with proximity to the predicted symptom onset(Weston et al., 2018), and has been recently shown as a good predictor of cognitive declineover 1 year in cognitively unimpaired older people(Wearn et al., 2020). These findings suggest that long-term memory assessments might be better suitedto detect early cognitive manifestations than standardized neuropsychological tests. However, in the present sample, the ALF measures of the 1WMB did not show any association with the SCD-Q measures. These results are in conflict with previous literature suggesting a potential sensitivity of ALF measures to detect subtle cognitive decline in at-risk populations (Tort-Merino, et al., 2017, 2021a, 2021b; Weston et al., 2018; Zimmerman & Butler, 2018; Wearn et al., 2020). The limited sample size and the fact that we only included in the study healthy volunteers (i.e., without clinically reported subjective cognitive complaints) could contribute to explain why these associations were not found. Further research is needed to determine whether the 1WMB could be a sensitive tool for detecting subtle long-term memory difficulties in this population.

Associativelearning difficulties havealso been associated to preclinical AD(Amariglio et al., 2012; Rentz et al., 2010). Evidence has shown that in addition to MTL involvement, frontal regions related to executive functions are also recruited during associative memory formation and retrieval(Fletcher & Henson, 2001).Associativelearning has been suggested as a more challenging method of assessing episodic memory, as it recruits a broader cortical network compared to standard word-recall memory tests(Rentz et al., 2011).In this regard, possibly given its associative learning demands, the Doll's House was the only test from the 1WMB to be associated with SCD measures and thus it could be considered as one of the most promising tests to capture subtle

cognitive dysfunction.Taken together, the 1WMB combines two potential sensitive measures (i.e., associative learning and ALF) for detecting early cognitive dysfunction in cognitively unimpaired population at risk of developing AD.

We did not find clear relationships between the long-term forgetting measures from the 1WMB and the SCD-Q scores.Here, it is important to note that the present sample is composed of a research cohort (i.e., all participants were volunteers recruited from several City Council centers). Compared to a memory clinic population, a volunteer-based sample would limit the SCD-Q scoring range. Research setting has been suggested to be an important variable in SCD studies (Molinuevo et al., 2016) and it would have been interesting to explore the 1WMB performance – and its relationship with the SCD-Q – in memory clinic individuals with clinically reported subjective cognitive complaints. Here, we also want to indicate that the present work is a preliminary and mainly descriptive study on a potential usefulness of the 1WMB to assess long-term forgetting in cognitively unimpaired samples. Conclusions on the usefulness of this battery on the early detection of subtle cognitive difficulties within the preclinical phase of the Alzheimer's continuum cannot be derived from the present findings and further research is called for to address this question.

The PCA results did not show a disentangling of different recall periods. Instead, they showed a test-driven grouping led by the Street Picture and the Doll's House, and followed by the Maze and News test. Regarding the capacity of a given test to detect subtle cognitive decline, these findings speak in favour of the significance of developing highly-demanding tasks measuring specific functions (e.g., associative

learning) rather thanmerely assessing long-term forgetting*per se*. Once again, the present results are preliminary and need to be taken with caution.

One critical aspect of the present work is the clinical applicability of the 1WMB. Although an administration time of 50 minutes is appropriate in a research setting, the current procedures would not be effective in the clinical routine. Some of the obtained results could help on determining what subtests or variables from the 1WMB would be included in a reduced, clinically-suitable version. For example, the Doll's House appeared to be more related to the SCD-Q scores than the other subtests. However, further investigations are needed to explore the clinical applicability of the 1WMB.

Another important point concerns the feasibility of administering the 1WMB longitudinally. In particular, assessing the long-term recall phase from the 1WMB at multiple time points (e.g., annually) in the same individual could increase the expectations of being asked to recall the previously learned information at 1-week. This is an interesting issue since the influence of tests expectations on long-term storage has been recently suggested to have a positive effect on memory performance (Alviarez-Schulze et al., 2022). Perhaps in the longitudinal sessions the individuals should be warned of the long-term recall in order to avoid rehearsing during the 1-week interval. In any case, this could be a potential limitation regarding the longitudinal assessment of the 1WMB.

Regarding the News Test, we found that participants exhibited higher forgetting of the negative news when compared to the neutral news. Little is known about how the emotional component could impact on the way that we learn and forget. Further research is necessary to answer such a complex question. Our findings provide

interesting data on task sensitivity when assessing emotionally negative vs. emotionally neutral information in cognitively healthy individuals.

Concerningto the association of the 1WMB with demographical variables, we found a significant correlation between the 1WMB scores and age and education level. There is growing evidence that the relationship between normal aging and AD-related changes could be considered on a continuum(Liddell, Paul, Brain, & Company, 2007). Therefore, the earliest difficulties inpreclinical AD are the most challenging to differentiate from normal-aging changes.Further validating the battery with a larger samplewould be necessary to find age-related and education-related normative scores. Another variable that may have an effect on the identification of early cognitive difficulties is cognitive reserve (Kemppainen et al., 2008; Rentz et al., 2010). We did not find significant associations between the 1WMB and the cognitive reserve questionnaire. On the other hand, all standard neuropsychological testscorrelated with this score. This finding suggests that the forgetting measures of the 1WMB could be less affected by cognitive reserve compared to standard neuropsychological measures.Other important variablesare the anxiety and depression levels. Controlling the effects of anxiety and depression on cognitive measures is challenging, and previous studies have reported an adverse effect of these psychological variables in standard episodic memory tests(Dotson et al., 2014; Kizilbash, Vanderploeg, & Curtiss, 2002), as well a strong relationship with SCD(Buckley et al., 2013; Slavin et al., 2010). Interestingly, we did not find associations between 1WMB and levels of anxiety and depression. This could help on minimizing the impact of these confounding factors when assessing cognitively healthy participants with the 1WMB.

An interesting point of the present work is the administration of the FCSRT with an additional one-week delay recall session, offering data on the long-term forgetting of this well-established test. The psychometric characteristics of FCSRT at one-week were optimal, showing a good reliability and convergent validity.Also, performance was not affected by demographic variables, cognitive reserve or levels of anxiety and depression. Our results suggest that using one-week recall in the administration of the FCSRT might give further insights into the initial memory deficits in AD. Further research is needed to explore whether the 1WMB, which was developed as a highly-demanding and more ecological approach, would capture the earliest signs of memory dysfunction within the preclinical phase of the Alzheimer's continuum.

The 1WMB tests (i.e., Doll's House, the Maze Test, the News Test and the Street Picture) were designed to obtain multimodal memory outcomes.However, three tests assessed visual memory. The main reasons for including more visual tasks were to reduce the impact of the participants' educational level on task performance and to design more ecological measures. Given that verbal memory (and particularly verbal associative memory) is typically assessed by word lists, we expected that visual memory would allow us to obtain a more ecological assessment. In any case, since associative memory has been suggested to be highlysensitiveit would have been interesting to include a verbal associative memory task in the battery.

Another interesting topic refers to the possibility of assessing remotely the recall phase of the 1WMB. In the present work, we decided to assess the participants on site in order to control all potential confounders that could derive from a remote assessment. However, the 1WMB materials and procedures could be adapted for online or remote

assessment, thus offering substantial benefits in terms of participant recruitment and engagement, data collection and time and resources optimization.

This study has some limitations. The sample favors women and those with more education;therefore, for future normalization studies it would be necessary to recruit a sample that was more representative of the general population. Furthermore, the sample size is relatively small and results from the factorial analyses should be interpreted with caution. Also, future validation in larger samples is needed for confirming our results.Subjects included in this study are relatively young compared to standard validation studies in AD. However, a younger cohort is adequate given that the battery was designed for detecting the earliest cognitive manifestations of AD, and preclinical AD is suggested to begin up to twenty years before the clinical onset of cognitive impairment.Considering the number of statistical analyses that were run, the fact that no corrections for multiple comparisons were done must be reported as a study limitation. Here, it is important to note that the study aim was to describe and report preliminary data on a new highly-demanding memory battery rather that evaluating the measures' sensitivity and specificity for detecting and assessing preclinical AD. Finally, the cross-sectional nature of this study did not allow exploring the predictive capacity of the 1WMB for conversion to cognitive impairment and dementia. Also, since longitudinal assessment would enhance early detection of individuals at risk of developing AD, further research is called for in order to determine test-retest reliability for the 1WMB. Future longitudinal studies in larger samples including AD biomarkers are crucial for better defining the specificity and sensitivity of the 1WMB for detecting subtle cognitive decline in the preclinical phase of the Alzheimer's continuum.

In conclusion, this initialstudy of the 1WMB shows that the battery has good psychometric properties and further research is needed to determine whether it will be a useful tool for the early detection of subtle difficulties in cognitively unimpaired individuals at risk of developing AD. The identification and monitoring of the first cognitive manifestations within the Alzheimer's continuum is criticalfor the development of secondary prevention trials and for allowing earlier interventionswhen the burden of AD-pathology has not yet extended massivelythroughthe brain.

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Appendix

The One-Week Battery: classifications by age and educational level.

	Population ≤ 66 years		Population > 66 years	
	Elementary and high school (≤12 years) n=9	**Bachelor's degree (>12 years) n=15**	**Elementary and high school (≤12 years) n=9**	**Bachelor´s degree (>12 years) n=12**
Doll's House				
Total	40.4 (8.4)	46.6 (11.1)	28.3 (13.8)	32.6 (6.3)
20-min FR	16.3 (3.3)	17.6(3.7)	11.8 (5.9)	13.3 (4.1)
1-week FR	13 (2.7)	14 (4.6)	9.4 (4.1)	9 (3.3)
Maze Test				
Trial 1	112.43 (54.6)	87.47 (46.8)	191.8 (141.1)	113.62 (52.7)
20-min FR	67.7 (49.2)	35.5 (10.6)	55 (20.8)	75 (46.1)
1-week FR	64.4 (37.6)	44.9 (14.8)	107.9 (83.6)	55.9 (18.4)
Neutral News				
IFR	13.3 (3.1)	14.5 (2.1)	11.4 (2.1)	13.8 (2.1)
20-min FR	13.6 (3.2)	14.1 (2.2)	11 (1.7)	12.8 (2.3)
1-week FR	8.4 (2.2)	8.1 (2.8)	6.6 (4.6)	8.3 (3.7)
Negative News				
IFR	14.4 (2.5)	14.7 (1.4)	12.6 (2.2)	13.1 (2.5)
20-min FR	14.7 (1.5)	13.5 (2.1)	12.3 (2.2)	12.5 (2.5)
1-week FR	8.1 (2.3)	6.6 (4.2)	7.1 (4.5)	5.8 (4.3)
Street Picture				
IFR (HF+LF)	23.3 (5.2)	26.3 (4.1)	21.1 (5.1)	22.6 (3.6)
20-min FR	24 (5.7)	26.2 (5.1)	21.1 (4.9)	22.6 (4.4)
1-week FR	21 (2.9)	20.9 (5.5)	16.1 (6.6)	15.4 (6.5)

Key: Total, trials summative score; FR, free recall; TR, total recall; IFR, immediate free recall; HF, high frequency; LF, low frequency.

Legends

Table 1. Characteristics of 1WMB tests

Table 2.Demographics and neuropsychological data.

Key: FCSRT, Free and Cued Selective Reminding Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; VOSP, Visual Object and Space Perception battery; HADS, Hospital Anxiety and Depression Scale; MyCog / TheirCog, self and informant reports of the SCD-Q (Subjective Cognitive Decline Questionnaire).

Table 3.Means and standards deviations of the One-Week Battery.

Key: FR, free recall; FFR, free forgetting rate; CFR, cued forgetting rate; IFR, immediate free recall; ICR, immediate cued recall; HF, high frequency; LF, low frequency.

Table 4.Pearson's correlations between the One-Week Battery and the standard neuropsychological tests.

Key: FCSRT, Free and Cued Selective Reminding Test; FR, free recall; TR, total recall; DFR, delayed free recall; DTR, delayed total recall; Total, trials summative score; IFR, immediate free recall; HF, high frequency; LF, low frequency. $^{*}p<0.05$ $^{**}p<0.01$

Table 5.Correlations between the 1WMB and age, education and gender.

Key: Total, trials summative score; FR, free recall; TR, total recall; IFR, immediate free recall; HF, high frequency; LF, low frequency. $^{*}p<0.05$ $^{**}p<0.01$.

Figure 1. The One-Week Memory Battery

Figure 2.Intercorrelations among the 1WMB variables

Key: FR, free recall; CR, cued recall; IFR, immediate free recall; ICR, immediate cued recall, HF, high frequency; LF, low frequency. * p<0.05 ** p<0.01 *** p<0.001

Figure 3.Forgetting curves of the 1WMB tests.

Key: HF, high frequency; LF, low frequency. Error bars represent SEM.* p<0.05 [difference between the negative and neutral news in the 1-week free forgetting rate (i.e., slope between the 20-min recall and the 1-week recall)].

Figure 4. Principal Component Analysis

Key: Panel A shows the percentage of explained variance for each PC and panel B shows the contribution of the 1WMB variables to the first PC. Red dashed line indicates the mean variable contribution. FR, free recall; CR, cued recall; IFR, immediate free recall; ICR, immediate cued recall, HF, high frequency; LF, low frequency.

Figure 5.Correlations between the Doll's House and Maze Test scores and the SCD-Q.

Key: TheirCog, informant-reported version of the subjective cognitive decline questionnaire (SCD-Q).

Table 1. Characteristics of 1WMB tests

Tests of 1WMB	Number of trials	20-min recall	1-week recall	Scoring (each trial)	Time of administration
DOLLS'S HOUSE *Visuospatial Binding Memory*	3	Free recall	Free recall + relearning + recall	0-20	20 min
THE MAZE TEST *2D visuospatial navigation and memory*	2	Free recall	Free recall (2 trials)	Time (s)	5 min
THE NEWS TEST *Verbal episodic Memory*	1	Free and cued recall	Free and cued recall	0-17	15 min
THE STREET PICTURE *Visual episodic Memory*	1	Free recall	Free recall	0-61	10 min

Table 2.Demographics and neuropsychological data.

Parameters	Mean (SD) N = 45
Demographics	
Gender (% women)	82.21
Age	66.96 (5.5)
Years of education	13.04 (3.8)
Global cognition	
Mini Mental State Examination	28.82 (1.2)
Memory Alteration Test	42.78 (4.7)
Word Accentuation Test	24.75 (4.6)
Memory	
FCSRT – Free recall	28.02 (5.8)
FCSRT – Total recall	43.44 (3.8)
FCSRT – Delayed free recall	10.64 (2.6)
FCSRT – Delayed total recall	14.77 (1.1)
FCSRT – 1-weekfree recall	3.30 (2.4)
FCSRT – 1-week total recall	9.03 (2.7)
CERAD – Visual memory	10.31 (1.2)
Language	
Boston naming test	50.94 (4.3)
Category fluency test	24.02 (5.6)
Perception and praxis	
VOSP – Incomplete letters subtest	19.82 (0.4)
CERAD – Constructional praxis	10.67 (0.6)
Executive Functions	
Trail Making Test – Form A	36.78 (12.6)
Trail Making Test – Form B	102.31 (59.8)
Questionnaires	
HADS-A (anxiety)	6.54 (3.6)
HADS-D (depression)	3.28 (3.2)
MyCog score	7.20 (5.7)
TheirCog score	4.63 (4.1)
Cognitive reserve questionnaire	16.49 (3.9)

Key: FCSRT, Free and Cued Selective Reminding Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; VOSP, Visual Object and Space Perception battery; HADS, Hospital Anxiety and Depression Scale; MyCog/TheirCog, self and informantreports of the SCD-Q (Subjective Cognitive Decline Questionnaire).

Table 3.Means and standards deviations of the One-Week Battery.

Variables	Mean (SD)	Variables	Mean (SD)
Doll'sHouse		**Negative News**	
Trial 1	9.31 (4.5)	IFR	13.83 (2.2)
Trial 2	13.22 (4.9)	ICR	15.32 (1.6)
Trial 3	15.95 (4.3)	20-min FR	13.22 (2.2)
20-min FR	15.16 (4.8)	20-min CR	15.41 (1.4)
1-week FR	11.73 (4.4)	1-week FR	6.83 (3.9)
Relearning	16.08 (4.1)	1-week CR	11.12 (3.1)
20-min FFR	0.05 (0.1)	20-min FFR	0.03 (0.2)
1-week FFR	0.21 (0.2)	1-week FFR	0.51 (0.3)
Maze Test		20-min CFR	0.01 (0.1)
Trial 1	123.15 (89.9)	1-week CFR	0.28 (0.2)
Trial 2	58.75 (30.6)		
20-min FR	53.93 (33.9)	**Street Picture**	
1-week FR	66.79 (51.6)	IFR (HF)	15.92 (2.6)
20-min FFR	0.04 (0.4)	IFR (LF)	7.81 (3.5)
1-week FFR	-0.29 (0.6)	IFR (HF+LF)	23.73 (4.8)
Relearning	49.03 (42.3)	20-min FR (HF)	15.88 (2.7)
Neutral News		20-min FR (LF)	7.98 (3.6)
IFR	13.35 (2.5)	20-min FR (HF+LF)	23.82 (5.3)
ICR	15.53 (1.5)	20-min FFR (HF)	0.01 (0.1)
20-min FR	12.98 (2.5)	20-min FFR (LF)	-0.07 (0.3)
20-min CR	15.45 (1.4)	20-min FFR (HF+LF)	-0.01 (0.1)
1-week FR	7.81 (3.4)	1-week FR (HF)	12.95 (4.2)
1-week CR	11.58 (2.8)	1-week FR (LF)	5.62 (2.8)
20-min FFR	0.02 (0.1)	1-week FR (HF+LF)	18.56 (6.0)
1-week FFR	0.40 (0.3)	1-week FFR (HF)	0.19 (0.2)
20-min CFR	0.01 (0.1)	1-week FFR (LF)	0.29 (0.2)
1-week CFR	0.25 (0.2)	1-week FFR (HF+LF)	0.23 (0.2)

Key: FR,free recall; FFR,free forgetting rate; CFR, cued forgetting rate; IFR, immediate free recall; ICR,immediate cued recall; HF, high frequency; LF, low frequency.

Table 4.Pearson's correlations between the One-Week Battery and the standard neuropsychological tests.

	FCSRT FR	FCSRTTR	FCSRTDFR	FCSRT DTR	TMT-A	TMT-B	FCSRT 1-week FR	FCSRT 1-week TR
Doll'sHouse								
Total	.321*	.391**	.375*	.346*	-.433**	-.307*	.110	.242
20-minFR	.327*	.397**	.478**	.392**	-.478**	-.359*	.088	.298
1-week FR	.290*	.337*	.375*	.354*	-.432*	-.320*	.032	.309
Maze Test								
Trial 1	-.230	-.399**	-.336*	-.345*	.498**	.522**	-.166	-.107
20-min FR	-.177	-.217	-.199	-.201	.485**	.515**	-.158	-.348
1-week FR	-.314*	-.291	-.361*	-.305*	.458**	.436**	-.227	-.501**
Neutral News								
20-min FR	.240	.365*	.334*	.285	-.261	-.264	-.094	.178
1-week FR	.215	.119	.097	.161	-.146	-.170	.478**	.364*
Negative News								
IFR	.177	.242	.245	.231	-.388**	-.310*	.064	.240
20-min FR	.454**	.375*	.483**	.391**	-.346*	-.269	.286	.368*
1-week FR	.464**	.179	.296	.178	-.157	-.197	.593**	.596**
Street Picture								
IFR (HF+LF)	.167	.101	.283	.123	-.337*	-.232	.185	.151
20-min FR	.248	.165	.375*	.141	-.328*	-.304*	.228	.129
1-week FR	.389**	.206	.433**	.237*	-.345*	-.388**	.375*	.454**

Key: FCSRT, Free and Cued Selective Reminding Test; FR, free recall; TR, total recall; DFR, delayed free recall; DTR, delayed total recall; Total, trials summative score; IFR, immediate free recall; HF, high frequency; LF, low frequency.

***p<0.05 ****p<0.01**

Table 5.Correlations between the 1WMB and age, education and gender.

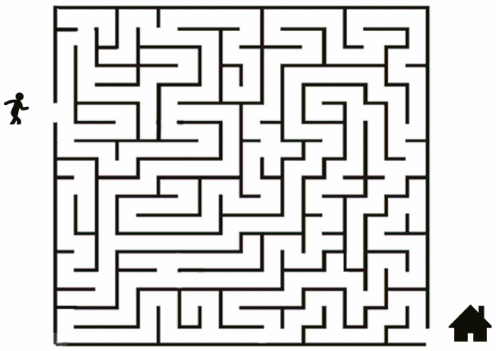
Variables	Age	Education	Gender
Doll's House			
Total	-.465**	.258	.351*
20-min FR	-.525**	.180	.246*
1-week FR	-.465**	.030	.422**
Maze Test			
Trial 1	.289	-.213	.060
20-min FR	.382**	-.097	-.013
1-week FR	.220	-.150	-.088
Neutral News			
IFR	-.261	.349*	.020
20-min FR	-.354*	.260	-.030
1-week FR	-.134	.261	-.126
Negative News			
IFR	-.326*	.085	-.111
20-min FR	-.162	-.109	.209
1-week FR	-.041	-.067	-.038
Street Picture			
IFR (HF+LF)	-.465**	.242	.099
20-min FR	-.433**	.169	.140
1-week FR	-.357*	.146	.035

Key: Total, trials summative score; FR, free recall; TR, total recall; IFR, immediate free recall; HF, high frequency; LF, low frequency.

***p<0.05 ****p<0.01.**

Figure 1. The One-Week Memory Battery

Panel A. The Doll's House. Twenty stimuli appeared consecutively on screen for 5 seconds. Participants had to retain both the stimuli and their location in the house (object-location binding).



Panel B. The Maze Test. Participants had to complete the maze as fast as possible while memorizing the route employed.

THE NEWS

Volume II XXI

Visiting a farmhouse

A group of journalists has been doing a report on old farmhouses in Tarragona. One of them especially caught their attention and they wanted to get closer to visit her.

The farmhouse was at the top of the mountain. It was made of wood and had blue windows. The journalists thought that no one lived there. However, when they went up to the fifth floor they saw Juan, the owner who had lived there for 20 years with his brother.

The owner offered them drinks. They sat by the fireplace and talked about the origin of the farmhouse, which was built by their grandfather Alfonso, who abandoned it when he moved to the city.

THE NEWS

Volume II XXI

A fire

Blanca, a 64-year-old Asturian lady, was burning leaves in her house last Monday. A strong wind caused a fire and the flames caused very serious burns to half of her body.

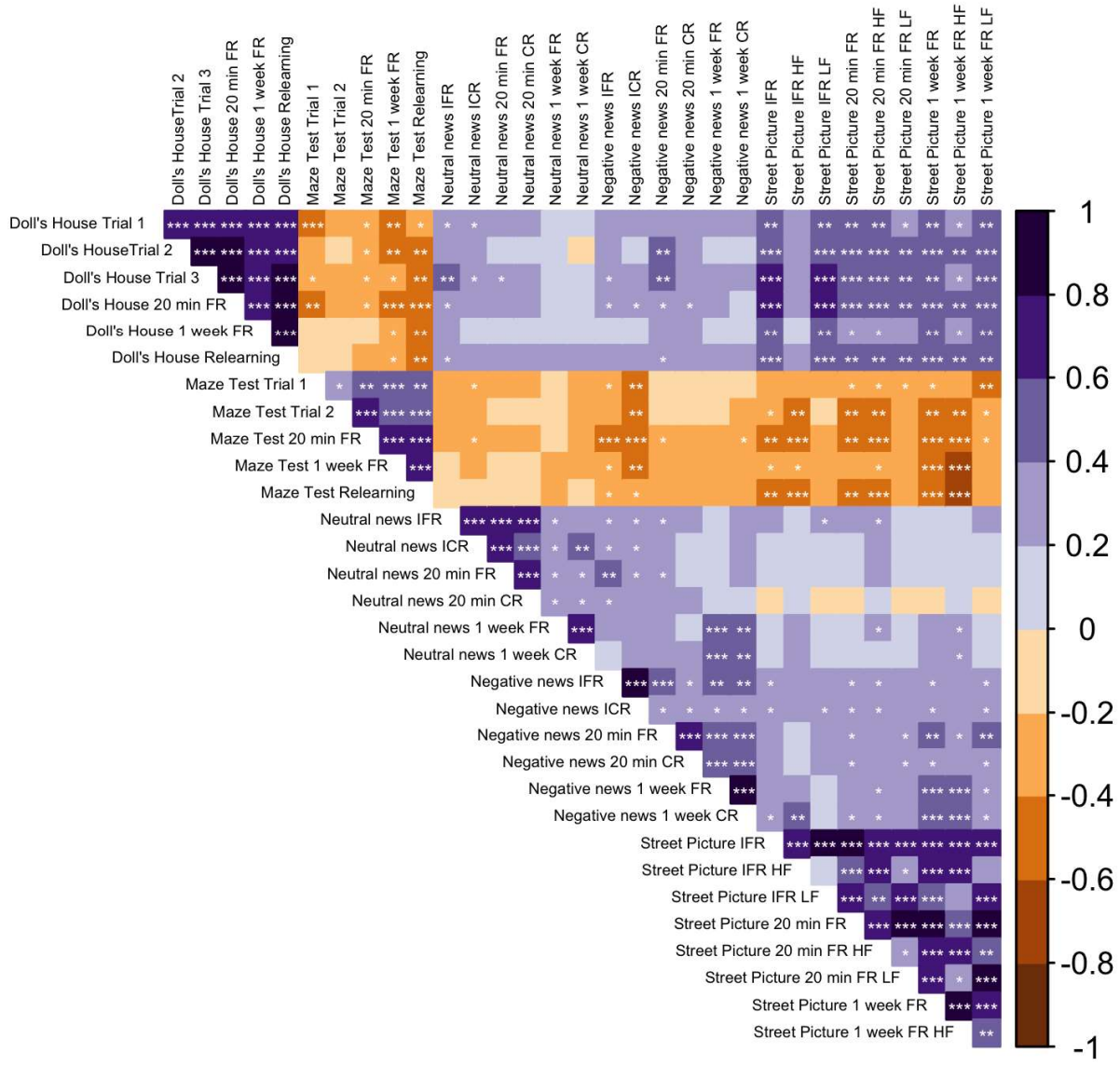
Seeing her wounded, her son, Gonzalo, drove her to the nearest hospital. On the way, he got a flat tire on his car and was stopped 15 kilometers from the hospital. The son phoned his aunt to pick them up, but it took him half an hour to answer the call as she was in a meeting. When she arrived, unfortunately, the woman had already died.

Panel C. The News Test. Participants had to read each text three times trying to retain the information on it with as much detail as possible in order to be able to repeat it back using the exact same words.

Panel D. The Street Picture. After a 2-min presentation, participants had to describe the scene with as much detail as possible.

Source: Panels A–C (own figures), Panel D (Image from Freepik.com [https://www.freepik.com/]).

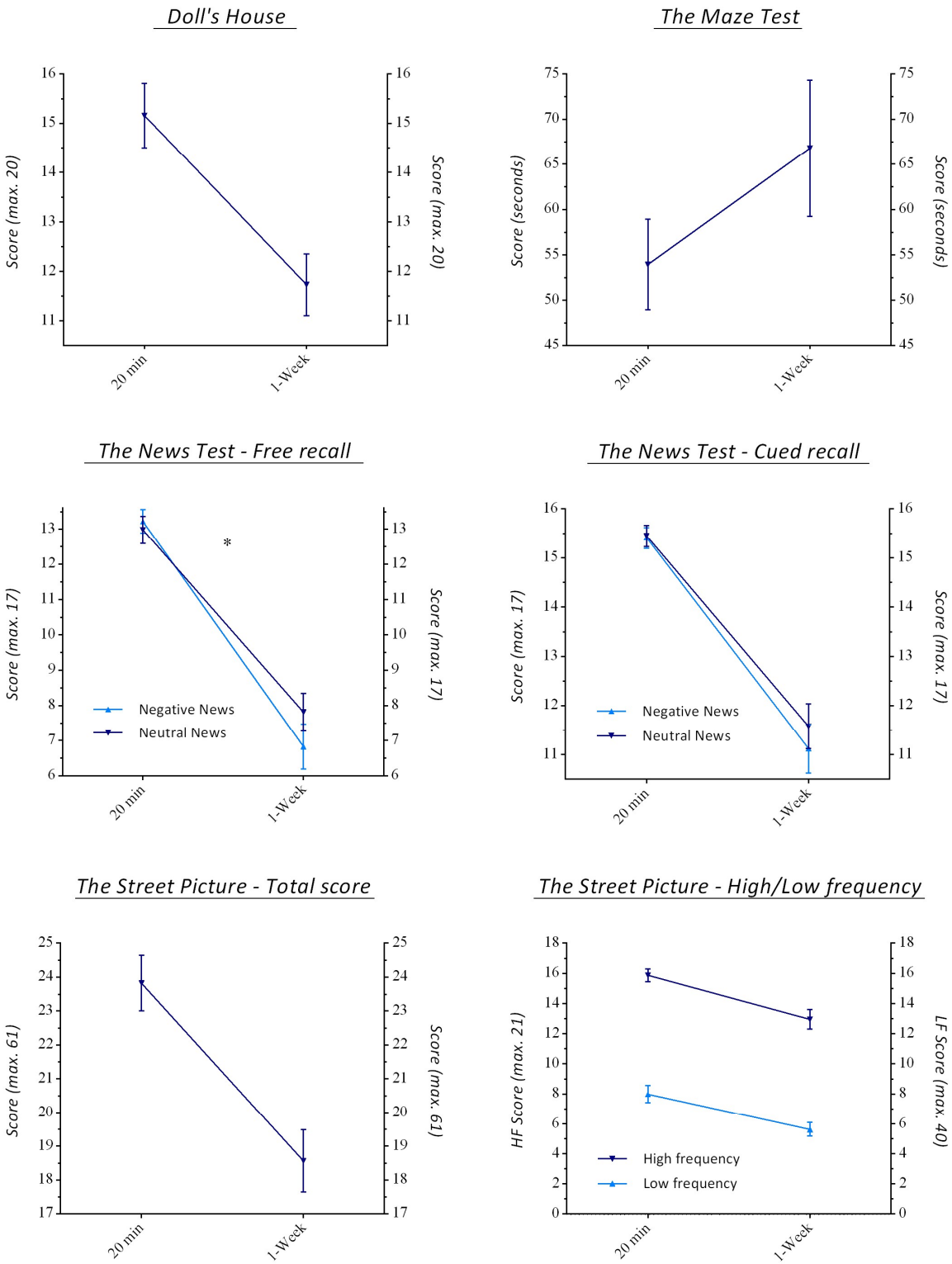
Figure 2. Intercorrelations among the 1WMB variables



Key: FR, free recall; CR, cued recall; IFR, immediate free recall; ICR, immediate cued recall, HF, high frequency; LF, low frequency.

*** p<0.05**
**** p<0.01**
***** p<0.001**

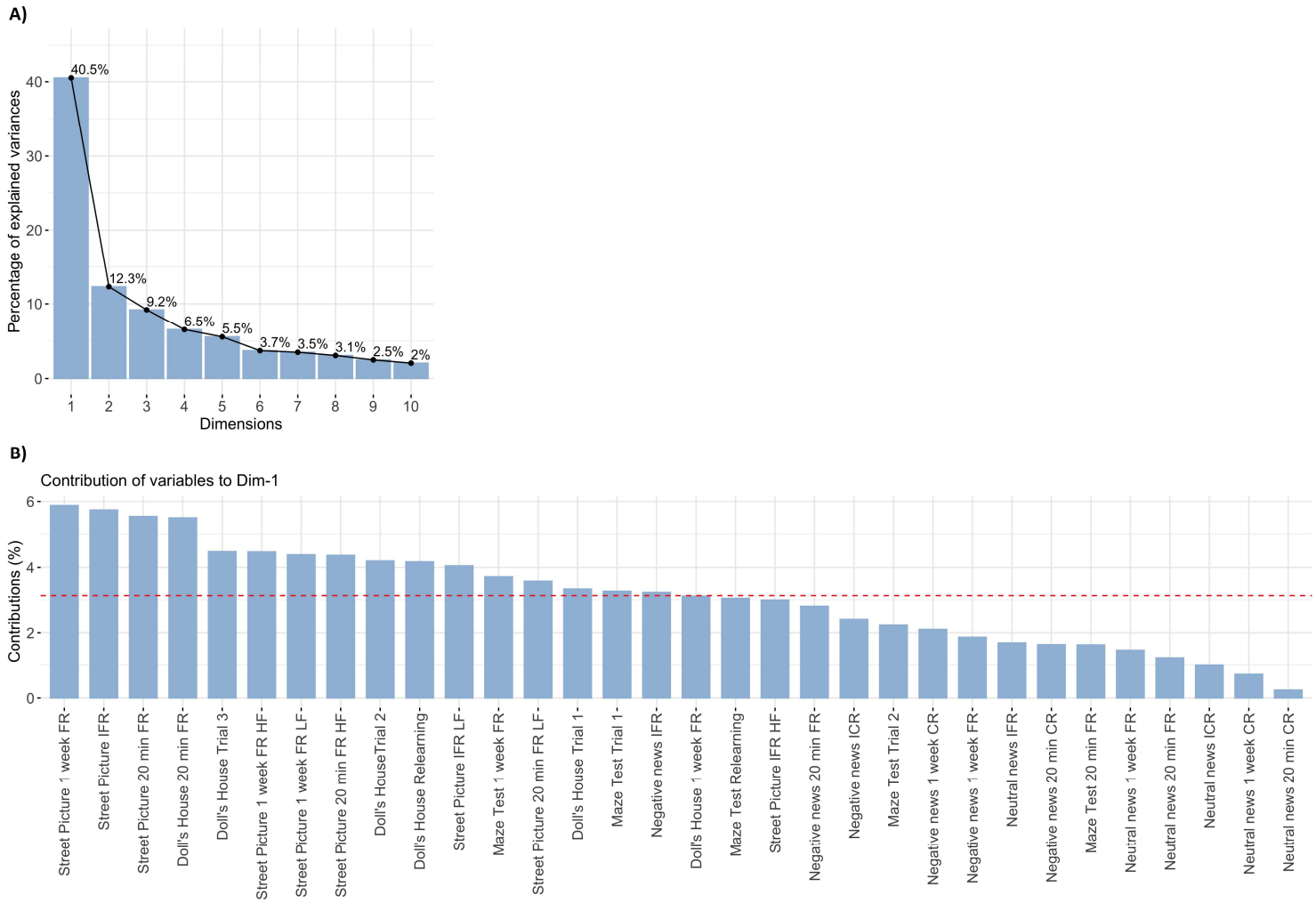
Figure 3.Forgetting curves of the 1WMB tests



Key: HF, high frequency; LF, low frequency. Error bars represent SEM.

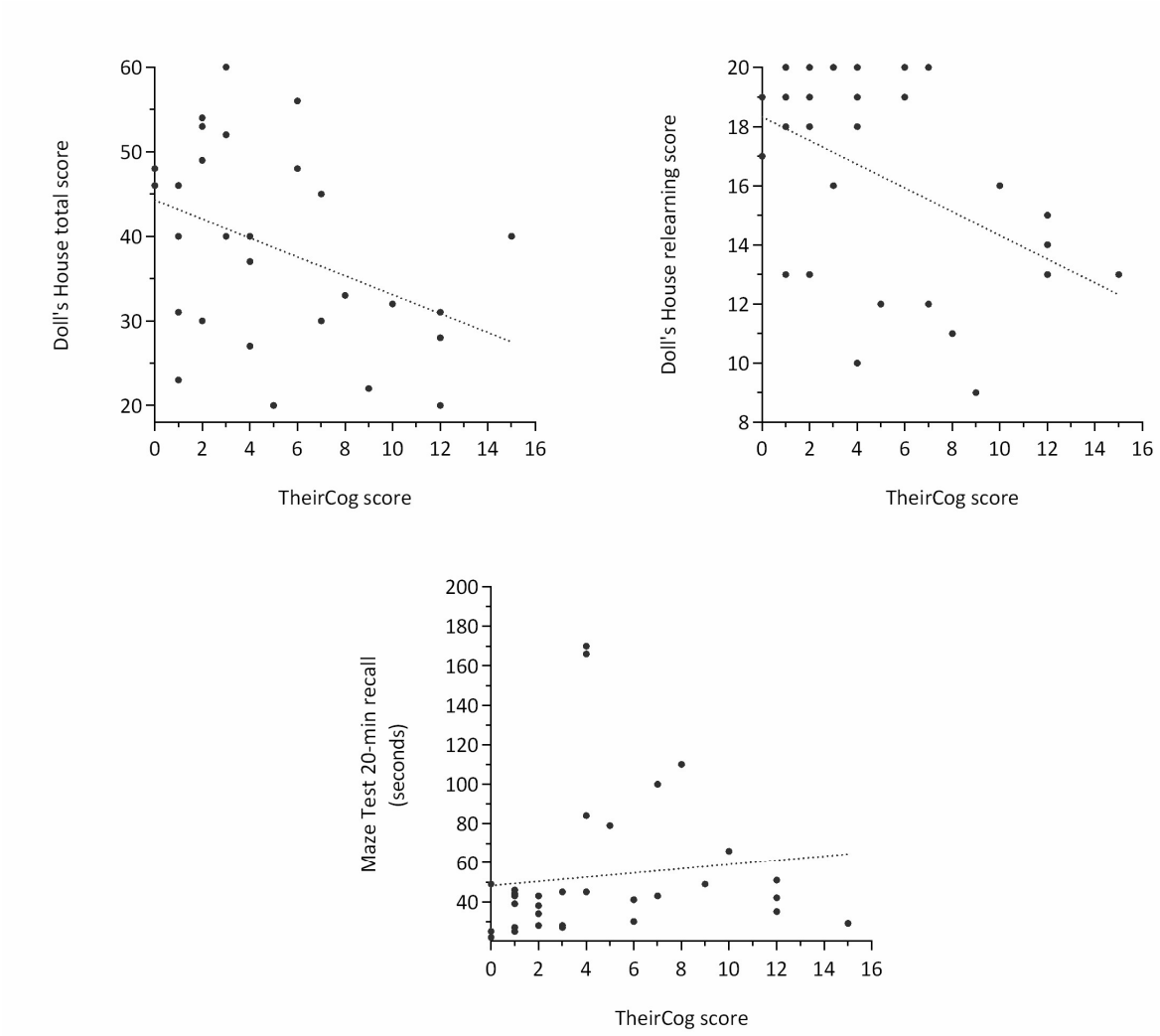
*** p<0.05 [difference between the negative and neutral news in the 1-week free forgetting rate (i.e., slope between the 20-min recall and the 1-week recall)].**

Figure 4. Principal Component Analysis



Key: Panel A shows the percentage of explained variance for each PC and panel B shows the contribution of the 1WMB variables to the first PC. Red dashed line indicates the mean variable contribution. FR, free recall; CR, cued recall; IFR, immediate free recall; ICR, immediate cued recall, HF, high frequency; LF, low frequency.

Figure5.Correlations between the Doll's House and Maze Testscores and the SCD-Q.



Key: TheirCog, informant-reported version of the subjective cognitive decline questionnaire (SCD-Q).