Short-Term Memory Conjunctive Binding in Alzheimer's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Short-term memory (STM) binding tests assess the ability to temporarily hold conjunctions between surface features, such as objects and their colors (i.e., feature binding condition), relative to the ability to hold the individual features (i.e., single feature condition). Impairments in performance of these tests have been considered cognitive markers of Alzheimer's disease (AD). The objective of the present study was to conduct a meta-analysis of results from STM binding tests used in the assessment of samples mapped along the AD clinical continuum. ***Methods***: We searched PubMed, Scopus and Web of Science for articles that assessed patients with AD (from preclinical to dementia) using the STM binding tests and compared their results with those of controls. From each relevant article, we extracted the number of participants, the mean and standard deviations from single feature and of feature binding conditions. Results across studies were combined using standardized mean differences (effect sizes) to produce overall estimates of effect. ***Results***: The feature binding condition of the STM binding showed large effects in all stages of AD. However, small sample sizes across studies, the presence of moderate to high heterogeneity and cross-sectional, case-controls designs decreased our confidence in the current evidence. ***Conclusions***: To be considered as a cognitive marker for AD, properly powered longitudinal designs and studies that clearly relate conjunctive memory tests with biomarkers (amyloid and tau) are still needed.

Key points

Question: What is the magnitude of difference in short-term memory conjunctive binding tests between controls and patients in the Alzheimer's disease continuum? ***Findings***: We found large differences in all Alzheimer's disease stages compared with controls, from the effect size of -1.10 (preclinical stage) to -2.40 (dementia stage). ***Importance***: Short-term memory conjunctive binding test can contribute to the early detection of Alzheimer's disease. ***Next Steps***: Longitudinal studies are needed relating the conjunctive tests to biomarkers (amyloid and tau).

Keywords: short-term memory binding; memory binding; conjunctive memory; working memory; Alzheimer's Disease; familial Alzheimer's Disease; mild cognitive impairment; preclinical Alzheimer's disease; subjective cognitive decline; systematic review; meta-analysis.

Over the last two decades, the role of feature binding in memory has attracted considerable interest and is now better understood (Luck & Vogel, 1997; Treisman, 2006; Vogel, Woodman, & Luck, 2001; Wheeler & Treisman, 2002). Binding, or the building of a mental representation of combinations of features such as color and shape, names and shapes, or word pairs, supports memory widely, across systems i.e., short-term and working memory (Allen, Baddeley, & Hitch, 2006; Baddeley, 2007a) and long term memory (LTM) (Buschke, 2014; Moses, Cole, & Ryan, 2005), and domains (i.e., verbal (Baddeley, 2001, 2007b; Baddeley, Hitch, & Allen, 2009) and visual (Baddeley, Allen, & Hitch, 2011; Hitch, Allen, & Baddeley, 2020; Hollingworth & Rasmussen, 2010; Logie, Brockmole, & Vandenbroucke, 2009; Shimi & Logie, 2019)). Different models have been proposed to explain how binding supports the representation, formation, and use of memory. The two most prevalent are the slot model (Luck & Vogel, 2013; Rouder, Morey, Morey, & Cowan, 2011) and the resource model (Bays, Wu, & Husain, 2011; Heinen et al., 2016; Liang et al., 2016), although a comparison of these models is outside the scope of the current paper.

In this systematic review and meta-analysis, we focus on the formation and temporary retention in short-term or working memory of arbitrary combinations of features referred to as temporary conjunctive binding. This contrasts with research that has focused on the learning of associations between features (e.g., Moses & Ryan, 2006; Barnett et al., 2015; Bier et al., 2008; Blackwell, et al., 2004; Liang et al., 2016; for reviews see Zimmer, Mecklinger, & Lindenberger, 2006; Schneegans & Bays, 2019). However, whereas there is a substantial and growing volume of research on short-term binding in healthy adults (for a recent review see Hakim, Awh, & Vogel, 2021), there are relatively fewer studies of temporary feature binding in patient groups (see e.g. Parra et al., 2015; van Geldorp, Parra & Kessels, 2014). In particular, we focus on how the temporary binding of visual features is impacted by pathological aging, in particular Alzheimer's disease (AD). AD is a neurodegenerative disease that progressively impairs cognition and functionality (Albert et al., 2011; McKhann et al., 2011), and it is the main cause of dementia in older adults (Ferri et al., 2005; Prince et al., 2014; Reitz & Mayeux, 2014; Cao et al., 2020).

Relational and conjunctive binding

Individual features can be bound in memory by means of two mechanisms: relational and conjunctive. Relational binding refers to the ability to associate stimuli in memory, whereby the individual elements forming such associations retain their original identity (Mayes et al., 2007). Conjunctive memory binding, on the other hand, refers to the ability to integrate stimuli or their features into unified representations (see Moses & Ryan, 2006 for evidence from long-term memory and Wheeler & Treisman, 2002 for evidence from working memory). To recognize a blue car in the car park, we do not need to recall the association between 'blue' and 'car' as separate features; rather we remember the car as a unique object (a blue car) whose

identity differs from that of other neighboring objects. While altering a constituent part in a conjunctive memory representation leads to the formation of a new identity (a red car is different from a blue car), changing a part in a relational representation modifies the nature of the association but not the identity of its parts (see for example Mayes et al., 2007; Moses & Ryan, 2006). The dissociation between relational and conjunctive bindings has been shown in a series of single-case studies of patients with specific impairments on relational but not on conjunctive binding and vice versa (Vargha-Khadem et al., 1997; Baddeley et al., 2010; Parra et al., 2009a, 2011a, Parra et al., 2015a; Jonin et al., 2019), and this dissociation is relevant because it translates into distinct aging effects and associations with brain areas. A further crucial dissociation is between long-term learning of conjunctive bindings (e.g. learning that your car is blue) and temporary combinations of features that may change on a moment to moment basis, such as the color of cars around you on a busy motorway, or whether a participant in an experiment or cognitive test is presented with a blue square and a red circle to remember on one trial, but a blue circle and a red square on a subsequent trial.

Relational binding is affected by normal aging, both in LTM (Naveh-Benjamin et al., 2007; Naveh-Benjamin et al., 2004ab; for a review, see Old & Naveh-Benjamin, 2008) and short-term memory (STM) (Chen & Naveh-Benjamin, 2012; Cowan et al., 2006; Fandakova et al., 2014; Mitchell et al., 2000). Short-term, or temporary conjunctive binding, on the other hand, has consistently shown to be insensitive to age (Bastin, 2018; Brockmole & Logie, 2013; Brockmole et al., 2008; Brown et al., 2017; van Geldorp et al., 2015; Hoefeijzers et al., 2017; Isella et al., 2015; Killin et al., 2018; Kirmsse et al., 2018; Yassuda et al., 2020). It is also important to note that temporary conjunctive binding is not affected by literacy (Yassuda et al., 2020).

Relational and conjunctive memory bindings are also subsumed by different neuronal activations. Relational binding requires the work of the hippocampus (Gold et al., 2006;

Hannula et al., 2006; Kan et al., 2007; Monti et al., 2015; Nichols et al., 2006; Olsen et al., 2012; Olson et al., 2006; Yonelinas, 2013), whereas conjunctive STM binding does not (Baddeley et al., 2010; Parra et al., 2014; Piekema et al., 2010; Staresina & Davachi, 2010; Valdés Hernández et al., 2020; Xu, 2007). In the latter case, there are short intervals between study and test phase, such as one second, and a small number of items in the study display for subsequent recognition or recall (e.g., Jeneson et al., 2012).

Piekema et al. (2010) found that the medial temporal lobe (MTL) was not activated when people perform intrinsic intra-item bindings (color-object), but the inter-item associations yielded MTL activation. Visual short-term memory for conjunctive bindings seems instead to be associated with posterior areas of the brain, especially regions within the parietal and occipital lobes (Parra et al., 2014; Todd & Marois, 2005; Shafritz et al., 2002; Song & Jiang, 2006; Staresina & Davachi, 2010; Xu, 2007).

Conjunctive short-term memory binding paradigms

Different paradigms assessing conjunctive STM binding have been used in clinical settings with patients. The main difference between them relies on the retrieval method: recognition or free recall. In recognition tasks using the change detection paradigm, participants assess a test screen and decide if the stimuli are the same or different from those presented in the previous screen (study phase). In free recall, participants are asked to say aloud the names of the stimuli they have just seen in the study screen. In addition to these differences, the tasks vary in terms of presentation time, in the study screen and in the number of items presented per trial.

Several studies compared single feature condition versus feature binding condition. The single feature condition refers to a task in which the stimuli are presented as individual features (color-only, shape-only). The participant should memorize and retrieve each individual feature. For

instance, in the shape-only task using the change detection paradigm, participants should memorize shapes (study phase) and then recognize if the shapes presented in the test phase are the same or different. The feature binding condition, on the other hand, requires participants to memorize and retrieve features integrated within object representations, such as the specific color-shape combinations for colored shapes or colored objects (i.e., bindings).

Conjunctive binding as a cognitive marker for AD

The identification of a sensitive and specific cognitive marker of AD will ultimately aid its differential diagnosis and assist the early detection of the disease, as well as its follow-up (Logie, Parra, & Della Sala, 2015). Improving early diagnosis and care of patients with dementia is a current primary target for the National Institutes of Health in the US and for the National Health Service within the UK, and will no doubt continue to be a national and international priority. It has been suggested that the STM binding test could significantly contribute to the early detection of AD (Logie, Parra, & Della Sala, 2015), showing not only high sensitivity but also high specificity for AD (Costa et al., 2017; Martínez, Trujillo, Arévalo, Ibáñez, & Cardona, 2019; Rentz et al., 2013). Therefore, it is important to review how conjunctive binding tests can detect impairments in each stage of the AD continuum (Sperling et al., 2011; 2013).

Previous reviews addressed this issue only partly. Rentz et al. (2013) carried out a selective review about tests promising to detect preclinical AD, showing that poor performance in tests like the Memory Capacity, Face-Name Association, Spatial Pattern Separation and Discrimination and Transfer was associated with the presence of biomarkers for AD. In addition, a range of studies has found that the dual-tasking and the STM binding tests could discriminate preclinical AD patients from controls (e.g., Della Sala, Foley, Parra & Logie,

2011; Kaschel, Logie, Kazén, & Della Sala, 2009; Logie, Cocchini, Della Sala, & Baddeley, 2004). Fuller et al. (2019) reviewed the literature on cognitive and biological markers of familial AD, showing that structural and functional brain abnormalities could be found in preclinical AD patients, as well as cerebral spinal fluid biomarkers. In addition, they highlighted cognitive impairments in preclinical AD patients, among which were deficits on the STM binding test. Martínez et al. (2019) conducted a broader review on theoretical cognitive models of conjunctive binding, also reviewing differences in test paradigms, brain areas associated with them, and the clinical use of the conjunctive STM binding in dementia. Pavisic et al. (2020) presented arguments to use the visual binding tasks, including relational and conjunctive types, in clinical settings. However, none of these reviews specifically addressed the issue of the clinical use of conjunctive STM binding in the AD continuum, from preclinical to dementia stages. Moreover, none of the previous reviews was conducted using transparent and reproducible methods or performed a meta-analysis of the results of multiple studies. As early detection of AD was the main goal driving the development of the conjunctive memory binding tasks, it is essential to review the evidence available to establish where the current knowledge sits and inform future research.

We aimed to analyze studies that have reported on one of the three stages of AD described in the literature: i) preclinical/subjective cognitive decline, during which patients do not show impairments in common cognitive measures (Dubois et al., 2016; Jessen et al., 2014; Koppara, et al., 2015a; Reisberg et al., 2010; Sperling et al., 2011) ii) prodromal: mild cognitive impairment (MCI - Mitchell and Shiri-Feshki, 2009; Petersen, 2004), which defines patients with high risk to convert to AD and iii) the clinical stage of full blown dementia (Jack et al., 2018; McKhann et al., 2011).

To perform a meta-analysis of studies using the STM binding in the context of AD is not an ill-posed question which confounded dementia with specific diseases (Della Sala & Morris,

2020), like AD, since the STM binding deficits have been suggested to be specific to AD. Other reasons for a review on a specific cognitive marker of AD are that 1) AD is the most common cause of dementia (Prince et al., 2014); 2) biomarkers and neuroimaging techniques are expensive and not sufficiently available in most developing countries, or even in remote areas of developed countries. Therefore, searching for cognitive markers of AD, especially in early stages, is an important goal.

Objectives

The objectives of the present study were to systematically review the current evidence in the literature and combine the results of studies assessing the clinical use of the STM conjunctive binding tests in the context of the AD clinical continuum in a meta-analysis.

Methods

This systematic review and meta-analysis was conducted according to the recommendations of the Cochrane Handbook for Reviews of Interventions (Higgins et al., 2019) and reported in adherence with the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

Criteria for considering studies for this review

Types of studies

Studies that used a conjunctive STM binding test with patients at any stage of AD were considered in this review. We considered AD on a continuum according to the level of

cognitive impairment from preclinical/subjective cognitive decline, to MCI up to full blown dementia. It is worth mentioning that most of these studies preceded the recent framework proposed for the biological definition of AD (Jack et al., 2018). We did not filter by the type of study design, but only cross-sectional case-control studies were found.

Participants

Adults at one of the following stages of AD preclinical/subjective cognitive decline, MCI or AD dementia. Furthermore, in this review we are using the term AD in a broader sense, acknowledging that the reviewed studies used different diagnostic criteria, such as the McKhan et al.'s (1984), McKhan et al.'s (2011) and the biological definition of Jack et al. (2018). In addition, studies involving the familial variant of AD recruited patients with genetic mutations E280A-PSEN1 that leads to early-onset autosomal dominant AD (Lopera et al., 1997). Different criteria for MCI were also considered, such as Petersen et al. (2004), Winblad et al. (2004), Albert et al. (2011) and for the familial MCI the Acosta-Baena et al. (2011).

Types of interventions

We aimed to analyze the performance of patients within the AD-continuum and related healthy controls on conjunctive STM binding tests. Different paradigms were included: change detection (Parra et al., 2010a, 2010b, 2011b, 2015b, 2017a, 2019; Koppara et al., 2015b; Della Sala et al., 2016; Pietto et al., 2016; Fernández et al., 2018; Cecchini et al., 2020; Kozlova et al., 2020; Norton et al., 2020; Valdés Hernández et al., 2020; Cecchini et al., 2021; Fernández & Parra, 2021; Martínez-Flores et al., 2021), free recall (Parra et al., 2009b; Della Sala et al., 2012; Cecchini et al., 2017a; Cecchini et al., 2020) and cued recall modalities (Guazzo et al.,

2020), different set sizes (i.e., from 2 to 4 items per screen), different stimuli (e.g., unnameable shapes or objects) and different amount of trials (from 6 to 32 trials).

Type of outcome measures

The primary outcome measures were the effect sizes for the scores of the STM binding tasks in controls and patients in AD continuum.

Search methods for identification of studies

Electronic searches

Comprehensive searches were designed using appropriate subject headings and free text terms. We searched PubMed, Scopus and Web of Science on 08 June 2020 with a combination of terms for memory binding ("short-term memory binding", "memory binding", "conjunctive memory", "working memory binding") and appropriate terms for dementia ("Alzheimer's disease", "mild cognitive impairment" and "subjective cognitive decline"). We performed another search on 24 November 2021 to check for new papers. No restrictions on date or language of publication were applied to the searches. All references were exported to StArt (Fabbri et al., 2016) for recording and deduplication. Further details of electronic searches are given in online Supplemental Material (S1).

Searching other resources

The reference lists of all selected studies were screened for additional studies and experts in the field contacted for further reports. Lists of included and excluded studies are fully presented in the online Supplemental Material (S2 and S3, respectively).

Data collection and analysis

Selection of studies

The titles and abstracts identified by the search strategies for eligibility were assessed and any disagreements were resolved by discussion. Articles were selected according to the following inclusion criteria: 1) studies assessing the conjunctive memory binding; 2) studies with patients at any stage of the AD continuum (pre-clinical/subjective cognitive decline; MCI; AD dementia). Articles were not deemed suitable for inclusion if they 1) dealt with other neuroscience or cognitive topics; 2) dealt with relational, associative, or other types of binding; 3) were reviews, opinion articles, single-case reports, or conference proceedings; 4) did not include an AD group. All potentially relevant articles were retrieved in full.

Data extraction and management

The search results were extracted to the StArt program (Fabbri et al., 2016), which was used to manage and select the articles. We extracted information on the testing procedure and methods (items per trial, quantity of trials, the encoding time, the type of single feature condition and the measure used in the study, sample size), the characteristics of participants (mean age and education level) and the target condition (diagnostic criteria used to categorize patients according to the stages of AD). The single feature condition refers to a task in which the stimuli are presented as isolated features (color-only, shape-only or objects and colors). To assess the

participants' performance on the single feature condition and feature binding condition of the STM binding tasks, we extracted mean scores for each tested group along with standard deviations and the number of participants. Parra et al. (2017a) study used the same MCI-FAD sample from Pietto et al. (2016), therefore the former was excluded from the meta-analysis.

Assessment of risk of bias and quality of evidence

The risk of bias of included studies was assessed using the ROBINS-I criteria (Higgins et al., 2019; Sterne et al., 2016). The confidence in the certainty of identified evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria (Guyatt et al., 2011; Higgins et al., 2019). The level of certainty was lowered if one of the following aspects were present: risk of bias, inconsistency, indirectness, imprecision, or publication bias. All studies included in this review were case-controls studies, which were considered as having low certainty of the effect estimation from the start due to their study design. We considered the 95% confidence intervals: if the lower and upper bound had different meanings (e.g., large effect for the upper bound and no effect for the lower bound), lowering the certainty was considered based on imprecision. The level of certainty was increased if the studies showed a large effect size or when it was considered plausible that the confound variables had undermined the potential effect size. Both the imprecision and increment in certainty judgements were based primarily on the feature binding conditions, as they were the focus of the included studies. The results of the risk of bias assessment and grading of evidence for each of the included studies are presented in online Supplemental Material (S4).

Measures of treatment effect

To assess the performance of controls and AD patients on the STM binding tasks we used mean differences and standard deviations of single feature condition and feature binding condition tasks. We included both tasks because the single feature condition was used as a control task against which the feature binding condition was compared to assess the presence of binding deficits. Age and level of education were considered possible confounded variables and notated in the Characteristics of Included Studies Table (see Table 1).

Unit of analysis issues

Each comparison between controls and AD patients was considered relevant. When a study had more than one comparison, such as comparing controls with preclinical AD and controls with AD, both comparisons were considered in the meta-analysis. The same occurred when a study used more than one experiment, comparing controls and patients in two different experimental settings. When a study had different test characteristics, such as comparing controls and patients with two or three items per screen, each comparison was considered as one unit of analysis.

Dealing with missing data

Mean and standard deviation values were not reported in ten papers (Della Sala et al., 2012; Fernández et al., 2018; Fernández & Parra, 2021; Martínez-Florez et al., 2021; Norton et al., 2020; Parra et al., 2009b; Parra et al., 2010a; Parra et al., 2017a; Parra et al., 2015b; Pietto et al., 2016). The authors of these papers, who were contacted for further information, kindly provided the relevant sets of data. We did not get the data from Fernández and Parra (2021),

but they used the same sample from Fernández et al. (2018), adding five more participants in each group, therefore, only the Fernández et al.'s (2018) data were included in the meta-analyses.

Assessment of heterogeneity

Heterogeneity between studies was assessed visually by inspection of the forest plots and statistically using the I^2 (on a scale from 0% to 100%) and the Chi-squared statistics (Higgins et al., 2019). The I^2 represents the variability in the effects that is due to heterogeneity (Borenstein et al., 2017). If $I^2 = 0$, all variability in the effect sizes is explained within studies instead of between studies (heterogeneity) (Huedo-Medina et al., 2006). An I^2 less than 40% was considered to indicate low inconsistency; 50% to 75% indicated moderate inconsistency, and greater than 75% considerable inconsistency (Higgins & Thompson, 2002; Higgins et al., 2019).

Assessment of reporting biases

We assessed the presence of publication bias, which refers to the fact that studies with negative results have less chance to be published, using funnel plots when at least ten studies assessing the same outcomes were identified. We acknowledge, however, that poor methodological study design (e.g., case-control design) can be an important source of funnel plot asymmetry.

Data synthesis

As studies used different number of items for the STM binding tasks, we calculated standardized mean differences. If appropriate, the results of included studies were combined in

random-effects meta-analyses to produce overall estimates of effect. The decision to combine data in meta-analyses was dependent upon the availability of outcome data and the heterogeneity observed between studies. The random-effects model assumes that the effect sizes represent a random sample from a distribution of these effect sizes, considering that there may be different effect sizes underlying different studies (Borenstein et al., 2010). We decided to use random effects models because between-study heterogeneity was expected due to the variability in experimental methods and sample characteristics. We combined studies using the inverse of the variance weighted approach and presented summary estimates alongside 95% confidence intervals.

To assess the effect size, the Hedges' g formula was used due to differences in sample sizes between the groups and because this formula is better for small sample sizes when compared to the Cohen's d (Cooper et al., 2009). To interpret the effect sizes, we used the following criteria (Cohen, 1988): 0.2 = small, 0.5 = medium and 0.8 = large.

Separate meta-analyses were performed according to the different stages of AD (i.e., preclinical AD /subjective cognitive decline versus controls, MCI versus controls, sporadic and familial AD versus controls).

The analyses were performed using the meta package v4.16-1 (Schwarzer, 2007) in R v.4.0.2 and the Review Manager (2020) software version 5.4.1.

'Summary of findings' table

The main results of this systematic review are shown in the 'Summary of findings' Table (Table 1). The table presents the magnitude of effects of the single feature condition and feature binding condition according to the different stages of AD, the total number of studies and participants, and information on the quality of evidence.

Subgroup analysis

The main aspects of the included studies that could increase heterogeneity and therefore reduce the strength of the conclusions were investigated using subgroup analyses. The following subgroup analyses were performed: 1) single feature condition vs. feature binding condition; 2) change detection vs. free recall tasks; 3) familial AD vs. sporadic AD; 4) Shape-color vs. color-color binding tasks; 5) titration vs. no-titration difficulty of the tasks between controls and patients. All these analyses were performed within each diagnostic group (e.g., preclinical/subjective cognitive decline, MCI and AD dementia). Analyses 2 to 5 were done for single feature conditions and feature binding conditions separately. A p-value ≤ 0.10 was considered significant (Richardson et al., 2019).

Results

Description of studies

Literature search results

In total, 320 reports were identified by the search strategies. Of the 320 identified reports, 301 were subsequently excluded for the following reasons: 103 were duplicates; 145 investigated neuroscience or cognitive topics not relevant to the purpose of this review; 27 focused on relational, associative, or other types of binding; 17 were reviews or opinion papers; 7 did not include an AD clinical group; 2 were conference proceedings, single-cases or we did not have access to the data. At last, one paper was included from perusing the lists of references. In total, 20 articles were considered in this review. The included and excluded studies are described in

online Supplemental Material (S2 and S3). Figure 1 presents the PRISMA flow diagram of study selection.

[INSERT FIGURE 1 HERE]

Included studies

Table 1 presents the summary of findings for the main comparisons and Table 2 presents the characteristics of the included studies. The studies varied in terms of the modality of the STM binding assessment, using either free recall, change detection or cued recall. They also used different set sizes in the task, ranging from 2 to 4 items per trial, and some studies titrated the cognitive load by using different set sizes for the control and experimental groups. All studies reviewed used small sample sizes, except for Martínez-Flores et al. (2021), which included 109 controls and 45 MCIs. The other studies varied from 6 to 37 participants within each group, with a mean sample size of 22.24 and a median of 23 participants per group.

Stimuli presentation time varied from 500 milliseconds to 12 seconds across studies. Concerning the change detection tasks, the number of trials varied from 32 to 100 across studies and most of them used 2000ms duration of the study phase, with only a few using 500ms. Across studies, the performance of participants in the change detection task was measured either using the number of correct responses, the proportion of correct responses, using A' (a measure of sensitivity, see Xu, 2002, pg. 1264 for the formula to calculate it), hit minus false alarms (corrected recognition) or Beta (β) (Stanislaw & Todorov, 1999). For the free recall

task, all studies used 6 trials and the same study time per feature (1.5 seconds). For the cued recall task, a 12-second delay between encoding and recall phases was used.

[INSERT TABLE 1 HERE]

[INSERT TABLE 2 HERE]

Meta-analysis results

AD / Familial AD versus Controls, single feature condition

Figure 2 shows the results of the single feature condition of the STM binding test for the comparison between sporadic/familial AD (343 patients in total) and controls (332 controls in total). The overall pooled standardized mean difference was -1.18 (95% CIs -1.61, -0.76). Substantial heterogeneity was observed between studies ($I^2 = 84\%$, $p < 0.01$). The analysis of the funnel plot (S5.1, online Supplemental Material) shows that there is no clear evidence of publication bias.

[INSERT FIGURE 2 HERE]

AD / Familial AD versus Controls, feature binding condition

Figure 3 shows the results of the feature binding condition of the STM binding test for the comparison between patients with sporadic/familial AD (390 patient in total) and controls (374 controls in total). Substantial heterogeneity was observed between studies ($I^2 = 78\%$, $p < 0.01$).

The overall pooled standardized mean difference was -2.41 (95% CIs -2.82, -1.99) ranging from -4.17 to -1.34 across studies. The analysis of the funnel plot (S5.2, online Supplemental Material) shows that there is no clear evidence of publication bias.

[INSERT FIGURE 3 HERE]

MCI / MCI-FAD versus controls, single feature condition

Figure 4 shows the results of the single feature condition of the STM binding test for the comparison between patients with MCI and MCI-FAD (249 in total) and controls (379 in total). Moderate heterogeneity was observed between studies ($I^2 = 53\%$, $p < 0.01$). The overall pooled standardized mean difference was -1.08 (95% CIs -1.35, -0.81); effect sizes ranged from -1.97 to -0.37 across studies. The analysis of the funnel plot (S5.3, online Supplemental Material) shows that there is no clear evidence of publication bias.

[INSERT FIGURE 4 HERE]

MCI / MCI-FAD versus controls, feature binding condition

Figures 5 shows the results of the feature binding condition of the STM binding test for the comparison between patients with MCI and MCI-FAD (363 in total) and controls (565 in total). The overall pooled standardized mean difference was -1.07 (95% CI -1.32, -0.82); effect sizes ranged from -2.52 to -0.61 across studies. Moderate heterogeneity ($I^2 = 63\%$, $p < 0.01$) was

observed across studies. It is worth noting that two studies used different set sizes and compared either two or three stimuli per screen (Parra et al., 2019; Valdés Hernández et al., 2020). In each study, the number of stimuli presented per screen did not affect the estimate of effect with similar standardized mean differences between the experimental and control groups. The analysis of the funnel plot (S5.4, online Supplemental Material) shows evidence of asymmetry with two studies outside the plot.

[INSERT FIGURE 5 HERE]

Preclinical AD and subjective cognitive decline versus controls, single feature condition

Figure 6 shows the results of the shape-only condition of the change detection modality of the STM binding test between patients with subjective cognitive decline (SCD)/preclinical AD (111 in total) and controls (130 in total). The overall standardized mean difference mean was -0.33 (95% CI -0.59, -0.07), with effect sizes ranging from -0.51 to -0.21 across studies. No statistical heterogeneity was observed across studies ($I^2 = 0\%$, $p = 0.93$).

[INSERT FIGURE 6 HERE]

Preclinical AD and subjective cognitive decline versus controls, feature binding tasks

Figures 7 present the results of the shape-color binding condition of the change detection modality of the STM binding task for patients with subjective cognitive decline and preclinical AD (111 in total) and for controls (130 in total). The overall standardized mean difference was

-1.10 (95% CI -1.48, -0.73) with effect sizes ranging from -1.52 to -0.56 across studies. Low inconsistency was observed across studies (I^2 = 46%, p = 0.11).

[INSERT FIGURE 7 HERE]

Subgroup analyses

All subgroups' analyses with the forest plots are presented in online Supplemental Material (S6).

Subgroup 1: single feature condition vs. feature binding condition

The test for subgroup differences suggests that there is a statistically significant subgroup effect comparing the single feature condition and the feature binding condition in AD and preclinical patients (both p < 0.001). The feature binding condition showed larger effects than the single feature condition. Although heterogeneity was evident in both comparisons [possibly explained by the variation between the tasks (free recall, change detection, difficulty titration or no-titration, etc.)], it is worth noting that almost all studies had negative effects (AD and preclinical showing worse performance than controls). The comparison of the effects of single feature condition and feature binding condition in the MCI group did not show statistically significant subgroup differences (p = 0.96).

Subgroup 2: Change detection vs. free recall

The subgroup analyses comparing the effects between change detection and free recall tasks in AD patients showed no effect in both single feature condition and feature binding condition tasks (single feature condition p = 0.52; feature binding condition p = 0.66). As only one study

used the free recall task (Cecchini et al., 2020) to assess patients in the MCI stage group and none used the free recall task in the preclinical stage of AD, it proved unfeasible to conduct subgroup analyses for patients in these groups.

Subgroup 3: Familial vs. sporadic AD

We were not able to conduct meaningful subgroup analyses comparing the effects between sporadic and familial AD because of the small number of participants in the familial AD group (63 familial AD vs. 280 sporadic AD in single feature condition and 63 familial AD vs. 327 sporadic AD in the feature binding condition). In addition, only one study assessed familial AD at the preclinical/subjective cognitive decline stage (Koppara et a., 2015b) or MCI stage (Pietto et al., 2016).

Subgroup 4: Shape-color vs. color-color binding

Shape-colour and colour-colour binding tasks did not show statistically significant effect differences in the AD group ($p = 0.67$). Only limited data on color-color task compared with the shape-color task were available in the AD and preclinical groups, and no study used the color-color task for MCI patients.

Subgroup 5: Difficulty titration vs. no-titration

The titration method involves presenting fewer to-be-remembered items within visual arrays (i.e., smaller set sizes) for patients than for controls. This procedure was used so the ability to hold temporary conjunctions could be compared properly between the groups controlling for working memory load as informed by single feature performance (i.e., equated across groups).

In AD group, the comparison between the titration vs. no-titration methods showed statistically significant results in the single feature condition ($p = 0.01$). As expected, the studies that did not titrated the task difficulty showed larger effects. However, the effects were similar in the feature binding condition ($p = 0.21$), meaning that even in an easier task, AD patients showed a binding deficit. None of the studies with MCI patients titrated the task difficulty. For the preclinical group, only three studies used the titration method (Parra et al., 2010a; 2011b; 2015b) and two used no-titration (Koppara et al., 2015b; Norton et al., 2020), hampering the possibility of conducting any meaningful analysis.

Discussion

In this systematic review, we assessed evidence from 20 published studies and performed a meta-analysis on 19 studies on the performance of patients at different stages of the AD continuum (from preclinical to dementia stage) using the STM binding task. The reviewed studies were published between 2009 and 2021. In total, 864 patients at different stages of AD and 1,069 controls were assessed with the feature binding condition and 703 patients at different stages of AD and 841 controls with the single feature condition.

It is worth noting that some studies included more than one experiment, had more than one group (e.g., two groups of patients), did more than one session, or compared the groups using tasks with different set sizes. A total of 38 comparisons were performed with the feature binding condition (shape-color binding or object-color binding) and 32 with the single feature condition tasks.

Different testing paradigms were used, with variation in presentation time, recall strategy, stimuli type or quantity displayed on the screen. Essentially, three types of retrieval strategy

were used by the authors of the studies included in this review: 1) recognition during change detection; 2) free recall; 3) cued recall. For the change detection two different versions were used across studies: a computerized version using the E-prime program and an analogue flash-card version. Examples of the various tasks used in the different studies entering the analyses can be found in online Supplemental Material (S7).

The mean effect size of the single feature condition was small in the preclinical stage and increased significantly in the MCI and AD dementia groups. The feature binding condition, on the other hand, had a large mean effect size even when comparing controls and preclinical AD, and the effect size increased in comparison with AD at dementia stage. MCI patients showed a similar effect size when compared with preclinical AD in the feature binding condition. This could be related to the fact that most preclinical AD patients in the study had a genetic mutation that leads 100% to AD dementia (Lopera, 1997), but the MCI groups were more heterogeneous, as expected. Notwithstanding the higher risk to develop AD dementia (Mitchell & Shiri-Feshki, 2009), some MCI patients could convert to other dementia types, stay stable or return to normality (Galluzzi et al., 2013; Ganguli et al., 2011; Grande et al., 2016; Overton et al., 2019; Roberts & Knopman, 2013). This occurs because MCI is essentially a cognitive status, not a disease itself, and it is diagnosed using essentially cognitive and functional measures and self-reported cognitive complaints. Furthermore, none of the studies with people with MCI titrated the task difficulty between control and MCI group (i.e., the groups did the same task) and most used a task with 3 items per trial. This can have overloaded the patients' working memory, hampering their performance not only in the feature binding condition task (Parra et al., 2019). As the reviewed studies did not include biomarkers to ascertain AD pathology, the heterogeneity in the MCI group should be expected. In the next sections we will provide an in-depth examination of the evidence according to the three different stages of AD.

Alzheimer's disease dementia

The meta-analyses indicated a large mean effect comparing controls and AD dementia patients. The effect size was larger in the feature binding conditions (-2.40) compared with the single feature ones (-1.18), indicating that the AD groups showed much more difficulty to hold bound information (i.e., shape-color, color-color or object-color bindings) than to hold individual features, and that binding deficits could not be explained by a general working memory deficit (i.e., they are specific deficits). In addition, the studies with both sporadic and familial AD dementia showed similar results. That is important because it suggests that STM binding deficits are independent of the disease variant (Parra et al., 2011), and hence evidence drawn from familial AD could help interpret behaviors observed during STM binding tests in sporadic AD. However, it should be noted that future studies will be needed to ascertain the relationship between genotype and phenotypes in AD (Holmes, 2002).

Mild cognitive impairment stage

The single feature condition in the studies showed effect sizes from -0.37 (set size two) to -1.46 (set size three), that is, small to large effects. The MCI group showed a performance similar to that of controls in the shape-only condition when two items per screen were used, but a significant deficit when three items were used. It was argued (Kozlova et al., 2020; Parra et al., 2019) that the deficit to bind shape-color would be more apparent using a smaller set size, in which patients would show similar performance in the shape-only condition, but deficits in the shape-color binding task. The effect sizes on feature binding conditions were large in all studies, while the mean effect sizes of the single feature condition and feature binding condition were similar (-0.95 and -1.06, respectively). That is, the MCI groups showed significant difficulties to hold bound and single feature information temporarily in the memory,

suggesting that the memory load used in such studies did not allow separating the general underlying working memory deficits present in these samples from the specific binding impairments previously found. Strategies to address this methodological caveat have been discussed in Parra et al. (2019).

These results could be further explained by the small sample sizes in the studies, but also by the fact that most of the MCI patients in the studies did not have biomarker data and did not follow the new biological criteria for AD (Jack et al., 2018). It is likely that the MCI groups were too heterogeneous. The conclusions from the MCI analyses highlight the importance to work with AD biomarkers in new studies with STM binding tests and MCI groups. Without long-term follow up assessments, it is not possible to ascertain that MCI patients assessed in such studies were in the AD biological continuum, making it difficult to determine the predictive role of STM binding deficits in the prodromal stages of the disease.

Pre-clinical and subjective cognitive decline stages

The meta-analyses indicated a large mean effect size comparing controls and pre-clinical patients in the feature binding condition (-1.10), and a small mean effect size in the single feature condition (-0.33). The studies showed a pattern of specific binding deficits in the preclinical stages of AD, in which the patients show a deficit to hold temporarily conjunctions, but not single items. All studies with asymptomatic carriers of the presenilin mutation and patients with subjective cognitive decline used a set size with three items per screen.

If the STM binding test can assist the detection of AD in the preclinical stage, it would be expected that this task should be related to the biomarkers that define the AD pathology. Three studies examined the comparison of STM binding test data with biomarkers (Cecchini et al., 2021; Norton et al., 2020; Parra et al., 2017b). Parra et al. (2017b) presented a poster in which

controls with amyloid PET (n=39) were assessed. The sample was split in two groups: strong binders and weak binders using the performance on the change detection shape-color binding task. The authors showed that the weak binders group had mode amyloid burden in the parietal-occipital-temporal regions and fusiform gyrus when compared with the strong binders (Parra et al., 2017b). Norton et al. (2020) studied a sample of controls, asymptomatic carriers of the presenilin-1 E280A mutation and familial MCI; the STM binding test significantly correlated with amyloid deposition in the brain ($r = -0.50$, $p = 0.03$), but not with tau deposition in the inferior temporal lobe ($r = -0.30$, $p = 0.21$) or the entorhinal cortex ($r = -0.26$, $p = 0.27$). Cecchini et al. (2021) showed that the STM binding was the only cognitive task that discriminated groups with and without amyloid deposition when compared with RAVLT and Short Cognitive Performance Test (SKT) (episodic memory tests). Therefore, the STM binding test seems to be related to amyloid deposition in the brain, but the relation with tau or the entorhinal activity still need to be better understood.

Heterogeneity analyses

The heterogeneity was high in the comparisons between controls and AD patients in both conditions (single feature and feature binding). Four studies showed a particularly large effect sizes in the feature binding condition (Della Sala et al., 2016; Fernández et al., 2018; Guazzo et al., 2020; Kozlova et al., 2020). If these studies were dropped from analyses, the heterogeneity would be significantly reduced (to $I^2 = 48\%$). The study by Guazzo et al. (2020) showed the largest effect size, and this could be related to differences in the paradigm: it was the only study that tested memory with cued recall. In addition, the large effect size of the other three discrepant studies could be related to the set size used, as the controls and AD patients were presented with a task with the same set size (only two items per screen). This was not the

case for the majority of studies with the change detection task in which the AD group was presented with a smaller set size than the controls (Parra et al., 2010a, 2010b; Parra et al., 2011b; Parra et al., 2015b), with the exception of Cecchini et al. (2020). However, in this last study, 16 trials were carried out, while the other studies with the change detection used 32 trials, which possibly increased the observed effect.

The strategy to titrate the working memory load across groups could also explain the high heterogeneity in the single feature condition tasks as well. Parra et al. (2011b), for instance, showed a positive effect, with controls showing worse performance than the AD patients (although these differences were non-significant). This occurred due to the use of a titration method in which controls were presented with a more challenging task than patients, thereby equating performance on the single feature conditions across groups. Studies that did not use titration, such as Cecchini et al. (2020), showed negative and large effect sizes. In addition, in a task with the same and easiest set size (two items per screen), the control group showed performance close to ceiling, with low standard deviations, which increased the effect sizes compared to the other groups. Sample characteristics also could be related to the heterogeneity found. AD patients were not taking cholinesterase inhibitors in the study of Fernández et al. (2018), which could have improved their cognitive performance (Rockwood, 2004; Wilkinson et al., 2004). It seems, also, that this group was heterogeneous, and probably some patients were in more advanced stages of the disease. This was observed in the cognitive measures, especially in the Mini-Mental State Exam (MMSE) (mean = 22.6, SD = 4.1) and Addenbrooke's Cognitive Examination - Revised (ACE-R) (mean = 65.3, SD = 16.9).

The high variability in the AD groups comparisons could be expected. Besides differences in age (from around 45 to 76 years old in mean age), education (from around 6.4 to 14.7 years of formal schooling), and the differences in methods cited above, it is impossible to ascertain that all patients were in the same stage of the disease. In addition, the disease itself is heterogeneous,

with patients showing different clinical and cognitive presentations (Binetti et al., 1993; Lam et al., 2013; Martorelli et al., 2019).

Caveats and suggestions for future studies

It is important to highlight some limitations of the memory binding studies included in this systematic review and to discuss which further evidence is necessary to accrue before STM binding tests could be reliably used in broader clinical settings.

Some studies with asymptomatic carriers of the presenilin mutation and with subjective cognitive decline patients (Koppara et al., 2015b; Parra et al., 2015b; Parra et al., 2011b; Parra et al., 2010a) argued that the STM binding can detect very early signs of the disease, therefore the task should be a good predictor of the dementia evolution. However, longitudinal studies should be carried out to verify whether the STM binding test is a good predictor of dementia in patients with suspected AD. Only one such study could be gleaned from the literature (Martínez-Flores et al., 2021). However, in this study the authors did not test the STM binding as a predictor of MCI to AD dementia conversion but used machine learning techniques to extract classifiers distinguishing between controls and MCI at baseline and tested their accuracy at the follow up assessment (i.e., by comparing MCI vs controls).

Another important issue is the fact that all studies reviewed used small sample sizes (median of 23 participants per group). Therefore, studies with larger samples would be recommended. In addition, most of the papers shared common authors; for instance, Parra authored 17 out of 19 articles, while Della Sala authored 13. The binding tasks should be used by different research groups, with no affiliation or relation with the original authors of the binding paradigm to assess independent replicability. Also, to facilitate the use of the STM binding test by other research groups, the tasks should be available on a free and open-access website. To address this issue, all STM binding test versions used by the authors of this review are now available from

https://www.strath.ac.uk/research/subjects/psychology/cognition/appliedcognitionlab/visualshort-termmemorybindingtestvstmbt/.

Studies testing the psychometric properties of the tasks should also be conducted, performing test-retest and inter-rater reliability, verify the validity and correlate the STM binding with other neuropsychological tests to better understand precisely what cognitive functions are being assessed.

Some aspects of the tasks could be improved. Around 8% of men and 0.4% of women show color-blindness (Birch, 2012), especially to distinguish red and green. To avoid difficulties driven from color blindness, a color-blind palette could be used to tailor a new version of the change detection task. In addition, it is important to note that in the change detection task participants could pay attention to x-1 stimuli, the x representing the number of items on the screen. For instance, as the colors swap between the shapes in the feature binding condition with two stimuli, to detect a change from previous screen participants could focus on only one stimulus. As this could not be clear in the instructions for the participants, some of them could be aware of that, and some not, causing an extra source of variation. That could be one of the causes for the large standard deviations in some studies, and maybe an instruction making this explicit could avoid this problem.

Studies varied also in terms of task titration. Many studies used a different set size to compare control and patient groups (Parra et al., 2015b; Parra et al., 2009b; Della Sala et al., 2012; Parra et al., 2011b; Valdés Hernández et al., 2020; Parra et al., 2010a, 2010b), the former doing a more difficult task than the latter. However, some variation within each group would be expected, since not every person has the same working memory capacity. It would probably be better to titrate the task individually, from one to four or five stimuli, as four is the average of stimuli limit storage in the visual STM (Cowan, 2001, 2010). In addition, some studies

suggested that the best set size for identifying MCI or AD using the change detection task is two stimuli per trial (Kozlova et al., 2020; Parra et al., 2019), while to detect preclinical AD three items per trial proved more sensitive (Koppara et al., 2015b; Parra et al., 2010a; Parra et al., 2011b). Therefore, in a clinical setting, both set sizes should be used, but this would significantly increase the time spent to do the task.

The same question about the number of stimuli applies to the free recall tasks. In addition, the relation between the single feature condition and feature binding condition tasks scores should be better investigated in the free recall paradigm. For instance, if a patient can recall three items out of four in a trial, she/he will achieve 75% in performance in the single feature condition, but only 50% in feature binding condition. This occurs because in the feature binding condition only the correct binding between objects and colors is scored, but in the single feature condition the participant score in each color or object recalled individually. Therefore, a binding cost would be expected, that is, to have worse performance in the feature binding condition task when compared with the single feature condition, and this could be amplified in the clinical groups, as presented by Cecchini et al. (2020). To address this question, the number of stimuli could vary from one or two stimuli to four/five, as explained before.

Another important topic of discussion is the specificity of the binding deficits. If binding deficits are specific to AD, as suggested by many studies here reviewed, the best measure to detect AD should be the binding cost, which represents the difference (or proportion) between single feature condition and the feature binding condition tasks. However, the best variable to detect AD is the feature binding condition alone, and even when the performance in the single feature condition was the same as controls, the variable used to discriminate the groups was still the feature binding condition alone, not the binding cost (Cecchini et al., 2020; Della Sala et al., 2012; Parra et al., 2010a, 2010b; Parra et al., 2011b). One possible explanation could be that this occurred due to a general working memory deficit in the AD groups in addition to a

binding deficit, decreasing the performance in both conditions (single feature and feature binding), interfering with the binding cost variable. However, if this is the case, it would be still necessary to create norms for non-pathological performance for the feature binding condition. Yassuda et al. (2020), for instance, showed that the performance between healthy participants divided in age groups was not different in the feature binding condition of the free recall task with two items per screen, but had differences using three items. Probably with more items the age impact in the performance would become more prominent due to general working memory deficits related to aging (Brockmole & Logie, 2013; for reviews see Logie & Morris, 2015).

To claim that a test is specific to one type of dementia (e.g., AD), it is not enough to compare it only with controls. A few studies compared AD with other types of dementia, and most of them used the free recall task (Cecchini et al., 2017a; Della Sala et al., 2012; Guazzo et al., 2020). Only one study used the change detection task (Kozlova et al., 2020). However, the differential diagnosis between AD and Parkinson's disease used in this latter study is not the most challenging in the clinical setting and these pathologies typically do not present with similar cognitive deficits (Bronnick et al., 2007). As far as we are aware, no article was published to this date comparing, for instance, AD and other dementia types (besides Parkinson's) using the change detection task, but this information was found in posters, conferences abstracts and in a dissertation. The posters from Yassuda et al. (2018), Cecchini et al. (2017b) and the Cecchini's dissertation (Cecchini & Yassuda, 2017) informed that the change detection and free recall modalities of the STM binding test showed a different pattern when controls, AD, and behavioral variant frontotemporal dementia (bvFTD) groups were compared. Only AD patients showed impairments in the free recall task [(Controls = bvFTD) > AD], while AD and bvFTD showed impairment in the change detection task [(Controls > (AD = bvFTD)]. In another poster, Cecchini et al. (2017c) showed that the free recall version

of the STM binding test could differentiate AD from amnestic bvFTD. That is important because AD and amnestic bvFTD showed the same pattern of episodic memory deficits on the RAVLT test, thus the free recall binding task could be used to differentiate AD from bvFTD even when the latter show episodic memory deficits, which is not unusual (Hornberger et al., 2010; van den Berg et al., 2020). Therefore, free recall and change detection tasks could assess binding through different brain networks.

With that in mind, it is necessary to better understand each paradigm of the STM binding. For instance, the color-color binding paradigms does not seem to assess the same ability as the shape-color binding (Wheeler & Treisman, 2002). Color-color binding probably is a form of relational binding because the combination does not define an object, whereas shape-color binding is conjunctive (Parra et al., 2011a). However, the color-color showed similar results as shape-color binding, with similar effect sizes in the meta-analyses. In the paradigm used by (Guazzo et al., 2020), it was also not clear how the cross-modal binding (i.e., binding visual and auditory stimuli) would be different from the relational binding. Without better understanding of each task, it is not possible to know, for instance, if AD and bvFTD patients are performing similarly but for different reasons. As AD patients have hippocampal atrophy and difficulties in binding conjunctive information, they can show poor performance on relational (hippocampal) and conjunctive (not hippocampal) binding. The same can occur with asymptomatic carriers of the presenilin mutation, which showed impairments in the color-color (Parra et al., 2011b) and shape-color binding (Koppara et al., 2015b; Parra et al., 2010a). The bvFTD patients, on the other hand, could show difficulties in the change detection task due to a disruption in networks related to the frontal lobe (e.g., salience network) (Filippi et al., 2013; Seeley et al., 2008; Yu et al., 2016), that probably is associated with this task (Parra et al., 2017a; Pietto et al., 2016). These discrepancies suggest that the free recall and change detection tasks may rely on different brain areas, and it is not clear if they assess the same construct or

how they assess conjunctive binding. As far as we are aware, all imaging studies to this date have used the change detection task.

One of the studies included in this review showed discrepant results (Norton et al., 2020). In this study with the STM binding test, the authors found a significant effect of condition (shape-only x shape-color binding) and a significant effect of group (controls x asymptomatic carriers x MCI-FAD), but no significant interaction between them ($p = 0.29$). That is, asymptomatic carriers and MCI-FAD patients had similar deficits on both conditions when compared with controls. In addition, the shape-only condition showed higher correlation with amyloid deposition in the brain and tau deposition on entorhinal and parietal inferior areas when compared to the feature binding condition. Lastly, the accuracy to detect amyloid and tau positivity was higher for the shape-only condition than for the shape-color one. These behavioral results contradict the initial hypotheses and results from previous findings (Parra et al., 2010a; Parra et al., 2015b). However, from a biomarker point of view, Norton et al. (2020) reported that performance on the shape-color condition correlated with Pittsburgh compound-B (PIB) (at a similar level as the shape condition) and that association was only significant when restricting the analysis to the asymptomatic carriers. They argue that a reason why such a correlation decreased as patients progressed to the tau stages is that performance on the task was reaching floor (in addition to a small sample size). This evidence calls for more studies to document not only “what” should be assessed along the continuum of AD but also “when”.

Conclusions

The articles reviewed showed evidence that patients in the AD continuum present with deficits in holding feature bindings in STM. The difficulties can be found even at preclinical stages of the disease. However, the studies used a cross-sectional design with small sample sizes, in

addition to a moderate to high heterogeneity, which could have contributed to some inconsistencies between the results. Future studies should investigate the STM binding test as predictor of dementia in asymptomatic participants in longitudinal designs and investigate how the task relates to AD biomarkers (amyloid and tau) in larger samples.

References

Acosta-Baena, N., Sepulveda-Falla, D., Lopera-Gómez, C.M., Jaramillo-Elorza, M. C., Moreno, S., Aguirre-Acevedo, D. C., et al. (2011). Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. *Lancet Neurol*., *10*(3), 213–20.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*, 270-279. https://doi.org/10.1016/j.jalz.2011.03.008.

Allen, R. J., Baddeley, A. D., & Hitch, G. J. (2006). Is the binding of visual features in working memory resource-demanding? *J. Exp. Psychol. Gen, 135*(2), 298-313. https://doi.org/10.1037/0096-3445.135.2.298.

Allen, R. J., Hitch, G. J., Baddeley, A. D. (2009). Cross-modal binding and working memory. *Visual Cognition, 17*(1–2), 83–102. https://doi.org/10.1080/13506280802281386.

Baddeley, A. (2001). The concept of episodic memory. *Philos. Trans. R. Soc. Lond B Biol. Sci, 356*(1413), 1345-1350. https://doi.org/10.1098/rstb.2001.0957.

Baddeley, A. (2007a). Exploring the episodic buffer. In A. Baddeley (Ed.), *Working memory, thought, and action* (pp. 157-169). Oxford: Oxford University Press.

Baddeley, A. (2007b). Long-term memory and the episodic buffer. In A. Baddeley (Ed.), *Working memory, though, and action* (pp. 139-148). Oxford: Oxford University Press.

Baddeley, A. D., Hitch, G. J., Allen, R. J. (2009). Working memory and binding in sentence recall. *Journal of Memory and Language, 61*(3), 438–456. https://doi.org/10.1016/j.jml.2009.05.004.

Baddeley, A. D., Allen, R. J., & Hitch, G. J. (2011). Binding in visual working memory: the role of the episodic buffer. *Neuropsychologia, 49*(6), 1393-1400. https://doi.org/10.1016/j.neuropsychologia.2010.12.042.

Baddeley, A., Allen, R., Vargha-Khadem, F. (2010). Is the hippocampus necessary for visual and verbal binding in working memory? *Neuropsychologia, 48*(4), 1089–1095. https://doi.org/10.1016/j.neuropsychologia.2009.12.009.

Barnett, J. H., Blackwell, A. D., Sahakian, B. J., Robbins, T. W. (2015). The Paired Associates Learning (PAL) Test: 30 Years of CANTAB Translational Neuroscience from Laboratory to Bedside in Dementia Research (pp. 449–474). Springer, Cham. https://doi.org/10.1007/7854_2015_5001.

Bastin, C. (2018). Differential age-related effects on conjunctive and relational visual short-term memory binding. *Memory, 26*(9), 1181–1190. https://doi.org/10.1080/09658211.2017.1421228.

Bays, P. M., Wu, E. Y., & Husain, M. (2011). Storage and binding of object features in visual working memory. *Neuropsychologia, 49*(6), 1622-1631. https://doi.org/10.1016/j.neuropsychologia.2010.12.023.

Bier, N., Van Der Linden, M., Gagnon, L., Desrosiers, J., Adam, S., Louveaux, S., Saint-Mleux, J. (2008). Face–name association learning in early Alzheimer's disease: A comparison of learning methods and their underlying mechanisms.

Neuropsychological Rehabilitation, 18(3), 343–371. https://doi.org/10.1080/09602010701694723.

Binetti, G., Magni, E., Padovani, A., Cappa, S. F., Bianchetti, A., Trabucchi, M. (1993). Neuropsychological Heterogeneity in Mild Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders 4*(6), 321–326. https://doi.org/10.1159/000107340.

Birch, J. (2012). Worldwide prevalence of red-green color deficiency. *Journal of the Optical Society of America, 29*(3), 313-320. https://doi.org/10.1364/JOSAA.29.000313.

Blackwell, A. D., Sahakian, B. J., Vesey, R., Semple, J. M., Robbins, T. W., Hodges, J. R. (2004). Detecting Dementia: Novel Neuropsychological Markers of Preclinical Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders, 17*(1–2), 42–48. https://doi.org/10.1159/000074081.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods, 1*(2), 97–111. https://doi.org/10.1002/jrsm.12.

Borenstein, M., Higgins, J. P. T., Hedges, L. V., Rothstein, H. R. (2017). Basics of meta-analysis: I 2 is not an absolute measure of heterogeneity. *Research Synthesis Methods, 8*(1), 5–18. https://doi.org/10.1002/jrsm.1230.

Brockmole, J. R., Logie, R. H. (2013). Age-Related Change in Visual Working Memory: A Study of 55,753 Participants Aged 8–75. *Frontiers in Psychology, 4*(1), 1–5. https://doi.org/10.3389/fpsyg.2013.00012.

Brockmole, J. R., Parra, M. A., Della Sala, S., Logie, R. H. (2008). Do binding deficits account for age-related decline in visual working memory? *Psychonomic Bulletin & Review, 15*(3), 543–547. https://doi.org/10.3758/PBR.15.3.543.

Bronnick, K., Emre, M., Lane, R., Tekin, S., Aarsland, D. (2007). Profile of cognitive impairment in dementia associated with Parkinson's disease compared with Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 78*(10), 1064–1068. https://doi.org/10.1136/jnnp.2006.108076.

Brown, L. A., Niven, E. H., Logie, R. H., Rhodes, S., Allen, R. J. (2017). Visual feature binding in younger and older adults: encoding and suffix interference effects. *Memory, 25*(2), 261–275. https://doi.org/10.1080/09658211.2016.1156705.

Buschke, H. (2014). Rationale of the memory binding test. In L. Nilsson & H. Ohta (Eds.), *Dementia and Memory* (First ed., pp. 55-71). East Sussex: Psychology Press. (Reprinted from: Not in File).

Cao, Q., Tan, C.-C., Xu, W., et al. (2020). The Prevalence of Dementia: A Systematic Review and Meta-Analysis. *J. Alzheimer's Dis., 73*, 1157–1166.

Cecchini, M. A., Yassuda, M. S., Bahia, V. S., de Souza, L. C., Guimarães, H. C., Caramelli, P., et al. (2017a). Recalling feature bindings differentiates Alzheimer's disease from frontotemporal dementia. *Journal of Neurology, 264*(10), 2162–2169. https://doi.org/10.1007/s00415-017-8614-9.

Cecchini, M. A., Yassuda, M. S., Bahia, V. S., de Souza, L. C., Guimarães, H. C., Caramelli, P., et al. (2017b). Is the specific memory binding deficit in Alzheimer's disease task-dependent? *Dement. Neuropsychol., 11*(Supl.1): p.31.

Cecchini, M. A., Yassuda, M. S., Bahia, V. S., Lima-Silva, T. B., Cassimiro, L., Cruz de Souza, L. et al. (2017c). [P2–269]: The short-term memory binding test differentiates Alzheimer's disease from behavioral variant frontotemporal dementia patients with amnestic deficits. *Alzheimer's & Dementia, 13*(7S_Part_14), P716-P717. https://doi.org/10.1016/j.jalz.2017.06.922.

Cecchini, M. A., Yassuda, M. S. (2017). Teste de memória integrativa: comparação de desempenho entre demência frontotemporal variante comportamental e doença de Alzheimer. Dissertation available from: http://www.teses.usp.br/teses/disponiveis/5/5138/tde-20022018-101250.

Cecchini, M. A., Foss, M. P., Tumas, V., Patrocinio, F. A. P., Chiari-Correia, R. D., Novaretti, N., et al. (2020). Profiles of cognitive impairment in the continuum from normal cognition to Alzheimer's clinical syndrome: Contributions of the short-term memory binding tests. *International Journal of Geriatric Psychiatry, 35*(11), 1331–1340. https://doi.org/10.1002/gps.5370.

Cecchini, M. A., Yassuda, M. S., Squarzoni, P., Coutinho, A. M., de Paula Faria, D., Duran, F.L.S., et al. (2021). Deficits in short-term memory binding are detectable in individuals with brain amyloid deposition in the absence of overt neurodegeneration in the Alzheimer's disease continuum. *Brain and Cognition, 152*, 105749. https://doi.org/10.1016/j.bandc.2021.105749.

Chen, T., Naveh-Benjamin, M. (2012). Assessing the associative deficit of older adults in long-term and short-term/working memory. *Psychology and Aging, 27*(3), 666–682. https://doi.org/10.1037/a0026943.

Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). New York: Hillsdale.

Cooper, H., Hedges, L.V., Valentine, J.C. (2009). The handbook of research synthesis and meta-analysis (2nd edition). In: The Hand. of Res. Synthesis and Meta-Analysis, 2nd Ed. Russell Sage Foundation.

Costa, A., Bak, T., Caffarra, P., Caltagirone, C., Ceccaldi, M., Collette, F., et al. (2017). The need for harmonisation and innovation of neuropsychological assessment in

neurodegenerative dementias in Europe: consensus document of the Joint Program for Neurodegenerative Diseases Working Group. *Alzheimer's Research & Therapy, 9*(1), 1-15. https://doi.org/10.1186/s13195-017-0254-x.

Cowan, N. (2001). The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *The Behavioral and Brain Sciences, 24*(1), 87–114; discussion 114-85. https://doi.org/10.1017/s0140525x01003922.

Cowan, N., Naveh-Benjamin, M., Kilb, A., Saults, J. S. (2006). Life-span development of visual working memory: when is feature binding difficult? *Developmental Psychology, 42*(6), 1089–1102. https://doi.org/10.1037/0012-1649.42.6.1089.

Cowan, N. (2010). The Magical Mystery Four: How Is Working Memory Capacity Limited, and Why? *Current Directions in Psychological Science, 19*(1), 51–57. https://doi.org/10.1177/0963721409359277.

Della Sala, S., Foley, J. A., Parra, M. A., Logie, R. H. (2011). Dual tasking and memory binding in Alzheimer's. *Journal of Alzheimer Disease*, *23*, s22-s24. https://doi.org/10.3233/JAD-2010-1433.

Della Sala, S., Parra, M. A., Fabi, K., Luzzi, S., Abrahams, S. (2012). Short-term memory binding is impaired in AD but not in non-AD dementias. *Neuropsychologia, 50*(5), 833-840. https://doi.org/10.1016/j.neuropsychologia.2012.01.018.

Della Sala, S., Kozlova, I., Stamate, A., Parra, M. A. (2016). A transcultural cognitive marker of Alzheimer's Disease. *International Journal of Geriatric Psychiatry, 33*, 849-856. https://doi.org/10.1002/gps.4610.

Della Sala, S., & Morris, R. (2020). When no more research is needed (without further reflection). *Cortex*, *123*, A1. https://doi.org/10.1016/j.cortex.2019.12.018

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., et al. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia, 12*(3), 292–323. https://doi.org/10.1016/j.jalz.2016.02.002.

Ezzyat, Y., Olson, I. R. (2008). The medial temporal lobe and visual working memory: Comparisons across tasks, delays, and visual similarity. *Cognitive, Affective, & Behavioral Neuroscience, 8*(1), 32–40. https://doi.org/10.3758/CABN.8.1.32.

Fabbri, S., Silva, C., Hernandes, E., Octaviano, F., Di Thommazo, A., Belgamo, A. (2016). Improvements in the StArt tool to better support the systematic review process. In Proceedings of the 20th International Conference on Evaluation and Assessment in Software Engineering - EASE'16, 1–5. New York, New York, USA: ACM Press. https://doi.org/10.1145/2915970.2916013.

Fandakova, Y., Sander, M.C., Werkle-Bergner, M., Shing, Y. L. (2014). Age differences in short-term memory binding are related to working memory performance across the lifespan. *Psychology and Aging, 29*(1), 140–149. https://doi.org/10.1037/a0035347.

Fernández, G., Orozco, D., Agamennoni, O., Schumacher, M., Sañudo, S., Biondi, J., Parra, M. A. (2018). Visual Processing during Short-Term Memory Binding in Mild Alzheimer's Disease. *Journal of Alzheimer's Disease, 63*(1), 185–194. https://doi.org/10.3233/JAD-170728.

Fernández, G., Parra, M. A. (2021). Oculomotor Behaviors and Integrative Memory Functions in the Alzheimer's Clinical Syndrome. *Journal of Alzheimer's Disease, 82*(3), 1033-1044. https://doi.org/10.3233/JAD-201189.

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., et al. (2005). Global prevalence of dementia: a Delphi consensus study. *The Lancet, 366*(9503), 2112–2117. https://doi.org/10.1016/S0140-6736(05)67889-0.

Filippi, M., Agosta, F., Scola, E., Canu, E., Magnani, G., Marcone, A., et al. (2013). Functional network connectivity in the behavioral variant of frontotemporal dementia. *Cortex, 49*(9), 2389–2401. https://doi.org/10.1016/j.cortex.2012.09.017.

Fuller, J. T., Cronin-Golomb, A., Gatchel, J. R., Norton, D. J., Guzmán-Vélez, E., Jacobs, H. I. L., et al. (2019). Biological and Cognitive Markers of Presenilin1 E280A Autosomal Dominant Alzheimer's Disease: A Comprehensive Review of the Colombian Kindred. *The Journal of Prevention of Alzheimer's Disease, 6*(2), 112–120. https://doi.org/10.14283/jpad.2019.6.

Galluzzi, S., Geroldi, C., Amicucci, G., Bocchio-Chiavetto, L., Bonetti, M., Bonvicini, C., et al. (2013). Supporting evidence for using biomarkers in the diagnosis of MCI due to AD. *Journal of Neurology, 260*(2), 640–650. https://doi.org/10.1007/s00415-012-6694-0.

Ganguli, M., Snitz, B. E., Saxton, J. A., Chang, C.-C. H., Lee, C.-W., Vander Bilt, J., et al. (2011). Outcomes of Mild Cognitive Impairment by Definition. *Archives of Neurology, 68*(6), 761-767. https://doi.org/10.1001/archneurol.2011.101.

Gold, J. J., Hopkins, R. O., Squire, L. R. (2006). Single-item memory, associative memory, and the human hippocampus. *Learning & Memory, 13*(5), 644–649. https://doi.org/10.1101/lm.258406.

Grande, G., Cucumo, V., Cova, I., Ghiretti, R., Maggiore, L., Lacorte, E., et al. (2016). Reversible Mild Cognitive Impairment: The Role of Comorbidities at Baseline Evaluation. *Journal of Alzheimer's Disease, 51*(1), 57–67. https://doi.org/10.3233/JAD-150786.

Guazzo, F., Allen, R. J., Baddeley, A. D., Della Sala, S. (2020). Unimodal and crossmodal working memory binding is not differentially affected by age or Alzheimer's disease. *Neuropsychology, 34*(4), 420–436. https://doi.org/10.1037/neu0000622.

Guyatt, G. H., Oxman, A.D., Schünemann, H. J., Tugwell, P., Knottnerus, A. (2011). GRADE guidelines: A new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology, 64*(4), 380–382. https://doi.org/10.1016/j.jclinepi.2010.09.011.

Hakim, N., Awh. E., & Vogel, E. K. (2021). Manifold visual working memory. In R.H. Logie, V. Camos, & N. Cowan (eds.) *Working Memory: State of the Science*. Oxford, UK: Oxford University Press.

Hannula, D. E., Tranel, D., Cohen, N. J. (2006). The Long and the Short of It: Relational Memory Impairments in Amnesia, Even at Short Lags. *Journal of Neuroscience, 26*(32), 8352–8359. https://doi.org/10.1523/JNEUROSCI.5222-05.2006.

Heinen, K., Sagliano, L., Candini, M., Husain, M., Cappelletti, M., & Zokaei, N. (2016). Cathodal transcranial direct current stimulation over posterior parietal cortex enhances distinct aspects of visual working memory. *Neuropsychologia, 87*, 35-42. https://doi.org/10.1016/j.neuropsychologia.2016.04.028.

Higgins, J. P. T., Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine, 21*(11), 1539–1558. https://doi.org/10.1002/sim.1186.

Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.). (2019). Cochrane handbook for systematic reviews of interventions (2nd edition). John Wiley & Sons.

Hitch, G. J., Allen, R. J., & Baddeley, A. D. (2020). Attention and binding in visual working memory: Two forms of attention and two kinds of buffer storage. *Attention,*

Perception & Psychophysics, 82(1), 280-293. https://doi.org/10.3758/s13414-019-01837-x.

Hoefeijzers, S., Gonzalez, H. A., Magnolia, R. A., & Parra, M. A. (2017). Feature Binding of Common Everyday Items Is Not Affected by Age. *Front Aging Neurosci, 9*, 122. https://doi.org/10.3389/fnagi.2017.00122.

Hollingworth, A., & Rasmussen, I. P. (2010). Binding objects to locations: the relationship between object files and visual working memory. *J. Exp. Psychol. Hum. Percept. Perform, 36*(3), 543-564. https://doi.org/10.1037/a0017836.

Holmes, C. (2002). Genotype and phenotype in Alzheimer's disease. *The British Journal of Psychiatry, 180*, 131-134.

Hornberger, M., Piguet, O., Graham, A. J., Nestor, P. J., Hodges, J. R. (2010). How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology, 74*(6), 472–479. https://doi.org/10.1212/WNL.0b013e3181cef85d.

Huedo-Medina, T. B., Sánchez-Meca, J., Marín-Martínez, F., Botella, J. (2006). Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychological Methods, 11* (2), 193–206. https://doi.org/10.1037/1082-989X.11.2.193.

Isella, V., Molteni, F., Mapelli, C., Ferrarese, C. (2015). Short term memory for single surface features and bindings in ageing: A replication study. *Brain and Cognition, 96*, 38–42. https://doi.org/10.1016/j.bandc.2015.02.002.

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease. *Alzheimer’s & Dementia, 14*(4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018.

Jefferies, E., Frankish, C.R., Lambon Ralph, M. A. (2006). Lexical and semantic binding in verbal short-term memory. *Journal of Memory and Language, 54*(1), 81–98. https://doi.org/10.1016/j.jml.2005.08.001.

Jeneson, A., Wixted, J.T., Hopkins, R. O., Squire, L. R. (2012). Visual Working Memory Capacity and the Medial Temporal Lobe. *Journal of Neuroscience, 32*(10), 3584–3589. https://doi.org/10.1523/JNEUROSCI.6444-11.2012.

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., et al. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & Dementia, 10*(6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001.

Jonin, P.-Y., Calia, C., Muratot, S., Belliard, S., Duché, Q., Barbeau, E.J., Parra, M. A. (2019). Refining understanding of working memory buffers through the construct of binding: Evidence from a single case informs theory and clinical practise. *Cortex, 112*, 37–57. https://doi.org/10.1016/j.cortex.2018.08.011.

Kan, I. P., Giovanello, K.S., Schnyer, D. M., Makris, N., Verfaellie, M. (2007). Role of the medial temporal lobes in relational memory: Neuropsychological evidence from a cued recognition paradigm. *Neuropsychologia, 45*(11), 2589–2597. https://doi.org/10.1016/j.neuropsychologia.2007.03.006.

Kaschel, R., Logie, R.H., Kazén, M & Della Sala, S. (2009). Alzheimer's Disease, but not ageing or chronic depression, affects dual-tasking. *Journal of Neurology*, *256*, 1860–1868. https://doi.org/10.1007/s00415-009-5210-7.

Killin, L., Abrahams, S., Parra, M. A., Della Sala, S. (2018). The effect of age on the FCSRT-IR and temporary visual memory binding. *International Psychogeriatrics, 30*(3), 331–340. https://doi.org/10.1017/S104161021700165X.

Kirmsse, A., Zimmer, H. D., Ecker, U.K.H. (2018). Age-related changes in working memory: Age affects relational but not conjunctive feature binding. *Psychology and Aging, 33* (3), 512–526. https://doi.org/10.1037/pag0000249.

Koppara, A., Wagner, M., Lange, C., Ernst, A., Wiese, B., König, H.-H., et al. (2015a). Cognitive performance before and after the onset of subjective cognitive decline in old age. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 1* (2), 194–205. https://doi.org/10.1016/j.dadm.2015.02.005.

Koppara, A., Frommann, I., Polcher, A., Parra, M. A., Maier, W., Jessen, F., et al. (2015b). Feature Binding Deficits in Subjective Cognitive Decline and in Mild Cognitive Impairment. *Journal of Alzheimer's Disease, 48*(S1), S161–S170. https://doi.org/10.3233/JAD-150105.

Kozlova, I., Parra, M.A., Titova, N., Gantman, M., Della Sala, S. (2020). Alzheimer's Disease and Parkinson Dementia Distinguished by Cognitive Marker. *Archives of Clinical Neuropsychology, 36*(3), 307–315. https://doi.org/10.1093/arclin/acz082.

Lam, B., Masellis, M., Freedman, M., Stuss, D.T., Black, S. E. (2013). Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. *Alzheimer's Research & Therapy, 5* (1), 1. https://doi.org/10.1186/alzrt155.

Liang, Y., Pertzov, Y., Nicholas, J. M., Henley, S., Crutch, S., Woodward, F., Leung, K., Fox, N. C., & Husain, M. (2016). Visual short-term memory binding deficit in familial Alzheimer's disease. *Cortex, 78*, 150–164. https://doi.org/10.1016/j.cortex.2016.01.015.

Livingstone, M., Hubel, D. (1988). Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science, 240*(4853), 740–749. https://doi.org/10.1126/science.3283936.

Logie, R. H., Cocchini, G., Della Sala, S., Baddeley, A. D. (2004). Is there a specific executive capacity for dual task co-ordination? Evidence from Alzheimer's Disease. *Neuropsychology, 18*, 504-513. https://doi.org/10.1037/0894-4105.18.3.504.

Logie, R. H., Brockmole, J. R., Vandenbroucke, A. (2009). Bound feature combinations in visual short-term memory are fragile but influence long-term learning. *Visual Cognition, 17*, 160-179. https://doi.org/10.1080/13506280802228411.

Logie, R.H. & Morris, R.G. (Eds.) (2015). Working Memory and Ageing. Hove, UK: Psychology Press.

Logie, R., Parra, M. A., Della Sala, S. (2015). From Cognitive Science to Dementia Assessment. *Policy Insights from the Behavioral and Brain Sciences, 2*(1), 81–91. https://doi.org/10.1177/2372732215601370.

Lopera, F., Ardilla, A., Martínez, A., Madrigal, L., Arango-Viana, J.C., Lemere, C.A., et al. (1997). Clinical Features of Early-Onset Alzheimer Disease in a Large Kindred With an E280A Presenilin-1 Mutation. *JAMA, 277*(10), 793-799. https://doi.org/10.1001/jama.1997.03540340027028.

Luck, S. J., Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature, 390*(6657), 279–281. https://doi.org/10.1038/36846.

Luck, S. J., & Vogel, E. K. (2013). Visual working memory capacity: from psychophysics and neurobiology to individual differences. *Trends in Cognitive Sciences, 17*(8), 391-400. https://doi.org/10.1016/j.tics.2013.06.006.

Martínez-Florez, J. F., Osorio, J. D., Cediel, J. C., Rivas, J. C., Granados-Sánchez, A. M., López-Peláez, J., et al. (2021). Short-Term Memory Binding Distinguishing Amnestic Mild Cognitive Impairment from Healthy Aging: A Machine Learning Study. *Journal of Alzheimer's Disease, 81* (2), 729–742. https://doi.org/10.3233/JAD-201447.

Martínez, J. F., Trujillo, C., Arévalo, A., Ibáñez, A., Cardona, J.F. (2019). Assessment of Conjunctive Binding in Aging: A Promising Approach for Alzheimer's Disease Detection. *Journal of Alzheimer's Disease, 69* (1), 71–81. https://doi.org/10.3233/JAD-181154.

Martorelli, M., Sudo, F. K., Charchat-Fichman, H. (2019). This is not only about memory: A systematic review on neuropsychological heterogeneity in Alzheimer's disease. *Psychology & Neuroscience, 12* (2), 271–281. https://doi.org/10.1037/pne0000149.

Mayes, A., Montaldi, D., Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Sciences, 11*(3), 126–135. https://doi.org/10.1016/j.tics.2006.12.003.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology,* (34), 939–44. https://doi.org/10.1212/WNL.34.7.939.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.

Mitchell, K. J., Johnson, M. K., Raye, C. L., Mather, M., D'Esposito, M., Mitchell, et al. (2000). Aging and reflective processes of working memory: Binding and test load deficits. *Psychology and Aging, 15*(3), 527–541. https://doi.org/10.1037/0882-7974.15.3.527.

Mitchell, A. J., Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia - meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica, 119*(4), 252–265. https://doi.org/10.1111/j.1600-0447.2008.01326.x.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine, 6* (7), e1000097. https://doi.org/10.1371/journal.pmed.1000097.

Monti, J. M., Cooke, G. E., Watson, P. D., Voss, M. W., Kramer, A. F., Cohen, N. J. (2015). Relating Hippocampus to Relational Memory Processing across Domains and Delays. *Journal of Cognitive Neuroscience, 27*(2), 234–245. https://doi.org/10.1162/jocn_a_00717.

Moses, S. N., Cole, C., & Ryan, J. D. (2005). Relational memory for object identity and spatial location in rats with lesions of perirhinal cortex, amygdala and hippocampus. *Brain Research Bulletin, 65*(6), 501-512. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15862922

Moses, S. N., Ryan, J. D. (2006). A comparison and evaluation of the predictions of relational and conjunctive accounts of hippocampal function. *Hippocampus, 16*(1), 43–65. https://doi.org/10.1002/hipo.20131.

Naveh-Benjamin, M., Brav, T. K., Levy, O. (2007). The associative memory deficit of older adults: The role of strategy utilization. *Psychology and Aging, 22*(1), 202–208. https://doi.org/10.1037/0882-7974.22.1.202.

Naveh-Benjamin, M., Guez, J., Kilb, A., Reedy, S. (2004a). The Associative Memory Deficit of Older Adults: Further Support Using Face-Name Associations. *Psychology and Aging, 19*(3), 541–546. https://doi.org/10.1037/0882-7974.19.3.541.

Naveh-Benjamin, M., Guez, J., Shulman, S. (2004b). Older adults' associative deficit in episodic memory: Assessing the role of decline in attentional resources. *Psychonomic Bulletin & Review, 11*(6), 1067–1073. https://doi.org/10.3758/BF03196738.

Nichols, E. A., Kao, Y.-C., Verfaellie, M., Gabrieli, J. D. E. (2006). Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. *Hippocampus, 16*(7), 604–616. https://doi.org/10.1002/hipo.20190.

Norton, D. J., Parra, M. A., Sperling, R. A., Baena, A., Guzman-Velez, E., Jin, D. S., et al. (2020). Visual short-term memory relates to tau and amyloid burdens in preclinical autosomal dominant Alzheimer's disease. *Alzheimer's Research & Therapy, 12*(1), 99. https://doi.org/10.1186/s13195-020-00660-z.

Old, S. R., Naveh-Benjamin, M. (2008). Differential effects of age on item and associative measures of memory: A meta-analysis. *Psychology and Aging, 23*(1), 104–118. https://doi.org/10.1037/0882-7974.23.1.104.

Olsen, R. K., Moses, S. N., Riggs, L., Ryan, J. D. (2012). The hippocampus supports multiple cognitive processes through relational binding and comparison. *Frontiers in Human Neuroscience, 6,* 1-13. https://doi.org/10.3389/fnhum.2012.00146.

Olson, I. R., Page, K., Moore, K. S., Chatterjee, A., Verfaellie, M. (2006). Working Memory for Conjunctions Relies on the Medial Temporal Lobe. *Journal of Neuroscience, 26*(17), 4596-4601. https://doi.org/10.1523/JNEUROSCI.1923-05.2006.

Overton, M., Pihlsgård, M., Elmståhl, S. (2019). Diagnostic Stability of Mild Cognitive Impairment, and Predictors of Reversion to Normal Cognitive Functioning. *Dementia and Geriatric Cognitive Disorders, 48*(5–6), 317–329. https://doi.org/10.1159/000506255.

Parra, M. A., Della Sala, S., Logie, R. H., Abrahams, S. (2009a). Selective impairment in visual short-term memory binding. *Cognitive Neuropsychology, 26*(7), 583-605. https://doi.org/10.1080/02643290903523286.

Parra, M.A., Abrahams, S., Fabi, K., Logie, R., Luzzi, S., Della Sala, S. (2009b). Short-term memory binding deficits in Alzheimer's disease. *Brain, 132*(4), 1057–1066. https://doi.org/10.1093/brain/awp036.

Parra, M. A., Abrahams, S., Logie, R. H., Méndez, L. G., Lopera, F., Della Sala, S. (2010a). Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain, 133*(9), 2702-2713. https://doi.org/10.1093/brain/awq148.

Parra, M. A., Abrahams, S., Logie, R. H., Della Sala, S. (2010b). Visual short-term memory binding in Alzheimer's disease and depression. *Journal of Neurology, 257*(7), 1160–1169. https://doi.org/10.1007/s00415-010-5484-9.

Parra, M. A., Cubelli, R., Della Sala, S. (2011a). Lack of color integration in visual short-term memory binding. *Memory & Cognition, 39*(7), 1187–1197. https://doi.org/10.3758/s13421-011-0107-y.

Parra, M. A., Della Sala, S., Abrahams, S., Logie, R. H., Méndez, L.G., Lopera, F. (2011b). Specific deficit of colour–colour short-term memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia, 49*(7), 1943-1952. https://doi.org/10.1016/j.neuropsychologia.2011.03.022.

Parra, M. A., Della Sala, S., Logie, R. H., Morcom, A. M. (2014). Neural correlates of shape-color binding in visual working memory. *Neuropsychologia, 52*(1), 27–36. https://doi.org/10.1016/j.neuropsychologia.2013.09.036.

Parra, M. A., Fabi, K., Luzzi, S., Cubelli, R., Hernandez Valdez, M., Della Sala, S. (2015a). Relational and conjunctive binding functions dissociate in short-term memory. *Neurocase, 21*(1), 56–66. https://doi.org/10.1080/13554794.2013.860177.

Parra, M. A., Saarimäki, H., Bastin, M. E., Londoño, A. C., Pettit, L., Lopera, F., et al. (2015b). Memory binding and white matter integrity in familial Alzheimer's disease. *Brain, 138*(5), 1355-1369. https://doi.org/10.1093/brain/awv048.

Parra, M. A., Mikulan, E., Trujillo, N., Della Sala, S., Lopera, F., Manes, F., et al. (2017a). Brain Information Sharing During Visual Short-Term Memory Binding Yields a Memory Biomarker for Familial Alzheimer's Disease. *Current Alzheimer Research, 14*(12), 1335-1347. https://doi.org/10.2174/1567205014666170614163316.

Parra, M. A., Gazes, Y., Stern, Y. (2017b). [P2-214]: From cognition to molecules: tracking brain amyloid-β with memory markers for Alzheimer's disease. *Alzheimer's & Dementia, 13*(7S_Part_14), P692–P692. https://doi.org/10.1016/j.jalz.2017.06.866.

Parra, M. A., Calia, C., García, A. F., Olazarán-Rodríguez, J., Hernandez-Tamames, J. A., Alvarez-Linera, J., et al. (2019). Refining memory assessment of elderly people with cognitive impairment: Insights from the short-term memory binding test. *Archives of Gerontology and Geriatrics, 83*, 114–120. https://doi.org/10.1016/j.archger.2019.03.025.

Pavisic, I. M., Suarez-Gonzalez, A., Pertzov, Y. (2020). Translating Visual Short-Term Memory Binding Tasks to Clinical Practice: From Theory to Practice. *Frontiers in Neurology, 11*, 1-5. https://doi.org/10.3389/fneur.2020.00458.

Pertzov, Y., Heider, M., Liang, Y., Husain, M. (2015). Effects of healthy ageing on precision and binding of object location in visual short term memory. *Psychology and Aging, 30*(1), 26–35. https://doi.org/10.1037/a0038396.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*(3), 183–194. https://doi.org/10.1111/j.1365-2796.2004.01388.x.

Peterson, D. J., Naveh-Benjamin, M. (2016). The role of aging in intra-item and item-context binding processes in visual working memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 42*(11), 1713–1730. https://doi.org/10.1037/xlm0000275.

Piekema, C., Rijpkema, M., Fernández, G., Kessels, R. C. (2010). Dissociating the neural correlates of intra-item and inter-item working-memory binding. *PLoS ONE, 5*(4), 1–8. https://doi.org/10.1371/journal.pone.0010214.

Pietto, M., Parra, M. A., Trujillo, N., Flores, F., García, A. M., Bustin, J., et al. (2016). Behavioral and Electrophysiological Correlates of Memory Binding Deficits in Patients at Different Risk Levels for Alzheimer's Disease. *Journal of Alzheimer's Disease, 53*(4), 1325-1340. https://doi.org/10.3233/JAD-160056.

Prince, M., Knapp, M., Guerchet, M., Mccrone, P., Prina, M., Comas Herrera, A., et al. (2014). Dementia UK: update. https://doi.org/10.13140/2.1.3629.3446.

Read, C. A., Rogers, J. M., Wilson, P. H. (2016). Working memory binding of visual object features in older adults. *Aging, Neuropsychology, and Cognition, 23*(3), 263-281. https://doi.org/10.1080/13825585.2015.1083937.

Reisberg, B., Shulman, M. B., Torossian, C., Leng, L., Zhu, W. (2010). Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimer's & Dementia, 6*(1), 11–24. https://doi.org/10.1016/j.jalz.2009.10.002.

Reitz, C., Mayeux, R. (2014). Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochemical Pharmacology, 88*(4), 640–651. https://doi.org/10.1016/j.bcp.2013.12.024.

Rentz, D. M., Parra Rodriguez, M. A., Amariglio, R., Stern, Y., Sperling, R., Ferris, S. (2013). Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: a selective review. *Alzheimer's Research & Therapy, 5*(6), 1-10. https://doi.org/10.1186/alzrt222.

Richardson, M., Garner, P., Donegan, S. (2019). Interpretation of subgroup analyses in systematic reviews: A tutorial. *Clinical Epidemiology and Global Health, 7*(2), 192–198. https://doi.org/10.1016/j.cegh.2018.05.005.

Roberts, R., Knopman, D.S. (2013). Classification and epidemiology of MCI. *Clinics in Geriatric Medicine, 29*(4), 753–772. https://doi.org/10.1016/j.cger.2013.07.003.

Rockwood, K. (2004). Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 75*(5), 677-685. https://doi.org/10.1136/jnnp.2003.029074.

Rouder, J. N., Morey, R. D., Morey, C. C., & Cowan, N. (2011). How to measure working memory capacity in the change detection paradigm. *Psychon. Bull. Rev, 18*(2), 324-330. https://doi.org/10.3758/s13423-011-0055-3.

Schneegans, S., Bays, P. M. (2019). New perspectives on binding in visual working memory. *Br. J. Psychol. 110*, 207–244. https://doi.org/10.1111/bjop.12345.

Schwarzer, G. (2007). meta: An R package for meta-analysis. R News 7 (3), 40–45.

Seeley, W. W., Crawford, R., Rascovsky, K., Kramer, J. H., Weiner, M., Miller, B. L., Gorno-Tempini, M. L. (2008). Frontal Paralimbic Network Atrophy in Very Mild

Behavioral Variant Frontotemporal Dementia. *Archives of Neurology, 65*(2), 249–255. https://doi.org/10.1001/archneurol.2007.38.

Shafritz, K. M., Gore, J. C., & Marois, R. (2002). The role of the parietal cortex in visual feature binding. *Proceedings of the National Academy of Sciences of the United States of America, 99*(16), 10917–10922. https://doi.org/10.1073/pnas.152694799.

Shimi, A., Logie, R. H. (2019). Feature binding in short-term memory and long-term learning. *Quarterly Journal of Experimental Psychology, 72*, 1387-1400. https://doi-org.ezproxy.is.ed.ac.uk/10.1177/1747021818807718.

Song, J.-H., Jiang, Y. (2006). Visual working memory for simple and complex features: An fMRI study. *NeuroImage, 30*(3), 963–972. https://doi.org/10.1016/j.neuroimage.2005.10.006.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003.

Sperling, R. A., Karlawish, J., & Johnson, K. A. (2013). Preclinical Alzheimer disease – the challenges ahead. *Nat Rev Neurol, 9*(1), 54-58. https://doi.org/10.1038/nrneurol.2012.241.

Stanislaw, H., & Todorov, N. (1999). Calculation of signal detection theory measures. *Behavior Research Methods, Instruments, & Computers: a Journal of the Psychonomic Society, Inc*, *31*(1), 137–149. https://doi.org/10.3758/bf03207704.

Staresina, B. P., Davachi, L. (2010). Object Unitization and Associative Memory Formation Are Supported by Distinct Brain Regions. *Journal of Neuroscience, 30*(29), 9890–9897. https://doi.org/10.1523/JNEUROSCI.0826-10.2010.

Sterne, J. A., Hernán, M. A., Reeves, B.C., Savović, J., Berkman, N. D., Viswanathan, M., et al. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ,* (355), i4919. https://doi.org/10.1136/bmj.i4919.

Todd, J. J., & Marois, R. (2005). Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity. *Cognitive, Affective & Behavioral Neuroscience*, *5*(2), 144–155. https://doi.org/10.3758/cabn.5.2.144.

Valdés Hernández, M. C., Clark, R., Wang, S.-H., Guazzo, F., Calia, C., Pattan, V., et al. (2020). The striatum, the hippocampus, and short-term memory binding: Volumetric analysis of the subcortical grey matter's role in mild cognitive impairment. *NeuroImage: Clinical, 25*, 102158. https://doi.org/10.1016/j.nicl.2019.102158.

van den Berg, E., Poos, J. M., Jiskoot, L. C., Heijnen, L. M., Franzen, S., Steketee, R. M. E., et al. (2020). Differences in Discriminability and Response Bias on Rey Auditory Verbal Learning Test Delayed Recognition in Behavioral Variant Frontotemporal Dementia and Alzheimer's Disease. *Journal of the International Neuropsychological Society, 26*(9), 918-926. https://doi.org/10.1017/S1355617720000375.

van Geldorp, B., Parra, M. A., Kessels, R. P. C. (2015). Cognitive and neuropsychological underpinnings of relational and conjunctive working memory binding across age. *Memory, 23*(8), 1112-1122. https://doi.org/10.1080/09658211.2014.953959.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., van Paesschen, W., Mishkin, M. (1997). Differential Effects of Early Hippocampal Pathology on Episodic and Semantic Memory. *Science, 277*(5324), 376–380. https://doi.org/10.1126/science.277.5324.376.

Vogel, E. K., Woodman, G. F., Luck, S. J. (2001). Storage of features, conjunctions, and objects in visual working memory. *Journal of Experimental Psychology: Human Perception and Performance, 27*(1), 92–114. https://doi.org/10.1037/0096-1523.27.1.92.

Wheeler, M. E., Treisman, A. M. (2002). Binding in short-term visual memory. *Journal of Experimental Psychology: General, 131*(1), 48-64. https://doi.org/10.1037//0096-3445.131.1.48.

Wilkinson, D.G., Francis, P.T., Schwam, E., Payne-Parrish, J. (2004). Cholinesterase Inhibitors Used in the Treatment of Alzheimer's Disease. *Drugs & Aging, 21*(7), 453–478. https://doi.org/10.2165/00002512-200421070-00004.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment–beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med, 256*, 240-246. https://doi.org/10.1111/j.1365-2796.2004.01380.x.

Xu, Y. (2007). The Role of the Superior Intraparietal Sulcus in Supporting Visual Short-Term Memory for Multifeature Objects. *Journal of Neuroscience, 27*(43), 11676–11686. https://doi.org/10.1523/JNEUROSCI.3545-07.2007.

Xu, Y. (2002). Encoding color and shape from different parts of an object in visual short-term memory. *Perception & Psychophysics, 64*(8), 1260–1280. https://doi.org/10.3758/BF03194770.

Yassuda, M. S., Cecchini, M. A., Foss, M. P., Souza, L., Nitrini, R., Della Sala, S., Parra, M. A. (2018). Comparing the change detection and free recall modalities in the short-term memory binding test. *Journal of the American Geriatrics Society, 66* (suppl.2, Special Issue), p.S93-S93.

Yassuda, M. S., Carthery-Goulart, M. T., Cecchini, M. A., Cassimiro, L., Fernandes, K. D., Baradel, R.R., et al. (2020). Free Recall of Bound Information Held in Short-Term Memory is Unimpaired by Age and Education. *Archives of Clinical Neuropsychology, 35*(2), 165–175. https://doi.org/10.1093/arclin/acz015.

Yonelinas, A. P., 2013. The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory. *Behavioural Brain Research, 254*, 34–44. https://doi.org/10.1016/j.bbr.2013.05.030.

Yu, M., Gouw, A. A., Hillebrand, A., Tijms, B. M., Stam, C.J., van Straaten, E. C. W., Pijnenburg, Y. A. L. (2016). Different functional connectivity and network topology in behavioral variant of frontotemporal dementia and Alzheimer's disease: an EEG study. *Neurobiology of Aging, 42*, 150–162. https://doi.org/10.1016/j.neurobiolaging.2016.03.018.

Zimmer, H.D., Mecklinger, A., & Lindenberger, U. (2006). Handbook of Binding and Memory. Oxford, UK: Oxford University Press.

Tables

Table 1. Summary of findings for the main comparisons. The clinical use of short-term memory bindi

Patient or population: patients with Alzheimer's disease (AD)

Setting: clinical setting in primary or secondary healthcare practices

Comparison: controls and AD patients assessed using the short-term memory binding test

Outcomes		**Effect size (95% CI)**	**Number of participants (studies)**	**Quality o evidence (GRADE**
Preclinical AD and subjective cognitive decline	Single feature condition	-0.33 (-0.59; -0.07)	241 (5)	⊕⊕⊕◯ Moderate
	Feature binding condition	-1.10 (-1.48; -0.73)	241 (5)	
Mild cognitive impairment	Single feature condition	-1.08 (-1.35; -0.81)	628 (8)	⊕⊕⊕◯ Moderate
	Feature binding condition	-1.07 (-1.32; -0.82)	928 (9)	
AD in dementia stage	Single feature condition	-1.18 (-1.61; -0.76)	675 (11)	⊕⊕⊕◯ Moderate
	Feature binding condition	-2.41 (-2.82; -1.99)	764 (13)	

CI: confidence interval; Effect Size was measured using the Hedges' g formula.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate o estimate.

Very low quality: We are very uncertain about the estimate.

Table 2. Characteristics of included studies.

	STM binding modality	Sample	N	Age Mean(SD)	Education Mean(SD)	Items per trial	Trials	Study / encoding time	Single feature condition	M
	Change detection	HC	30	40.9(9.3)	9.5(3.2)	3	32	2000	Shape-only	Perce corre and A
		AC	30	35.6(6.6)	9.3(4.4)	3				
	Change detection (color-color)	HC_2	29	39.55(8.82)	9.21(2.90)	3	32	2000	Colors-only	Perce corre
		AC	25	37.24(5.21)	9.12(3.68)	3				
al.,	Change Detection	HC	23	68.00(8.31)	14.39(3.07)	3	32	2000	Shape-only	Hit m alarm
		SCD	19	66.79(7.58)	16.53(3.03)	3				
	Change detection	HC	21	39.30(83)	10.30(27)	3	32	2000	Shape-only	Perce corre
		AC	18	35.10(5.5)	10.20(3.9)	3				
.,	Change detection	HC	27	37.0(6.5)	9.9(4.1)	3	32	2000	Shape-only	A’
		AC	19	37.5(6.5)	11.4(3.8)	3				
al.,	Change detection	HC	23	68.00(8.31)	14.39(3.07)	3	32	2000	Shape-only	Hit m alarm
		MCI	23	72.82(4.37)	13.27(2.96)	3				
2016	Change detection	HC	14	67.21(10.14)	16.50(1.99)	3	100	500	Shape-only	Hit m alarm
		HC_2	10	44.30(5.60)	11.30(13.90)	3				
		MCI	13	73.08(9.01)	14.08(4.44)	3				
		MCI-FAD	10	44.40(3.20)	7.30(4.10)	3				
	Change detection	HC	10	44.30(5.60)	11.30(13.90)	3	100	500	Shape-only	Hit m alarm
		MCI-FAD	10	44.40(3.20)	7.30(4.10)	3				
2019		HC	25	74.73(4.74)	10.84(5.02)	2	32	2000	Shape-only	

	Change detection	HC_2	29	72.34(3.76)	11.00(5.11)	3				
		MCI	27	75.07(5.30)	10.86(5.80)	2				Perce corre
		MCI_2	23	75.43(5.77)	9.43(2.90)	3				
et al.,	Change detection	HC	25	76.24(5.37)	15.08(3.58)	3	32	2000	Shape-only	Perce corre
		MCI	21	74.00(5.49)	13.57(3.88)	2				
al.,	Change Detection	HC	23	67.83(6.06)	12.83(4.06)	2	32	2000	Shapes and colors	Perce corre
		MCI	24	70.33(6.89)	9.54(5.82)	2				
al.,	Free Recall	HC	21	67.83(6.06)	12.83(4.06)	3	6	9000	Objects and Colors	Perce corre
		MCI	24	70.33(6.89)	9.54(5.82)	3				
.,	Change detection	HC	27	37.0(6.5)	9.9(4.1)	3	32	2000	Shape-only	A’
		MCI-FAD	6	44.8(1.4)	9.3(3.4)	3				
ores	Change Detection	HC	109	66.53(7.15)	12.55(4.07)	2	32	2000	Shape-only	Perce corre
		HC	109	66.53(7.15)	12.55(4.07)	3				
		HC_2	38	66.10(7.12)	13.81(4.05)	2				
		HC_2	38	66.10(7.12)	13.81(4.05)	3				
		MCI	45	68.33(7.09)	11.28(3.67)	2				
		MCI	45	68.33(7.09)	11.28(3.67)	3				
		MCI_2	18	67.83(6.33)	12.38(3.58)	2				
		MCI_2	18	67.83(6.33)	12.38(3.58)	3				
al.,	Change Detection	HC	18	72.39(5.84)	12.33(4.97)	2	16	2000	None (only bound condition)	Numb corre
		MCI	30	73.67(4.69)	9.57(4.76)	2				
	Free recall	HC	23	69.78(6.47)	7.08(2.81)	3	6	9000	Objects and Colors	Perce corre
		HC_2	20	69.35(6.02)	7.25(2.97)	4		12000		
		AD	23	73.26(6.09)	6.39(3.34)	2		3000		
		AD	21	73.33(6.71)	6.81(3.66)	2		3000		
	Change detection	HC	30	40.9(9.3)	9.5(3.2)	3	32	2000	Shape-only	Perce corre and A
		FAD	22	45.2(4.8)	8.5(4.2)	2				

	Change detection	HC	14	70.71(4.30)	15.57(3.32)	3	32	2000	Shape-only	A' and
		AD	14	76.29(5.78)	12.71(3.77)	2				
	Change detection (color-color)	HC	14	70.71(4.30)	15.57(3.32)	3	32	2000	Colors-only	Perce correc
		HC_2	29	39.55(8.82)	9.21(2.90)	3				
		AD	14	76.29(5.78)	12.71(3.77)	2				
		FAD	22	45.18(4.82)	8.45(4.18)	2				
t al.,	Free recall	HC	20	69.35(6.21)	7.25(2.97)	4	6	12000	Objects and Colors	Perce correc
		AD	15	72.93(5.79)	7.13(3.74)	2		6000		
	Change detection	HC	21	39.30(83)	10.30(27)	3	32	2000	Shape-only	Perce correc
		FAD	19	47.50(6.4)	7.30(3.7)	2				
t al.,	Change detection	HC	33	73.87(8.51)	13.30(3.32)	2	32	2000	Shape-only	Perce correc
		AD	33	75.24(7.72)	13.27(3.17)	2				
al.,	Free Recall	HC	32	67.84(6.82)	12.25(3.69)	3	6	9000	Objects and Colors	Perce correc
		AD	35	71.40(7.96)	10.09(5.41)	3				
t al.,	Change detection (color-color)	HC	13	68(4.2)	18.2*	2	32	2000	Colors-only	Perce correc
		AD	13	67(2.6)	13.4*	2				
al.,	Change detection	HC	31	69.10(8.42)	14.42(2.87)	2	32	2000	Shape-only	Perce correc
		AD	24	72.58(8.16)	14.67(2.87)	2				
l.,	Cued recall	HC	24	74.54(4.12)	10.20(3.47)	2	12	2000	Shape-only	Perce correc
		HC_2	24	74.75(3.92)	9.56(2.90)	3		3000		
		AD	24	76.29(5.18)	9.08(1.18)	2		2000		
al.,	Change Detection	HC	23	67.83(6.06)	12.83(4.06)	2	32	2000	Shapes and colors	Perce correc
		AD	37	71.14(7.58)	10.05(5.23)	2				
al.,	Free Recall	HC	21	67.83(6.06)	12.83(4.06)	3	6	9000	Objects and colors	Perce correc
		AD	37	71.14(7.58)	10.05(5.23)	3				
al.,	Change Detection	HC	18	72.39(5.84)	12.33(4.97)	2	16	2000	None (only bound condition)	Numb correc
		AD	23	73.78(5.99)	8.57(4.15)	2				

&	Change Detection	HC	18	69.00(3.60)	17.1*	2	32	2000	Colors-only	Perce corre
		AD	18	68.00(2.20)	13.6*	2				

Legend. STM = short-term memory; HC = healthy controls; AD = Alzheimer's disease; MCI = mild cognitive impairment; MCI = mild cognitive impairment; AC = asymptomatic carrier of the presenilin-1 E280A mutation; FAD = familial AD (mutation of the presenilin-1 E280A in the dementia stage); MCI-FAD = MCI in familial AD; SCD = subjective cognitive decline. The samples presented in this table are only related to the AD continuum, from normal controls to AD dementia; other types of dementia on these studies were omitted. * Standard deviation for Education was not presented.

SUPPLEMENTAL MATERIAL

Short-Term Memory Conjunctive Binding in Alzheimer's Disease: A Systematic Review and Meta-Analysis

S1. Details of the terms used to search the electronic databases.

The terms combinations used to search the databases were:

"short-term memory binding" AND "Alzheimer's disease"

"short-term memory binding" AND "mild cognitive impairment"

"short-term memory binding" AND "subjective cognitive decline"

"memory binding" AND "Alzheimer's disease"

"memory binding" AND "mild cognitive impairment"

"memory binding" AND "subjective cognitive decline"

conjunctive memory AND "Alzheimer's disease"

conjunctive memory AND "mild cognitive impairment"

conjunctive memory AND "subjective cognitive decline"

"working memory binding" AND "Alzheimer's disease"

"working memory binding" AND "mild cognitive impairment"

"working memory binding" AND "subjective cognitive decline"

S2. List of studies included in meta-analyses

Cecchini, M.A., Yassuda, M.S., Bahia, V.S., de Souza, L.C., Guimarães, H.C., Caramelli, P., et al. (2017a). Recalling feature bindings differentiates Alzheimer's disease from frontotemporal dementia. *Journal of Neurology, 264*(10), 2162–2169. https://doi.org/10.1007/s00415-017-8614-9.

Cecchini, M.A., Foss, M.P., Tumas, V., Patrocinio, F.A.P., Chiari-Correia, R.D., Novaretti, N., et al. (2020). Profiles of cognitive impairment in the continuum from normal cognition to Alzheimer's clinical syndrome: Contributions of the short-term memory binding tests. *International Journal of Geriatric Psychiatry, 35*(11), 1331–1340. https://doi.org/10.1002/gps.5370.

Cecchini, M.A., Yassuda, M.S., Squarzoni, P., Coutinho, A.M., de Paula Faria, D., Duran, F.L.S., et al. (2021). Deficits in short-term memory binding are detectable in individuals with brain amyloid deposition in the absence of overt neurodegeneration in the Alzheimer's disease continuum. *Brain and Cognition, 152*, 105749. https://doi.org/10.1016/j.bandc.2021.105749.

Della Sala, S., Parra, M.A., Fabi, K., Luzzi, S., Abrahams, S. (2012). Short-term memory binding is impaired in AD but not in non-AD dementias. *Neuropsychologia, 50*(5), 833-840. https://doi.org/10.1016/j.neuropsychologia.2012.01.018.

Della Sala, S., Kozlova, I., Stamate, A., Parra, M.A. (2016). A transcultural cognitive marker of Alzheimer's Disease. *International Journal of Geriatric Psychiatry, 33*, 849-856. https://doi.org/10.1002/gps.4610.

Fernández, G., Orozco, D., Agamennoni, O., Schumacher, M., Sañudo, S., Biondi, J., Parra, M.A. (2018). Visual Processing during Short-Term Memory Binding in Mild

Alzheimer's Disease. *Journal of Alzheimer's Disease, 63*(1), 185–194. https://doi.org/10.3233/JAD-170728.

Guazzo, F., Allen, R.J., Baddeley, A.D., Della Sala, S. (2020). Unimodal and crossmodal working memory binding is not differentially affected by age or Alzheimer's disease. *Neuropsychology, 34*(4), 420–436. https://doi.org/10.1037/neu0000622.

Koppara, A., Frommann, I., Polcher, A., Parra, M.A., Maier, W., Jessen, F., et al. (2015b). Feature Binding Deficits in Subjective Cognitive Decline and in Mild Cognitive Impairment. *Journal of Alzheimer's Disease, 48*(S1), S161–S170. https://doi.org/10.3233/JAD-150105.

Kozlova, I., Parra, M.A., Titova, N., Gantman, M., Della Sala, S. (2020). Alzheimer's Disease and Parkinson Dementia Distinguished by Cognitive Marker. *Archives of Clinical Neuropsychology, 36*(3), 307–315. https://doi.org/10.1093/arclin/acz082.

Martínez-Florez, J.F., Osorio, J.D., Cediel, J.C., Rivas, J.C., Granados-Sánchez, A.M., López-Peláez, J., et al. (2021). Short-Term Memory Binding Distinguishing Amnestic Mild Cognitive Impairment from Healthy Aging: A Machine Learning Study. *Journal of Alzheimer's Disease, 81*(2), 729–742. https://doi.org/10.3233/JAD-201447.

Norton, D.J., Parra, M.A., Sperling, R.A., Baena, A., Guzman-Velez, E., Jin, D.S., et al. (2020). Visual short-term memory relates to tau and amyloid burdens in preclinical autosomal dominant Alzheimer's disease. *Alzheimer's Research & Therapy, 12*(1), 99. https://doi.org/10.1186/s13195-020-00660-z.

Parra, M.A., Abrahams, S., Fabi, K., Logie, R., Luzzi, S., Della Sala, S. (2009b). Short-term memory binding deficits in Alzheimer's disease. *Brain, 132*(4), 1057–1066. https://doi.org/10.1093/brain/awp036.

Parra, M.A., Abrahams, S., Logie, R.H., Méndez, L.G., Lopera, F., Della Sala, S. (2010a). Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain, 133*(9), 2702-2713. https://doi.org/10.1093/brain/awq148.

Parra, M.A., Abrahams, S., Logie, R.H., Della Sala, S. (2010b). Visual short-term memory binding in Alzheimer's disease and depression. *Journal of Neurology, 257*(7), 1160–1169. https://doi.org/10.1007/s00415-010-5484-9.

Parra, M.A., Della Sala, S., Abrahams, S., Logie, R. H., Méndez, L.G., Lopera, F. (2011b). Specific deficit of colour–colour short-term memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia, 49*(7), 1943-1952. https://doi.org/10.1016/j.neuropsychologia.2011.03.022.

Parra, M.A., Saarimäki, H., Bastin, M.E., Londoño, A.C., Pettit, L., Lopera, F., et al. (2015b). Memory binding and white matter integrity in familial Alzheimer's disease. *Brain, 138*(5), 1355-1369. https://doi.org/10.1093/brain/awv048.

Parra, M.A., Calia, C., García, A.F., Olazarán-Rodríguez, J., Hernandez-Tamames, J.A., Alvarez-Linera, J., et al. (2019). Refining memory assessment of elderly people with cognitive impairment: Insights from the short-term memory binding test. *Archives of Gerontology and Geriatrics, 83*, 114–120. https://doi.org/10.1016/j.archger.2019.03.025.

Pietto, M., Parra, M.A., Trujillo, N., Flores, F., García, A.M., Bustin, J., et al. (2016). Behavioral and Electrophysiological Correlates of Memory Binding Deficits in Patients at Different Risk Levels for Alzheimer's Disease. *Journal of Alzheimer's Disease, 53*(4), 1325-1340. https://doi.org/10.3233/JAD-160056.

Valdés Hernández, M. C., Clark, R., Wang, S.-H., Guazzo, F., Calia, C., Pattan, V., et al. (2020). The striatum, the hippocampus, and short-term memory binding: Volumetric

analysis of the subcortical grey matter's role in mild cognitive impairment. *NeuroImage: Clinical, 25*, 102158. https://doi.org/10.1016/j.nicl.2019.102158.

S3. List of excluded studies

S3.1 Other neuroscience or cognitive topics

Acquaah-Mensah, G. K., Agu, N., Khan, T., & Gardner, A. (2015). A regulatory role for the insulin-and BDNF-linked RORA in the hippocampus: implications for Alzheimer's disease. *Journal of Alzheimer's Disease*, *44*(3), 827-838. https://doi.org/10.3233/JAD-141731.

Adlam, A. L. R., Patterson, K., Bozeat, S., & Hodges, J. R. (2010). The Cambridge Semantic Memory Test Battery: Detection of semantic deficits in semantic dementia and Alzheimer's disease. *Neurocase*, *16*(3), 193-207. https://doi.org/10.1080/13554790903405693.

Aggleton, J. P. (2010). Understanding retrosplenial amnesia: insights from animal studies. *Neuropsychologia*, *48*(8), 2328-2338. https://doi.org/10.1016/j.neuropsychologia.2009.09.030.

Ahmed, S., Irish, M., Loane, C., Baker, I., Husain, M., Thompson, S., ... & Butler, C. (2018). Association between precuneus volume and autobiographical memory impairment in posterior cortical atrophy: Beyond the visual syndrome. *NeuroImage: Clinical*, *18*, 822-834. https://doi.org/10.1016/j.nicl.2018.03.008.

Álvarez, I., Diez-Fairen, M., Aguilar, M., González, J. M., Ysamat, M., Tartari, J. P., ... & Pastor, P. (2021). Added value of cerebrospinal fluid multimarker analysis in diagnosis

and progression of dementia. *European Journal of Neurology*, *28*(4), 1142-1152. https://doi.org/10.1111/ene.14658.

Andersson, C., Marklund, K., Walles, H., Hagman, G., & Miley-Akerstedt, A. (2019). Lifestyle Factors and Subjective Cognitive Impairment in Patients Seeking Help at a Memory Disorder Clinic: The Role of Negative Life Events. *Dementia and Geriatric Cognitive Disorders*, *48*(3-4), 196-206. https://doi.org/10.1159/000505573.

Bastin, C., Besson, G., Simon, J., Delhaye, E., Geurten, M., Willems, S., & Salmon, E. (2019). An integrative memory model of recollection and familiarity to understand memory deficits. *Behavioral and Brain Sciences*, *42*. https://doi.org/10.1017/S0140525X19000621.

Beuzeron-Mangina, J. H., & Mangina, C. A. (2000). Event-related brain potentials to memory workload and 'analytical-specific perception'(Mangina-Test) in patients with early Alzheimer's disease and in normal controls. *International Journal of Psychophysiology*, *37*(1), 55-69. https://doi.org/10.1016/s0167-8760(00)00095-7.

Blesa, R., Adroer, R., Santacruz, P., Ascaso, C., Tolosa, E., & Oliva, R. (1996). High apolipoprotein E ε4 allele frequency in Age-related memory decline. *Annals of Neurology*, *39*(4), 548-551. https://doi.org/10.1002/ana.410390419.

Bonardi, C., Pardon, M. C., & Armstrong, P. (2016). Deficits in object-in-place but not relative recency performance in the APPswe/PS1dE9 mouse model of Alzheimer's disease: Implications for object recognition. *Behavioural Brain Research, 313*, 71–81. https://doi.org/10.1016/j.bbr.2016.07.008.

Bond, R. L., Downey, L. E., Weston, P. S., Slattery, C. F., Clark, C. N., Macpherson, K., ... & Warren, J. D. (2016). Processing of self versus non-self in Alzheimer's

Disease. *Frontiers in Human Neuroscience*, *10*, 97. https://doi.org/10.3389/fnhum.2016.00097.

Bonello, M., & Larner, A. J. (2016). Applause sign: screening utility for dementia and cognitive impairment. *Postgraduate Medicine*, *128*(2), 250-253. https://doi.org/10.1080/00325481.2016.1118353.

Bouix, S., Pruessner, J. C., Collins, D. L., & Siddiqi, K. (2005). Hippocampal shape analysis using medial surfaces. *Neuroimage*, *25*(4), 1077-1089. https://doi.org/10.1016/j.neuroimage.2004.12.051.

Brandt, J., Blehar, J., Anderson, A., & Gross, A. L. (2014). Further validation of the Internet-based Dementia Risk Assessment. *Journal of Alzheimer's Disease, 41*(3), 937–945. https://doi.org/10.3233/JAD-140297.

Brooks, B. L., Iverson, G. L., Feldman, H. H., & Holdnack, J. A. (2009). Minimizing misdiagnosis: Psychometric criteria for possible or probable memory impairment. *Dementia and Geriatric Cognitive Disorders*, *27*(5), 439-450. https://doi.org/10.1159/000215390.

Bucci, M., Savitcheva, I., Farrar, G., Salvadó, G., Collij, L., Doré, V., ... & Nordberg, A. (2021). A multisite analysis of the concordance between visual image interpretation and quantitative analysis of [18F] flutemetamol amyloid PET images. *European Journal of Nuclear Medicine and Molecular Imaging*, *48*(7), 2183-2199. https://doi.org/10.1007/s00259-021-05311-5.

Buckley, R., Saling, M. M., Ames, D., Rowe, C. C., Lautenschlager, N. T., Macaulay, S. L., ... & Lifestyle Study of Aging (AIBL) Research Group. (2013). Factors affecting subjective memory complaints in the AIBL aging study: biomarkers, memory, affect,

and age. *International Psychogeriatrics*, *25*(8), 1307-1315. https://doi.org/10.1017/S1041610213000665.

Calderón-Garcidueñas, L., San Juan Chávez, V., Vacaseydel-Aceves, N. B., Calderón-Sánchez, R., Macías-Escobedo, E., Frías, C., Giacometto, M., Velasquez, L., Félix-Villarreal, R., Martin, J. D., Draheim, C., & Engle, R. W. (2016). Chocolate, Air Pollution and Children's Neuroprotection: What Cognition Tools should be at Hand to Evaluate Interventions? *Frontiers in Pharmacology, 7*, 232. https://doi.org/10.3389/fphar.2016.00232.

Calvo, N., García, A. M., Manoiloff, L., & Ibáñez, A. (2016). Bilingualism and Cognitive Reserve: A Critical Overview and a Plea for Methodological Innovations. *Frontiers in Aging Neuroscience, 7*, 249. https://doi.org/10.3389/fnagi.2015.00249.

Carmeli, C., Donati, A., Antille, V., Viceic, D., Ghika, J., von Gunten, A., ... & Knyazeva, M. G. (2013). Demyelination in mild cognitive impairment suggests progression path to Alzheimer's disease. *PloS One*, *8*(8), e72759. https://doi.org/10.1371/journal.pone.0072759.

Chen, J. C., Espeland, M. A., Brunner, R. L., Lovato, L. C., Wallace, R. B., Leng, X., ... & Mysiw, W. J. (2016). Sleep duration, cognitive decline, and dementia risk in older women. *Alzheimer's & Dementia*, *12*(1), 21-33. https://doi.org/10.1016/j.jalz.2015.03.004.

Cho, B. G., Veillon, L., & Mechref, Y. (2019). N-Glycan profile of cerebrospinal fluids from Alzheimer's disease patients using liquid chromatography with mass spectrometry. *Journal of Proteome Research*, *18*(10), 3770-3779. https://doi.org/10.1021/acs.jproteome.9b00504.

Choi, Y. S., Kang, S., Ko, S. Y., Lee, S., Kim, J. Y., Lee, H., ... & Lee, J. E. (2018). Hyperpolarized [1-13C] pyruvate MR spectroscopy detect altered glycolysis in the brain of a cognitively impaired mouse model fed high-fat diet. *Molecular Brain*, *11*(1), 1-12. https://doi.org/10.1186/s13041-018-0415-2.

Cholerton, B., Johnson, C. O., Fish, B., Quinn, J. F., Chung, K. A., Peterson-Hiller, A. L., ... & Edwards, K. L. (2018). Sex differences in progression to mild cognitive impairment and dementia in Parkinson's disease. *Parkinsonism & Related Disorders*, *50*, 29-36. https://doi.org/10.1016/j.parkreldis.2018.02.007.

Christos, G. A. (1993). Is Alzheimer's disease related to a deficit or malfunction of rapid eye movement (REM) sleep?. *Medical Hypotheses*, *41*(5), 435-439. https://doi.org/10.1016/0306-9877(93)90121-6.

Chua, N. J., Dimopoulos, G., Scott, D. A., Silbert, B. S., & Evered, L. A. (2021). Impaired cognitive performance on MoCA testing at discharge in elderly patients following day endoscopy and its relationship to preoperative mild cognitive impairment. *Anaesthesia and Intensive Care*, *49*(5), 357-365. https://doi.org/10.1177/0310057X21997459.

Cissé, M., & Checler, F. (2015). Eph receptors: new players in Alzheimer's disease pathogenesis. *Neurobiology of Disease*, *73*, 137-149. https://doi.org/10.1016/j.nbd.2014.08.028.

Cretin, B., Sellal, F., Philippi, N., Bousiges, O., Di Bitonto, L., Martin-Hunyadi, C., & Blanc, F. (2016). Epileptic prodromal Alzheimer’s disease, a retrospective study of 13 new cases: expanding the spectrum of Alzheimer’s disease to an epileptic variant? *Journal of Alzheimer's Disease*, *52*(3), 1125-1133. https://doi.org/10.3233/JAD-150096.

Cullen, S., Borrie, M., Carroll, S., Sarquis-Adamson, Y., Pieruccini-Faria, F., McKay, S., & Montero-Odasso, M. (2019). Are cognitive subtypes associated with dual-task gait

performance in a clinical setting?. *Journal of Alzheimer's Disease*, *71*(s1), S57-S64. https://doi.org/10.3233/JAD-181196.

Das, S. R., Mancuso, L., Olson, I. R., Arnold, S. E., & Wolk, D. A. (2016). Short-term memory depends on dissociable medial temporal lobe regions in amnestic mild cognitive impairment. *Cerebral Cortex*, *26*(5), 2006-2017. https://doi.org/10.1093/cercor/bhv022.

Daulatzai, M. A. (2016). Dysfunctional sensory modalities, locus coeruleus, and basal forebrain: early determinants that promote neuropathogenesis of cognitive and memory decline and Alzheimer's disease. *Neurotoxicity Research*, *30*(3), 295-337. https://doi.org/10.1007/s12640-016-9643-3.

Daulatzai, M. A. (2015). "Boomerang Neuropathology" of Late-Onset Alzheimer's Disease is Shrouded in Harmful "BDDS": Breathing, Diet, Drinking, and Sleep During Aging. *Neurotoxicity Research*, *28*(1), 55-93. https://doi.org/10.1007/s12640-015-9528-x.

Daulatzai, M. A. (2010). Early stages of pathogenesis in memory impairment during normal senescence and Alzheimer's disease. *Journal of Alzheimer's Disease*, *20*(2), 355-367. https://doi.org/10.3233/JAD-2010-1374.

De Roeck, A., Van den Bossche, T., van der Zee, J., Verheijen, J., De Coster, W., Van Dongen, J., ... & Sleegers, K. (2017). Deleterious ABCA7 mutations and transcript rescue mechanisms in early onset Alzheimer's disease. *Acta Neuropathologica*, *134*(3), 475-487. https://doi.org/10.1007/s00401-017-1714-x.

Della Sala, S., Foley, J., Parra, M., & Logie, R. (2011). Dual tasking and memory binding in Alzheimer's disease. In *Journal of Alzheimer's Disease: VI Sindem MEETING: Italian*

Association for the Study of Dementia Linked to the Italian Neurological Society (SIN) (pp. S22-S24).

Deng, Y., Shi, L., Lei, Y., Liang, P., Li, K., Chu, W. C., ... & Alzheimer's Disease Neuroimaging Initiative. (2016). Mapping the "what" and "where" visual cortices and their atrophy in Alzheimer's disease: Combined activation likelihood estimation with voxel-based morphometry. *Frontiers in Human Neuroscience*, *10*, 333. https://doi.org/10.3389/fnhum.2016.00333.

Denney, D. A., & Prigatano, G. P. (2019). Subjective ratings of cognitive and emotional functioning in patients with mild cognitive impairment and patients with subjective memory complaints but normal cognitive functioning. *Journal of Clinical and Experimental Neuropsychology*, *41*(6), 565-575. https://doi.org/10.1080/13803395.2019.1588229.

Dong, H., Yuede, C. M., Yoo, H. S., Martin, M. V., Deal, C., Mace, A. G., & Csernansky, J. G. (2008). Corticosterone and related receptor expression are associated with increased β-amyloid plaques in isolated Tg2576 mice. *Neuroscience*, *155*(1), 154-163. https://doi.org/10.1016/j.neuroscience.2008.05.017.

Dringenberg, H. C. (2000). Alzheimer's disease: more than a 'cholinergic disorder'—evidence that cholinergic–monoaminergic interactions contribute to EEG slowing and dementia. *Behavioural Brain Research*, *115*(2), 235-249. https://doi.org/10.1016/s0166-4328(00)00261-8.

Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K., DeKosky, S. T., Gauthier, S., Selkoe, D., Bateman, R., Cappa, S., Crutch, S., Engelborghs, S., Frisoni, G. B., Fox, N. C., Galasko, D., Habert, M. O., Jicha, G. A., Nordberg, A., Pasquier, F., … Cummings, J. L. (2014). Advancing research diagnostic

criteria for Alzheimer's disease: the IWG-2 criteria. *The Lancet. Neurology, 13*(6), 614–629. https://doi.org/10.1016/S1474-4422(14)70090-0.

Duffy, S. L., Lagopoulos, J., Hickie, I. B., Diamond, K., Graeber, M. B., Lewis, S. J., & Naismith, S. L. (2014). Glutathione relates to neuropsychological functioning in mild cognitive impairment. *Alzheimer's & Dementia*, *10*(1), 67-75. https://doi.org/10.1016/j.jalz.2013.01.005.

El Haj, M., Antoine, P., & Kapogiannis, D. (2015). Flexibility decline contributes to similarity of past and future thinking in Alzheimer's disease. *Hippocampus*, *25*(11), 1447-1455. https://doi.org/10.1002/hipo.22465.

El Haj, M., Badcock, J. C., & Larøi, F. (2020). Hallucinations and source monitoring in Alzheimer’s disease. *Cognitive Neuropsychiatry*, *25*(6), 435-446. https://doi.org/10.1080/13546805.2020.1832457.

Emrani, S., Lamar, M., Price, C. C., Wasserman, V., Matusz, E., Au, R., ... & Libon, D. J. (2020). Alzheimer’s/vascular spectrum dementia: classification in addition to diagnosis. *Journal of Alzheimer's Disease*, *73*(1), 63-71. https://doi.org/10.3233/JAD-190654.

Evans, S. L., Dowell, N. G., Prowse, F., Tabet, N., King, S. L., & Rusted, J. M. (2020). Mid age APOE ε4 carriers show memory-related functional differences and disrupted structure-function relationships in hippocampal regions. *Scientific Reports*, *10*(1), 1-11. https://doi.org/10.1038/s41598-020-59272-0.

Farina, E., Baglio, F., Pomati, S., D'Amico, A., Campini, I. C., Di Tella, S., Belloni, G., & Pozzo, T. (2017). The Mirror Neurons Network in Aging, Mild Cognitive Impairment, and Alzheimer Disease: A functional MRI Study. *Frontiers in Aging Neuroscience*, *9*, 371. https://doi.org/10.3389/fnagi.2017.00371.

Fisher, A. (1997). Muscarinic agonists for the treatment of Alzheimer's disease: progress and perspectives. *Expert Opinion on Investigational Drugs*, *6*(10), 1395-1411. https://doi.org/10.1517/13543784.6.10.1395.

Fitz, N. F., Castranio, E. L., Carter, A. Y., Kodali, R., Lefterov, I., & Koldamova, R. (2014). Improvement of memory deficits and amyloid-β clearance in aged APP23 mice treated with a combination of anti-amyloid-β antibody and LXR agonist. *Journal of Alzheimer's Disease*, *41*(2), 535-549. https://doi.org/10.3233/JAD-132789.

Fodero-Tavoletti, M. T., Cappai, R., McLean, C. A., Pike, K. E., Adlard, P. A., Cowie, T., ... & Villemagne, V. L. (2009). Amyloid imaging in Alzheimer's disease and other dementias. *Brain Imaging and Behavior*, *3*(3), 246-261. https://doi.org/10.1007/s11682-009-9067-2.

Freiherr, J., Hallschmid, M., Frey, W. H., 2nd, Brünner, Y. F., Chapman, C. D., Hölscher, C., Craft, S., De Felice, F. G., & Benedict, C. (2013). Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. *CNS Drugs*, *27*(7), 505–514. https://doi.org/10.1007/s40263-013-0076-8.

Friedman, G. (2000). The effects of estrogen on short-term memory in genetic men. *Journal of the American Medical Directors Association*, *1*(1), 4-7.

Frisch, S., Dukart, J., Vogt, B., Horstmann, A., Becker, G., Villringer, A., ... & Schroeter, M. L. (2013). Dissociating memory networks in early Alzheimer's disease and frontotemporal lobar degeneration-a combined study of hypometabolism and atrophy. *PloS One*, *8*(2), e55251. https://doi.org/10.1371/journal.pone.0055251.

Fuller, J. T., Cronin-Golomb, A., Gatchel, J. R., Norton, D. J., Guzmán-Vélez, E., Jacobs, H. I., ... & Quiroz, Y. T. (2019). Biological and cognitive markers of presenilin1 E280A

autosomal dominant Alzheimer's disease: A comprehensive review of the Colombian kindred. *The Journal of Prevention of Alzheimer's Disease*, *6*(2), 112-120. https://doi.org/10.14283/jpad.2019.6.

Garbóczy, S., Magócs, É., Szőllősi, G. J., Harsányi, S., Égerházi, A., & Kolozsvári, L. R. (2020). The use of the Hungarian Test Your Memory (TYM-HUN), MMSE, and ADAS-Cog tests for patients with mild cognitive impairment (MCI) in a Hungarian population: a cross-sectional study. *BMC Psychiatry*, *20*(1), 1-7. https://doi.org/10.1186/s12888-020-02982-6.

Ge, T., Sabuncu, M. R., Smoller, J. W., Sperling, R. A., Mormino, E. C., & Alzheimer's Disease Neuroimaging Initiative. (2018). Dissociable influences of APOE ε4 and polygenic risk of AD dementia on amyloid and cognition. *Neurology*, *90*(18), e1605-e1612. https://doi.org/10.1212/WNL.0000000000005415.

Geldmacher, D. S. (2007). Treatment guidelines for Alzheimer's disease: redefining perceptions in primary care. *Primary Care Companion to the Journal of Clinical Psychiatry*, *9*(2), 113. https://doi.org/10.4088/pcc.v09n0205.

Grosse, D. A., Gilley, D. W., & Wilson, R. S. (1991). Episodic and semantic memory in early versus late onset Alzheimer's disease. *Brain and language*, *41*(4), 531-537. https://doi.org/10.1016/0093-934x(91)90172-w.

Halliday, D. W., Gawryluk, J. R., Garcia-Barrera, M. A., & MacDonald, S. W. (2019). White matter integrity is associated with intraindividual variability in neuropsychological test performance in healthy older adults. *Frontiers in Human Neuroscience*, *13*, 352. https://doi.org/10.3389/fnhum.2019.00352.

Haroutunian, V., Kanof, P. D., Tsuboyama, G., & Davis, K. L. (1990). Restoration of cholinomimetic activity by clonidine in cholinergic plus noradrenergic lesioned rats. *Brain Research*, *507*(2), 261-266. https://doi.org/10.1016/0006-8993(90)90280-o.

Henry, J. D., Ruffman, T., McDonald, S., O'Leary, M. A. P., Phillips, L. H., Brodaty, H., & Rendell, P. G. (2008). Recognition of disgust is selectively preserved in Alzheimer's disease. *Neuropsychologia*, *46*(5), 1363-1370. https://doi.org/10.1016/j.neuropsychologia.2007.12.012.

Hornberger, M., Wong, S., Tan, R., Irish, M., Piguet, O., Kril, J., ... & Halliday, G. (2012). In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. *Brain*, *135*(10), 3015-3025. https://doi.org/10.1093/brain/aws239.

Idland, A. V., Wyller, T. B., Støen, R., Eri, L. M., Frihagen, F., Raeder, J., ... & Watne, L. O. (2017). Preclinical amyloid-β and axonal degeneration pathology in delirium. *Journal of Alzheimer's Disease*, *55*(1), 371-379. https://doi.org/10.3233/JAD-160461.

Ishiwata, A., & Kimura, K. (2016). Homonymous hemianopsia associated with probable Alzheimer's disease. *Journal of Nippon Medical School*, *83*(2), 87-92. https://doi.org/10.1272/jnms.83.87.

Jack Jr, C. R., Lowe, V. J., Senjem, M. L., Weigand, S. D., Kemp, B. J., Shiung, M. M., ... & Petersen, R. C. (2008). 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain*, *131*(3), 665-680. https://doi.org/10.1093/brain/awm336.

Johns, B. T., Taler, V., Pisoni, D. B., Farlow, M. R., Hake, A. M., Kareken, D. A., Unverzagt, F. W., & Jones, M. N. (2018). Cognitive modeling as an interface between brain and behavior: Measuring the semantic decline in mild cognitive

impairment. *Canadian Journal of Experimental Psychology = Revue Canadienne de Psychologie Experimentale*, *72*(2), 117–126. https://doi.org/10.1037/cep0000132.

Jordan, N., Gvalda, M., Cody, R., Galante, O., Haywood, C., & Yates, P. (2021). Frailty, MRI, and FDG-PET Measures in an Australian Memory Clinic Cohort. *Frontiers in Medicine*, *7*, 578243. https://doi.org/10.3389/fmed.2020.578243.

Kondo, D., Ota, K., Kasanuki, K., Fujishiro, H., Chiba, Y., Murayama, N., ... & Iseki, E. (2016). Characteristics of mild cognitive impairment tending to convert into Alzheimer's disease or dementia with Lewy bodies: A follow-up study in a memory clinic. *Journal of the Neurological Sciences*, *369*, 102-108. https://doi.org/10.1016/j.jns.2016.08.011.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (1999). Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage*, *10*(6), 695-704. https://doi.org/10.1006/nimg.1999.0503.

Lam, B., Masellis, M., Freedman, M., Stuss, D. T., & Black, S. E. (2013). Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. *Alzheimer's Research & Therapy*, *5*(1), 1. https://doi.org/10.1186/alzrt155.

Lamar, M., Dannhauser, T. M., Walker, Z., Rodda, J. E., Cutinha, D. J., & Shergill, S. S. (2011). Memory complaints with and without memory impairment: the impact of leukoaraiosis on cognition. *Journal of the International Neuropsychological Society*, *17*(6), 1104–1112. https://doi.org/10.1017/S1355617711001123.

Lee, J. Y., Kho, S., Yoo, H. B., Park, S., Choi, J. S., Kwon, J. S., Cha, K. R., & Jung, H. Y. (2014). Spatial memory impairments in amnestic mild cognitive impairment in a virtual

radial arm maze. *Neuropsychiatric Disease and Treatment*, *10*, 653–660. https://doi.org/10.2147/NDT.S58185.

Lenehan, M. E., Klekociuk, S. Z., & Summers, M. J. (2012). Absence of a relationship between subjective memory complaint and objective memory impairment in mild cognitive impairment (MCI): is it time to abandon subjective memory complaint as an MCI diagnostic criterion?. *International Psychogeriatrics*, *24*(9), 1505-1514. https://doi.org/10.1017/S1041610212000695.

Li, W., Antuono, P. G., Xie, C., Chen, G., Jones, J. L., Ward, B. D., ... & Li, S. J. (2014). Aberrant functional connectivity in Papez circuit correlates with memory performance in cognitively intact middle-aged APOE4 carriers. *Cortex*, *57*, 167-176. https://doi.org/10.1016/j.cortex.2014.04.006.

Liu, Y., Tong, S., Ding, L., Liu, N., & Gao, D. (2020). Serum levels of glial cell line-derived neurotrophic factor and multiple neurotransmitters: in relation to cognitive performance in Parkinson's disease with mild cognitive impairment. *International Journal of Geriatric Psychiatry*, *35*(2), 153-162. https://doi.org/10.1002/gps.5222.

Llorens-Martín, M., Rábano, A., & Ávila, J. (2016). The ever-changing morphology of hippocampal granule neurons in physiology and pathology. *Frontiers in Neuroscience*, *9*, 526. https://doi.org/10.3389/fnins.2015.00526.

Loewenstein, D. A., Greig, M. T., Schinka, J. A., Barker, W., Shen, Q., Potter, E., Raj, A., Brooks, L., Varon, D., Schoenberg, M., Banko, J., Potter, H., & Duara, R. (2012). An investigation of PreMCI: subtypes and longitudinal outcomes. *Alzheimer's & Dementia*, *8*(3), 172–179. https://doi.org/10.1016/j.jalz.2011.03.002.

Love, B. C., & Gureckis, T. M. (2007). Models in search of a brain. *Cognitive, Affective, & Behavioral Neuroscience*, *7*(2), 90-108. https://doi.org/10.3758/CABN.7.2.90.

Low, L. F., & Purwaningrum, F. (2020). Negative stereotypes, fear and social distance: a systematic review of depictions of dementia in popular culture in the context of stigma. *BMC Geriatrics*, *20*(1), 1-16. https://doi.org/10.1186/s12877-020-01754-x.

Maiese, K. (2021). Neurodegeneration, memory loss, and dementia: the impact of biological clocks and circadian rhythm. *Frontiers in Bioscience (Landmark edition)*, *26*(9), 614-627. https://doi.org/10.52586/4971.

Maiese, K. (2014). Taking aim at Alzheimer's disease through the mammalian target of rapamycin. *Annals of Medicine*, *46*(8), 587-596. https://doi.org/10.3109/07853890.2014.941921.

Mandzia, J. L., McAndrews, M. P., Grady, C. L., Graham, S. J., & Black, S. E. (2009). Neural correlates of incidental memory in mild cognitive impairment: an fMRI study. *Neurobiology of Aging*, *30*(5), 717-730. https://doi.org/10.1016/j.neurobiolaging.2007.08.024.

Marchant, N. L., Reed, B. R., Sanossian, N., Madison, C. M., Kriger, S., Dhada, R., ... & Jagust, W. J. (2013). The aging brain and cognition: contribution of vascular injury and aβ to mild cognitive dysfunction. *JAMA Neurology*, *70*(4), 488-495. https://doi.org/10.1001/2013.jamaneurol.405.

Marra, C., Gainotti, G., Scaricamazza, E., Piccininni, C., Ferraccioli, M., & Quaranta, D. (2013). The Multiple Features Target Cancellation (MFTC): an attentional visual conjunction search test. Normative values for the Italian population. *Neurological Sciences*, *34*(2), 173-180. https://doi.org/10.1007/s10072-012-0975-3.

McGough, E. L., Kelly, V. E., Logsdon, R. G., McCurry, S. M., Cochrane, B. B., Engel, J. M., & Teri, L. (2011). Associations between physical performance and executive

function in older adults with mild cognitive impairment: gait speed and the timed “up & go” test. *Physical Therapy*, *91*(8), 1198-1207. https://doi.org/10.2522/ptj.20100372.

McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., ... & Cantu, R. C. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, *136*(1), 43-64. https://doi.org/10.1093/brain/aws307.

McMillan, P., Wheeler, J., Gatlin, R. E., Taylor, L., Strovas, T., Baum, M., ... & Liachko, N. F. (2020). Adult onset pan-neuronal human tau tubulin kinase 1 expression causes severe cerebellar neurodegeneration in mice. *Acta Neuropathologica Communications*, *8*(1), 1-15. https://doi.org/10.1186/s40478-020-01073-7.

McMurdo, M. E., Grant, D. J., Kennedy, N. S., Gilchrist, J., Findlay, D., & McLennan, J. M. (1994). The value of HMPAO SPECT scanning in the diagnosis of early Alzheimer's disease in patients attending a memory clinic. *Nuclear Medicine Communications*, *15*(6), 405-409. https://doi.org/10.1097/00006231-199406000-00002.

Missonnier, P., Gold, G., Fazio-Costa, L., Michel, J. P., Mulligan, R., Michon, A., ... & Giannakopoulos, P. (2005). Early event-related potential changes during working memory activation predict rapid decline in mild cognitive impairment. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *60*(5), 660-666. https://doi.org/10.1093/gerona/60.5.660.

Molinder, A., Ziegelitz, D., Maier, S. E., & Eckerström, C. (2021). Validity and reliability of the medial temporal lobe atrophy scale in a memory clinic population. *BMC Neurology*, *21*(1), 289. https://doi.org/10.1186/s12883-021-02325-2.

Moodley, K. K., & Chan, D. (2014). The hippocampus in neurodegenerative disease. *The Hippocampus in Clinical Neuroscience*, *34*, 95-108. https://doi.org/10.1159/000356430.

Mormino, E. C., & Papp, K. V. (2018). Amyloid accumulation and cognitive decline in clinically normal older individuals: implications for aging and early Alzheimer's disease. *Journal of Alzheimer's Disease*, *64*(s1), S633-S646. https://doi.org/10.3233/JAD-179928.

Ochoa, J. F., Alonso, J. F., Duque, J. E., Tobón, C. A., Mañanas, M. A., Lopera, F., & Hernández, A. M. (2017). Successful Object Encoding Induces Increased Directed Connectivity in Presymptomatic Early-Onset Alzheimer's Disease. *Journal of Alzheimer's Disease, 55*(3), 1195–1205. https://doi.org/10.3233/JAD-160803.

Medical Advisory Secretariat (2006). Functional brain imaging: an evidence-based analysis. *Ontario Health Technology Assessment Series*, *6*(22), 1–79.

Ouchi, Y., & Kikuchi, M. (2012). A review of the default mode network in aging and dementia based on molecular imaging. *Reviews in the Neurosciences*, *23*(3), 263-268. https://doi.org/10.1515/revneuro-2012-0029.

Pardini, M., Huey, E. D., Spina, S., Kreisl, W. C., Morbelli, S., Wassermann, E. M., ... & Grafman, J. (2019). FDG-PET patterns associated with underlying pathology in corticobasal syndrome. *Neurology*, *92*(10), e1121-e1135. https://doi.org/10.1212/WNL.0000000000007038.

Parent, M. J., Zimmer, E. R., Shin, M., Kang, M. S., Fonov, V. S., Mathieu, A., ... & Rosa-Neto, P. (2017). Multimodal imaging in rat model recapitulates Alzheimer's disease biomarkers abnormalities. *Journal of Neuroscience*, *37*(50), 12263-12271. https://doi.org/10.1523/JNEUROSCI.1346-17.2017.

Peel, E. (2015). Diagnostic communication in the memory clinic: a conversation analytic perspective. *Aging & Mental Health*, *19*(12), 1123-1130. https://doi.org/10.1080/13607863.2014.1003289.

Pruessner, J. C., Collins, D. L., Pruessner, M., & Evans, A. C. (2001). Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. *Journal of Neuroscience*, *21*(1), 194-200. https://doi.org/10.1523/JNEUROSCI.21-01-00194.2001.

Rafii, M. S., Ances, B. M., Schupf, N., Krinsky-McHale, S. J., Mapstone, M., Silverman, W., ... & O'Bryant, S. (2020). The AT (N) framework for Alzheimer's disease in adults with Down syndrome. *Alzheimer's & Dementia (Amst)*, *12*(1), e12062. https://doi.org/10.1002/dad2.12062.

Ray, K. M., Wang, H., Chu, Y., Chen, Y. F., Bert, A., Hasso, A. N., & Su, M. Y. (2006). Mild cognitive impairment: apparent diffusion coefficient in regional gray matter and white matter structures. *Radiology*, *241*(1), 197-205. https://doi.org/10.1148/radiol.2411051051.

Reber, P. J., Martinez, L. A., & Weintraub, S. (2003). Artificial grammar learning in Alzheimer's disease. *Cognitive, Affective, & Behavioral Neuroscience*, *3*(2), 145-153. https://doi.org/10.3758/cabn.3.2.145.

Reiman, E. M., Uecker, A., Caselli, R. J., Lewis, S., Bandy, D., De Leon, M. J., ... & Thibodeau, S. N. (1998). Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *44*(2), 288-291. https://doi.org/10.1002/ana.410440226.

Ries, M. L., McLaren, D. G., Bendlin, B. B., Rowley, H. A., Birn, R., Kastman, E. K., ... & Johnson, S. C. (2012). Medial prefrontal functional connectivity—relation to memory self-appraisal accuracy in older adults with and without memory disorders. *Neuropsychologia*, *50*(5), 603-611. https://doi.org/10.1016/j.neuropsychologia.2011.12.014.

Ries, M. L., Schmitz, T. W., Kawahara, T. N., Torgerson, B. M., Trivedi, M. A., & Johnson, S. C. (2006). Task-dependent posterior cingulate activation in mild cognitive impairment. *Neuroimage*, *29*(2), 485-492. https://doi.org/10.1016/j.neuroimage.2005.07.030.

Sabbagh, M., Miller, J., Jones, S., Ritter, A., Shi, J., DeCourt, B., & Wint, D. (2021). Does Informant-Based Reporting of Cognitive Decline Correlate with Age-Adjusted Hippocampal Volume in Mild Cognitive Impairment and Alzheimer's Disease?. *Journal of Alzheimer's Disease Reports*, *5*(1), 207-211. https://doi.org/10.3233/ADR-200260.

Samartgis, J. R., Schachte, L., Hazi, A., & Crowe, S. F. (2012). Memantine facilitates memory consolidation and reconsolidation in the day-old chick. *Neurobiology of Learning and Memory*, *97*(4), 380-385. https://doi.org/10.1016/j.nlm.2012.02.009.

Sankowski, R., Huerta, T. S., Kalra, R., Klein, T. J., Strohl, J. J., Al-Abed, Y., ... & Huerta, P. T. (2019). Large-scale validation of the paddling pool task in the clockmaze for studying hippocampus-based spatial cognition in mice. *Frontiers in Behavioral Neuroscience*, *13*, 121. https://doi.org/10.3389/fnbeh.2019.00121.

Scholtzova, H., Wadghiri, Y. Z., Douadi, M., Sigurdsson, E. M., Li, Y. S., Quartermain, D., ... & Wisniewski, T. (2008). Memantine leads to behavioral improvement and amyloid reduction in Alzheimer's-disease-model transgenic mice shown as by micromagnetic resonance imaging. *Journal of Neuroscience Research*, *86*(12), 2784-2791. https://doi.org/10.1002/jnr.21713.

Schwartz, M., Meyer, B., Wirnitzer, B., & Hopf, C. (2015). Standardized processing of MALDI imaging raw data for enhancement of weak analyte signals in mouse models of

gastric cancer and Alzheimer's disease. *Analytical and Bioanalytical Chemistry*, *407*(8), 2255-2264. https://doi.org/10.1007/s00216-014-8356-9.

Sheldon, S., Vandermorris, S., Al-Haj, M., Cohen, S., Winocur, G., & Moscovitch, M. (2015). Ill-defined problem solving in amnestic mild cognitive impairment: Linking episodic memory to effective solution generation. *Neuropsychologia*, *68*, 168-175. https://doi.org/10.1016/j.neuropsychologia.2015.01.005.

Shi, Z., Fu, L. P., Zhang, N., Zhao, X., Liu, S., Zuo, C., ... & Ji, Y. (2020). Amyloid PET in Dementia Syndromes: A Chinese Multicenter Study. *Journal of Nuclear Medicine*, *61*(12), 1814-1819. https://doi.org/10.2967/jnumed.119.240325.

Sindi, I. A., Tannenberg, R. K., & Dodd, P. R. (2014). A role for the neurexin–neuroligin complex in Alzheimer's disease. *Neurobiology of Aging*, *35*(4), 746-756. https://doi.org/10.1016/j.neurobiolaging.2013.09.032.

Smith, B., Chur-Hansen, A., Neale, A., & Symon, J. (2008). Quality of life and cholinesterase inhibitors: a qualitative study of patients with Alzheimer's disease and their carers. *Australasian Psychiatry*, *16*(6), 433-437. https://doi.org/10.1080/10398560802375990.

Snaedal, J., Johannesson, G. H., Gudmundsson, T. E., Gudmundsson, S., Pajdak, T. H., & Johnsen, K. (2010). The use of EEG in Alzheimer's disease, with and without scopolamine - a pilot study. *Clinical Neurophysiology*, *121*(6), 836–841. https://doi.org/10.1016/j.clinph.2010.01.008.

Soulsby, W. D., El-Ruwie, N., Gatla, S., Najmi, S., Chen, A., Chibnall, J. T., & Grossberg, G. T. (2016). Ideomotor limb apraxia as a staging tool in individuals with Alzheimer's disease (ILIAD). *Annals of Clinical Psychiatry*, *28*(4), 255-262.

Spyrou, L., Parra, M., & Escudero, J. (2019). Complex Tensor Factorization With PARAFAC2 for the Estimation of Brain Connectivity From the EEG. In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering: a Publication of the IEEE Engineering in Medicine and Biology Society, 27*(1), 1–12. https://doi.org/10.1109/TNSRE.2018.2883514.

Tröster, A. I. (2008). Neuropsychological characteristics of dementia with Lewy bodies and Parkinson's disease with dementia: differentiation, early detection, and implications for "mild cognitive impairment" and biomarkers. *Neuropsychology Review*, *18*(1), 103-119. https://doi.org/10.1007/s11065-008-9055-0.

Triplett, J. C., Swomley, A. M., Cai, J., Klein, J. B., & Butterfield, D. A. (2016). Quantitative phosphoproteomic analyses of the inferior parietal lobule from three different pathological stages of Alzheimer's disease. *Journal of Alzheimer's Disease*, *49*(1), 45-62. https://doi.org/10.3233/JAD-150417.

Tu, M. C., Lo, C. P., Chen, C. Y., & Huang, C. F. (2015). Correlation of Tc-99 m ethyl cysteinate dimer single-photon emission computed tomography and clinical presentations in patients with low cobalamin status. *BMC Neurology*, *15*(1), 1-11. https://doi.org/10.1186/s12883-015-0500-4.

Ullah, G., Demuro, A., Parker, I., & Pearson, J. E. (2015). Analyzing and modeling the kinetics of amyloid beta pores associated with Alzheimer's disease pathology. *PloS One*, *10*(9), e0137357. https://doi.org/10.1371/journal.pone.0137357.

Verma, S., Sharma, S., Ranawat, P., & Nehru, B. (2020). Modulatory effects of ginkgo biloba against amyloid aggregation through induction of heat shock proteins in aluminium induced neurotoxicity. *Neurochemical Research*, *45*(2), 465-490. https://doi.org/10.1007/s11064-019-02940-z.

Vidoni, E. D., Honea, R. A., & Burns, J. M. (2010). Neural correlates of impaired functional independence in early Alzheimer's disease. *Journal of Alzheimer's Disease*, *19*(2), 517-527. https://doi.org/10.3233/JAD-2010-1245.

Villain, N., & Dubois, B. (2019). Alzheimer's Disease Including Focal Presentations. *Seminars in neurology, 39*(2), 213–226. https://doi.org/10.1055/s-0039-1681041.

Villemagne, V. L., Fodero-Tavoletti, M. T., Pike, K. E., Cappai, R., Masters, C. L., & Rowe, C. C. (2008). The ART of loss: Aβ imaging in the evaluation of Alzheimer's disease and other dementias. *Molecular Neurobiology*, *38*(1), 1-15. https://doi.org/10.1007/s12035-008-8019-y.

Viskontas, I. V., Boxer, A. L., Fesenko, J., Matlin, A., Heuer, H. W., Mirsky, J., & Miller, B. L. (2011). Visual search patterns in semantic dementia show paradoxical facilitation of binding processes. *Neuropsychologia*, *49*(3), 468-478. https://doi.org/10.1016/j.neuropsychologia.2010.12.039.

Walker, J. M., Klakotskaia, D., Ajit, D., Weisman, G. A., Wood, W. G., Sun, G. Y., ... & Schachtman, T. R. (2015). Beneficial effects of dietary EGCG and voluntary exercise on behavior in an Alzheimer's disease mouse model. *Journal of Alzheimer's Disease*, *44*(2), 561-572. https://doi.org/10.3233/JAD-140981.

Wallert, J., Westman, E., Ulinder, J., Annerstedt, M., Terzis, B., & Ekman, U. (2018). Differentiating patients at the memory clinic with simple reaction time variables: a predictive modeling approach using support vector machines and bayesian optimization. *Frontiers in Aging Neuroscience*, *10*, 144. https://doi.org/10.3389/fnagi.2018.00144.

Walls, K. C., Ager, R. R., Vasilevko, V., Cheng, D., Medeiros, R., & LaFerla, F. M. (2014). p-Tau immunotherapy reduces soluble and insoluble tau in aged 3xTg-AD mice. *Neuroscience Letters*, *575*, 96-100. https://doi.org/10.1016/j.neulet.2014.05.047.

Wang, D., Zhang, Q., Hu, X., Wang, W., Zhu, X., & Yuan, Z. (2018). Pharmacodynamics in Alzheimer's disease model rats of a bifunctional peptide with the potential to accelerate the degradation and reduce the toxicity of amyloid β-Cu fibrils. *Acta Biomaterialia*, *65*, 327-338. https://doi.org/10.1016/j.actbio.2017.10.039.

Wang, Q., Wang, Y., Liu, J., Sutphen, C. L., Cruchaga, C., Blazey, T., ... & Benzinger, T. L. (2019). Quantification of white matter cellularity and damage in preclinical and early symptomatic Alzheimer's disease. *NeuroImage: Clinical*, *22*, 101767. https://doi.org/10.1016/j.nicl.2019.101767.

Wang, Y., Lian, M., Xiu, X., Zhang, Z., Song, L., & Wu, S. (2021). Dicer1 promotes Aβ clearance via blocking B2 RNA-mediated repression of apolipoprotein E. *Biochimica et Biophysica Acta. Molecular Basis of Disease*, *1867*(2), 166038. https://doi.org/10.1016/j.bbadis.2020.166038.

Wang, H., Fan, Z., Shi, C., Xiong, L., Zhang, H., Li, T., ... & Yu, X. (2019). Consensus statement on the neurocognitive outcomes for early detection of mild cognitive impairment and Alzheimer dementia from the Chinese Neuropsychological Normative (CN-NORM) Project. *Journal of Global Health*, *9*(2), 020320. https://doi.org/10.7189/jogh.09.020320.

Webster, S. J., Bachstetter, A. D., Nelson, P. T., Schmitt, F. A., & Van Eldik, L. J. (2014). Using mice to model Alzheimer's dementia: an overview of the clinical disease and the preclinical behavioral changes in 10 mouse models. *Frontiers in Genetics*, *5*, 88. https://doi.org/10.3389/fgene.2014.00088.

Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Cedarbaum, J., ... & Alzheimer's Disease Neuroimaging Initiative. (2015). Impact of the Alzheimer's disease neuroimaging initiative, 2004 to 2014. *Alzheimer's & Dementia*, *11*(7), 865-884. https://doi.org/10.1016/j.jalz.2015.04.005.

Weinstein, A. M., Gujral, S., Butters, M. A., Bowie, C. R., Fischer, C. E., Flint, A. J., Herrmann, N., Kennedy, J. L., Mah, L., Ovaysikia, S., Pollock, B. G., Rajji, T. K., Mulsant, B. H., & PACt-MD Study Group. (2021). Diagnostic Precision in the Detection of Mild Cognitive Impairment: A Comparison of Two Approaches. *The American Journal of Geriatric Psychiatry*, S1064-7481(21)00291-8. https://doi.org/10.1016/j.jagp.2021.04.004.

Weis, S., Leube, D., Erb, M., Heun, R., Grodd, W., & Kircher, T. (2011). Functional neuroanatomy of sustained memory encoding performance in healthy aging and in Alzheimer's disease. *International Journal of Neuroscience*, *121*(7), 384-392. https://doi.org/10.3109/00207454.2011.565892.

Wengenack, T. M., Jack, C. R., Garwood, M., & Poduslo, J. F. (2008). MR microimaging of amyloid plaques in Alzheimer’s disease transgenic mice. *European Journal of Nuclear Medicine and Molecular Imaging*, *35*(1), 82-88. https://doi.org/10.1007/s00259-007-0706-9.

Williams, J. M., Klein, K., Little, M., & Haban, G. (1986). Family observations of everyday cognitive impairment in dementia. *Archives of Clinical Neuropsychology*, *1*(2), 103-109.

Wilson, R. S., & Martin, E. M. (1988). New intrathecal drugs in Alzheimer's disease and psychometric testing. *Annals of the New York Academy of Sciences*, *531*(1), 180-186. https://doi.org/10.1111/j.1749-6632.1988.tb31825.x.

Wolf, O. T., Convit, A., Thorn, E., & de Leon, M. J. (2002). Salivary cortisol day profiles in elderly with mild cognitive impairment. *Psychoneuroendocrinology*, *27*(7), 777-789. https://doi.org/10.1016/s0306-4530(01)00079-8.

Xie, C., Bai, F., Yu, H., Shi, Y., Yuan, Y., Chen, G., ... & Li, S. J. (2012). Abnormal insula functional network is associated with episodic memory decline in amnestic mild cognitive impairment. *Neuroimage*, *63*(1), 320-327. https://doi.org/10.1016/j.neuroimage.2012.06.062.

Yang, C., Moore, A., Mpofu, E., Dorstyn, D., Li, Q., & Yin, C. (2020). Effectiveness of combined cognitive and physical interventions to enhance functioning in older adults with mild cognitive impairment: a systematic review of randomized controlled trials. *The Gerontologist*, *60*(8), 633-642. https://doi.org/10.1093/geront/gnz149.

Zhang, J., Little, C. J., Tremmel, D. M., Yin, J. C., & Wesley, C. S. (2013). Notch-inducible hyperphosphorylated CREB and its ultradian oscillation in long-term memory formation. *Journal of Neuroscience*, *33*(31), 12825-12834. https://doi.org/10.1523/JNEUROSCI.0783-13.2013.

Zhaoyang, R., Scott, S. B., Martire, L. M., & Sliwinski, M. J. (2021). Daily social interactions related to daily performance on mobile cognitive tests among older adults. *PloS One*, *16*(8), e0256583. https://doi.org/10.1371/journal.pone.0256583.

Zhu, Z., Yang, Y., Xiao, Z., Zhao, Q., Wu, W., Liang, X., ... & Ding, D. (2021). TOMM40 and APOE variants synergistically increase the risk of Alzheimer's disease in a Chinese population. *Aging Clinical and Experimental Research*, *33*(6), 1667-1675. https://doi.org/10.1007/s40520-020-01661-6.

S3.2 Relational, associative or other types of binding

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society*, *7*(5), 631-639. https://doi.org/10.1017/s1355617701755105.

Bäckman, L., & Herlitz, A. (1990). The relationship between prior knowledge and face recognition memory in normal aging and Alzheimer's disease. *Journal of Gerontology*, *45*(3), P94-P100. https://doi.org/10.1093/geronj/45.3.p94.

Bastin, C., Bahri, M. A., Miévis, F., Lemaire, C., Collette, F., Genon, S., Simon, J., Guillaume, B., Diana, R. A., Yonelinas, A. P., & Salmon, E. (2014). Associative memory and its cerebral correlates in Alzheimer's disease: evidence for distinct deficits of relational and conjunctive memory. *Neuropsychologia, 63*, 99–106. https://doi.org/10.1016/j.neuropsychologia.2014.08.023.

Borg, C., Leroy, N., Favre, E., Laurent, B., & Thomas-Antérion, C. (2011). How emotional pictures influence visuospatial binding in short-term memory in ageing and Alzheimer's disease? *Brain and Cognition, 76*(1), 20–25. https://doi.org/10.1016/j.bandc.2011.03.008.

Brugulat-Serrat, A., Salvadó, G., Sudre, C. H., Grau-Rivera, O., Suárez-Calvet, M., Falcon, C., Sánchez-Benavides, G., Gramunt, N., Fauria, K., Cardoso, M. J., Barkhof, F., Molinuevo, J. L., Gispert, J. D., & ALFA Study. (2019). Patterns of white matter hyperintensities associated with cognition in middle-aged cognitively healthy individuals. *Brain Imaging and Behavior, 14*, 2012–2023. https://doi.org/10.1007/s11682-019-00151-2

Buschke, H., Mowrey, W. B., Ramratan, W. S., Zimmerman, M. E., Loewenstein, D. A., Katz, M. J., & Lipton, R. B. (2017). Memory Binding Test Distinguishes Amnestic

Mild Cognitive Impairment and Dementia from Cognitively Normal Elderly. Archives of clinical neuropsychology: the official journal of the National Academy of *Neuropsychologists, 32*(1), 29–39. https://doi.org/10.1093/arclin/acw083.

Curiel, R. E., Crocco, E., Rosado, M., Duara, R., Greig, M. T., Raffo, A., & Loewenstein, D. A. (2016). A Brief Computerized Paired Associate Test for the Detection of Mild Cognitive Impairment in Community-Dwelling Older Adults. *Journal of Alzheimer's Disease, 54*(2), 793–799. https://doi.org/10.3233/JAD-160370.

de Rover, M., Pironti, V. A., McCabe, J. A., Acosta-Cabronero, J., Arana, F. S., Morein-Zamir, S., ... & Sahakian, B. J. (2011). Hippocampal dysfunction in patients with mild cognitive impairment: a functional neuroimaging study of a visuospatial paired associates learning task. *Neuropsychologia*, *49*(7), 2060-2070. https://doi.org/10.1016/j.neuropsychologia.2011.03.037.

Gagliardi, G., Epelbaum, S., Houot, M., Bakardjian, H., Boukadida, L., Revillon, M., Dubois, B., Dalla Barba, G., La Corte, V., & INSIGHT-preAD study group (2019). Which Episodic Memory Performance is Associated with Alzheimer's Disease Biomarkers in Elderly Cognitive Complainers? Evidence from a Longitudinal Observational Study with Four Episodic Memory Tests (Insight-PreAD). *Journal of Alzheimer's Disease, 70*(3), 811–824. https://doi.org/10.3233/JAD-180966.

Genon, S., Collette, F., Feyers, D., Phillips, C., Salmon, E., & Bastin, C. (2013). Item familiarity and controlled associative retrieval in Alzheimer's disease: an fMRI study. *Cortex, 49*(6), 1566–1584. https://doi.org/10.1016/j.cortex.2012.11.017.

Gramunt, N., Buschke, H., Sánchez-Benavides, G., Lipton, R. B., Peña-Casanova, J., Diéguez-Vide, F., Masramon, X., Gispert, J. D., Fauria, K., Camí, J., & Molinuevo, J. L. (2015). Reference Data of the Spanish Memory Binding Test in a Midlife Population

from the ALFA STUDY (Alzheimer's and Family). *Journal of Alzheimer's Disease, 48*(3), 613–625. https://doi.org/10.3233/JAD-150237.

Gramunt, N., Sánchez-Benavides, G., Buschke, H., Diéguez-Vide, F., Peña-Casanova, J., Masramon, X., Fauria, K., Gispert, J. D., & Molinuevo, J. L. (2016). The Memory Binding Test: Development of Two Alternate Forms into Spanish and Catalan. *Journal of Alzheimer's Disease, 52*(1), 283–293. https://doi.org/10.3233/JAD-151175.

Gramunt, N., Sánchez-Benavides, G., Buschke, H., Lipton, R. B., Masramon, X., Gispert, J. D., Peña-Casanova, J., Fauria, K., & Molinuevo, J. L. (2016). Psychometric Properties of the Memory Binding Test: Test-Retest Reliability and Convergent Validity. *Journal of Alzheimer's Disease, 50*(4), 999–1010. https://doi.org/10.3233/JAD-150776.

Janos, A., Duncanson, H., Erwin, S., Colvin, M., & Sherman, J. (2017). A-14Verbal Memory Binding and Markers of Brain Pathology in Preclinical Autosomal-dominant Alzheimer's Disease. *Archives of Clinical Neuropsychology, 32*(6), 667–765. https://doi.org/10.1093/arclin/acx076.14.

Liang, Y., Pertzov, Y., Nicholas, J. M., Henley, S., Crutch, S., Woodward, F., Leung, K., Fox, N. C., & Husain, M. (2016). Visual short-term memory binding deficit in familial Alzheimer's disease. *Cortex, 78*, 150–164. https://doi.org/10.1016/j.cortex.2016.01.015.

Monacelli, A. M., Cushman, L. A., Kavcic, V., & Duffy, C. J. (2003). Spatial disorientation in Alzheimer's disease: the remembrance of things passed. *Neurology*, *61*(11), 1491-1497. https://doi.org/10.1212/wnl.61.11.1491.

Mowrey, W. B., Lipton, R. B., Katz, M. J., Ramratan, W. S., Loewenstein, D. A., Zimmerman, M. E., & Buschke, H. (2018). Memory Binding Test Predicts Incident Dementia: Results from the Einstein Aging Study. *Journal of Alzheimer's Disease, 62*(1), 293–304. https://doi.org/10.3233/JAD-170714.

Mowrey, W. B., Lipton, R. B., Katz, M. J., Ramratan, W. S., Loewenstein, D. A., Zimmerman, M. E., & Buschke, H. (2016). Memory Binding Test Predicts Incident Amnestic Mild Cognitive Impairment. *Journal of Alzheimer's Disease, 53*(4), 1585–1595. https://doi.org/10.3233/JAD-160291.

Nashiro, K., & Mather, M. (2009). Does emotional content enhance older adults' and Alzheimer's disease patients' memory binding?. *Gerontologist* (Vol. 49, pp. 226-226).

Nashiro, K., & Mather, M. (2011). Effects of emotional arousal on memory binding in normal aging and Alzheimer's disease. *The American Journal of Psychology, 124*(3), 301–312. https://doi.org/10.5406/amerjpsyc.124.3.0301.

Roman, F., Iturry, M., Rojas, G., Barceló, E., Buschke, H., & Allegri, R. F. (2016). Validation of the Argentine version of the Memory Binding Test (MBT) for Early Detection of Mild Cognitive Impairment. *Dementia & Neuropsychologia, 10*(3), 217–226. https://doi.org/10.1590/S1980-5764-2016DN1003008.

Sánchez-Benavides, G., Grau-Rivera, O., Cacciaglia, R., Suárez-Calvet, M., Falcon, C., Minguillon, C., ... & Molinuevo, J. L. (2018). Distinct cognitive and brain morphological features in healthy subjects unaware of informant-reported cognitive decline. *Journal of Alzheimer's Disease*, *65*(1), 181-191. https://doi.org/10.3233/JAD-180378.

Sapkota, R. P., van der Linde, I., Lamichhane, N., Upadhyaya, T., & Pardhan, S. (2017). Patients with Mild Cognitive Impairment Show Lower Visual Short-Term Memory Performance in Feature Binding Tasks. *Dementia and Geriatric Cognitive Disorders Extra, 7*(1), 74–86. https://doi.org/10.1159/000455831.

Swainson, R., Hodges, J. R., Galton, C. J., Semple, J., Michael, A., Dunn, B. D., Iddon, J. L., Robbins, T. W., & Sahakian, B. J. (2001). Early detection and differential diagnosis of

Alzheimer's disease and depression with neuropsychological tasks. *Dementia and Geriatric Cognitive Disorders, 12*(4), 265–280. https://doi.org/10.1159/000051269.

van Geldorp, B., Heringa, S. M., van den Berg, E., Olde Rikkert, M. G., Biessels, G. J., & Kessels, R. P. (2015). Working memory binding and episodic memory formation in aging, mild cognitive impairment, and Alzheimer's dementia. *Journal of Clinical and Experimental Neuropsychology, 37*(5), 538–548. https://doi.org/10.1080/13803395.2015.1037722.

Villeneuve, S., & Belleville, S. (2012). The nature of memory failure in mild cognitive impairment: examining association with neurobiological markers and effect of progression. *Neurobiology of Aging, 33*(9), 1967–1978. https://doi.org/10.1016/j.neurobiolaging.2011.10.004.

Wang, X., Li, T., Zhang, H., Sun, T., Xiong, L., Zhang, Y., Sun, Z., Yu, X., & Wang, H. (2019). Validation of the Chinese version of the memory binding test for distinguishing amnestic mild cognitive impairment from cognitively normal elderly individuals. *International Psychogeriatrics, 31*(12), 1721–1730. https://doi.org/10.1017/S1041610219001649.

S3.3 Review, single-case, comment or answer letters, erratum or opinion articles

Allen, R. J. (2015) Memory Binding. In: Wright, J. D. (ed.) International Encyclopedia of the Social & Behavioral Sciences (Second Edition). Elsevier, 140 - 146. https://doi.org/10.1016/B978-0-08-097086-8.51046-0.

Birba, A., Hesse, E., Sedeño, L., Mikulan, E. P., García, M. D. C., Ávalos, J., ... & Ibáñez, A. (2017). Enhanced working memory binding by direct electrical stimulation of the

parietal cortex. *Frontiers in Aging Neuroscience*, *9*, 178. https://doi.org/10.3389/fnagi.2017.00178.

Burke, S. L., Naseh, M., Rodriguez, M. J., Burgess, A., & Loewenstein, D. (2019). Dementia-related neuropsychological testing considerations in non-Hispanic White and Latino/Hispanic populations. *Psychology & Neuroscience*, *12*(2), 144-168. https://doi.org/10.1037/pne0000163.

Buschke, H., Mowrey, W. B., Ramratan, W. S., Zimmerman, M. E., Loewenstein, D. A., Katz, M. J., & Lipton, R. B. (2017). "Memory Binding Test distinguishes amnestic mild cognitive impairment and dementia from cognitively normal elderly": Corrigendum. *Archives of Clinical Neuropsychology, 32*(8), 1037–1038. https://doi.org/10.1093/arclin/acx046.

Cerami, C., Dubois, B., Boccardi, M., Monsch, A. U., Demonet, J. F., Cappa, S. F., & for the Roadmap, G. T. F. (2017). Clinical validity of delayed recall tests as a gateway biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiology of Aging*, *52*, 153-166. https://doi.org/10.1016/j.neurobiolaging.2016.03.034.

Hutchinson, A. D., & Mathias, J. L. (2007). Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(9), 917-928. https://doi.org/10.1136/jnnp.2006.100669.

Ibanez, A., & Parra, M. A. (2014). Mapping memory binding onto the connectome's temporal dynamics: toward a combined biomarker for Alzheimer's disease. *Frontiers in Human Neuroscience*, *8*, 237. https://doi.org/10.3389/fnhum.2014.00237.

Jonin, P. Y., Calia, C., Muratot, S., Belliard, S., Duché, Q., Barbeau, E. J., & Parra, M. A. (2019). Refining understanding of working memory buffers through the construct of

binding: Evidence from a single case informs theory and clinical practise. *Cortex*, *112*, 37-57. https://doi.org/10.1016/j.cortex.2018.08.011.

Liang, Y., Pertzov, Y., Nicholas, J. M., Henley, S. M., Crutch, S., Woodward, F., & Husain, M. (2016). Visual short-term memory binding deficits in Alzheimer's disease: a reply to Parra's commentary. *Cortex*, *88*, 201-204. https://doi.org/10.1016/j.cortex.2016.11.003.

Martínez, J. F., Trujillo, C., Arévalo, A., Ibáñez, A., & Cardona, J. F. (2019). Assessment of conjunctive binding in aging: A promising approach for Alzheimer's disease detection. *Journal of Alzheimer's Disease*, *69*(1), 71-81. https://doi.org/10.3233/JAD-181154.

Mathias, J. L., & Burke, J. (2009). Cognitive functioning in Alzheimer's and vascular dementia: A meta-analysis. *Neuropsychology*, *23*(4), 411-423. https://doi.org/10.1037/a0015384.

Mowrey, W. B., Lipton, R. B., Katz, M. J., Ramratan, W. S., Loewenstein, D. A., Zimmerman, M. E., & Buschke, H. (2017). Erratum: Memory Binding Test predicts incident amnestic mild cognitive impairment. *Journal of Alzheimer's Disease*, *58*(3), 951-952. https://doi.org/10.3233/JAD-179003.

Pavisic, I. M., Suarez-Gonzalez, A., & Pertzov, Y. (2020). Translating visual short-term memory binding tasks to clinical practice: From theory to practice. *Frontiers in Neurology*, *11*, 458. https://doi.org/10.3389/fneur.2020.00458.

Rentz, D. M., Rodriguez, M. A. P., Amariglio, R., Stern, Y., Sperling, R., & Ferris, S. (2013). Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: a selective review. *Alzheimer's Research & Therapy*, *5*(6), 58. https://doi.org/10.1186/alzrt222.

Sepulveda-Falla, D., Glatzel, M., & Lopera, F. (2012). Phenotypic profile of early-onset familial Alzheimer's disease caused by presenilin-1 E280A mutation. *Journal of Alzheimer's Disease*, *32*(1), 1-12. https://doi.org/10.3233/JAD-2012-120907.

Sun, M.-K. (2016). Research progress in Alzheimer's disease and dementia: Volume 6. Nova Science Publishers.

Vyhnálek, M., Marková, H., Laczó, J., De Beni, R., & Di Nuovo, S. (2019). Assessment of Memory Impairment in Early Diagnosis of Alzheimer's Disease. *Current Alzheimer Research*, *16*(11), 975-985. https://doi.org/10.2174/1567205016666191113125303.

S3.4 No AD continuum group

Chapman, S., Sunderaraman, P., Joyce, J. L., Azar, M., Colvin, L. E., Barker, M. S., McKeague, I., Kreisl, W. C., & Cosentino, S. (2021). Optimizing Subjective Cognitive Decline to Detect Early Cognitive Dysfunction. *Journal of Alzheimer's Disease*, *80*(3), 1185–1196. https://doi.org/10.3233/JAD-201322.

Isella, V., Molteni, F., Mapelli, C., & Ferrarese, C. (2015). Short term memory for single surface features and bindings in ageing: A replication study. *Brain and Cognition, 96*, 38-42. https://doi.org/10.1016/j.bandc.2015.02.002.

Killin, L., Abrahams, S., Parra, M., & Della Sala, S. (2018). The effect of age on the FCSRT-IR and temporary visual memory binding. *International Psychogeriatrics, 30*(3), 331-340. https://doi.org/10.1017/S104161021700165X.

Loughrey, D. G., Parra, M. A., & Lawlor, B. A. (2019). Visual short-term memory binding deficit with age-related hearing loss in cognitively normal older adults. *Scientific Reports, 9*(1), 12600. https://doi.org/10.1038/s41598-019-49023-1.

Smith, K., Azami, H., Escudero, J., Parra, M. A., & Starr, J. M. (2015). Comparison of network analysis approaches on EEG connectivity in beta during Visual Short-term Memory binding tasks. In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 2207-2210).

Smith, K., Ricaud, B., Shahid, N., Rhodes, S., Starr, J. M., Ibáñez, A., ... & Vandergheynst, P. (2017). Locating temporal functional dynamics of visual short-term memory binding using graph modular dirichlet energy. *Scientific Reports, 7*, 42013. https://doi.org/10.1038/srep42013.

Yassuda, M. S., Carthery-Goulart, M. T., Cecchini, M. A., Cassimiro, L., Fernandes, K. D., Baradel, R. R., ... & Parra, M. A. (2020). Free recall of bound information held in short-term memory is unimpaired by age and education. *Archives of Clinical Neuropsychology, 35*(2), 165-175. https://doi.org/10.1093/arclin/acz015.

S3.5 Poster, meeting abstract, single-case or no access to data

Cerea, E. & Caratozzolo, Salvatore & Riva, Maddalena & Chilovi, Barbara & Rozzini, L. & Padovani, Alessandro. (2012). Short-term memory binding in mild cognitive impairment: a preclinical marker of Alzheimer's disease?. 113-113.

Josefsson, A., Ibáñez, A., Parra, M., & Escudero, J. (2019). Network analysis through the use of joint-distribution entropy on EEG recordings of MCI patients during a visual short-term memory binding task. *Healthcare Technology Letters*, *6*(2), 27-31.

S4. Quality of evidence and risk of bias assessment of the included studies following GRADE guidelines

Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Observations	Effect size (95%CI)	Quality
Parra, Abrahams, Fabi, Logie, Luzzi & Della Sala (2009). Two groups of controls and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AD (1) = -1.61 (-2.28; -0.94) HC x AD (2) = -0.51 (-1.13; 0.12) Feature binding condition HC x AD (1) = -2.89 (-3.74; -2.04) HC x AD (2) = -2.22 (-3.02; -1.43)	Moderate
Parra, Abrahams, Logie, & Della Sala (2010). Controls and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AD (ss2) = -1.17 (-1.98; -0.35) HC x AD (ss3) = -2.66 (-3.72; -1.61) Feature binding condition HC x AD (ss2) = -2.47 (-3.48; -1.45) HC x AD (ss3) = -2.50 (-3.52; -1.48)	Moderate
Parra, Abrahams, Logie, Mendez, Lopera & Della Sala (2010). Controls, asymptomatic carriers and FAD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AC = -0.24 (-0.75; 0.27) HC x FAD = -0.13 (-0.68; 0.43) Feature binding condition HC x AC = -1.52 (-2.10; -0.94) HC x FAD = -1.65 (-2.29; -1.01)	Moderate
Parra, Della Sala, Abrahams, Logie, Méndez & Lopera (2011). Controls, sporadic and familial patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x SAD = 0.41 (-0.34; 1.16) HC x FAD = 0.04 (-0.58; 0.65) Feature binding condition HC x SAD = -1.35 (-2.19; -0.52) HC x FAD = -1.48 (-2.19; -0.78)	Moderate

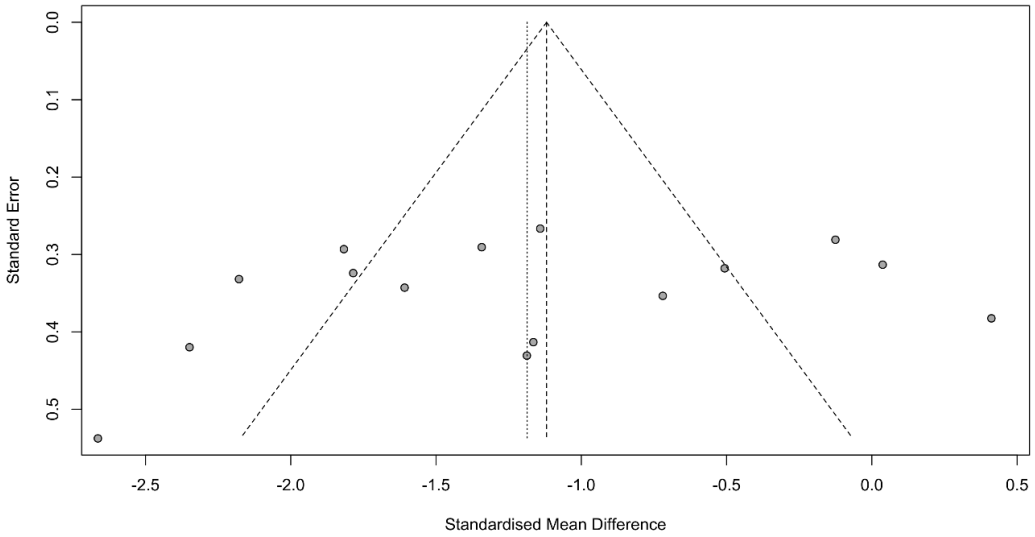
Della Sala, Parra, Fabi, Luzzi & Abrahams (2012). Controls and AD were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AD = -0.72 (-1.41; -0.03) Feature binding condition HC x AD = -2.89 (-3.87; -1.90)	Moderate
Koppara, Frommann, Polcher, Parra, Maier, Jessen, Klockgether & Wagner (2015). Controls, Subjective cognitive decline and MCI were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x SCD = -0.21 (-0.82; 0.40) HC x MCI = -1.16 (-1.79; -0.54) Feature binding condition HC x SCD = -0.85 (-1.49; -0.21) HC x MCI = -1.33 (-1.97; -0.68)	Moderate
Parra, Saarimaki, Bastin, Londono, Pettit, Lopera, Della Sala & Abrahams (2015). Controls, Asymptomatic carriers and FAD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AC = -0.51 (-1.15; 0.13) HC x FAD = -2.35 (-3.17; -1.52) Feature binding condition HC x AC = -1.06 (-1.73; -0.38) HC x FAD = -2.09 (-2.88; -1.31)	Moderate
Della Sala, S., Kozlova, I., Stamate, A., & Parra, M. A. (2016). Controls and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AD = -1.14 (-1.66; -0.62) Feature binding condition HC x AD = -3.89 (-4.73; -3.05)	Moderate
Pietto, Parra, Trujillo, Flores, García, Bustin, Richly, Manes, Lopera, Ibáñez & Baez (2016). Controls, MCI and MCI-FAD were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	-1. 95%CI upper and lower bounds with different meaning.	No publication bias identified.		Single feature condition HC x MCI = -0.86 (-1.66; -0.07) HC x MCI-FAD = -0.98 (-1.91; -0.04) Feature binding condition HC x MCI = -0.90 (-1.69; -0.10) HC x MCI-FAD = -0.89 (-1.81; 0.04)	Low

Cecchini, Yassuda, Bahia, et al. (2017). Controls and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AD = -1.82 (-2.39; -1.24) Feature binding condition HC x AD = -1.49 (-2.03; -0.94)	Moderate
Fernandez, Orozco, Agamennoni, Schumacher, Sanudo, Biondi & Parra (2018). Controls and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x AD = -1.19 (-2.03; -0.34) Feature binding condition HC x AD = -4.01 (-5.42; -2.60)	Moderate
Parra, Calia, García, Olazarán-Rodríguez, Hernandez-Tamames, Alvarez-Linera, Della Sala, Fernandez & Guinea (2019). Two groups of controls and MCI patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x MCI (ss2) = -0.37 (-0.92; 0.18) HC x MCI (ss3) = -1.46 (-2.08; -0.84) Feature binding condition HC x MCI (ss2) = -1.25 (-1.85; -0.65) HC x MCI (ss3) = -1.21 (-1.80; -0.61)	Moderate
Cecchini et al. (2020). Controls, MCI and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x MCI (CD) = -1.19 (-1.81; -0.57) HC x MCI (FR) = -1.95 (-2.64; -1.25) HC x AD (CD) = -1.34 (-1.91; -0.77) HC x AD (FR) = -2.18 (-2.83; -1.53) Feature binding condition HC x MCI (CD) = -1.58 (-2.24; -0.92) HC x MCI (FR) = -2.52 (-3.32; -1.72) HC x AD (CD) = -1.83 (-2.45; -1.22) HC x AD (FR) = -2.48 (-3.17; -1.80)	Moderate
Guazzo, Allen, Baddeley & Della Sala (2020). Controls and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Feature binding condition HC x AD = -4.17 (-5.21; -3.14)	Moderate

Kozlova, Parra, Titova, Gantman, & Sala (2020). Controls, amnestic MCI and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Single feature condition HC x aMCI = -1.26 (-1.94; -0.59) HC x AD = -1.79 (-2.42; -1.15) Feature binding condition HC x aMCI = -2.36 (-3.16; -1.56) HC x AD = -3.37 (-4.22; -2.53)	Moderate
Norton et al. (2020). Controls, asymptomatic carriers and MCI patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	-1. 95%CI upper and lower bounds with different meaning.	No publication bias identified.		Single feature condition HC x AC = -0.49 (-1.08; 0.11) HC x MCI = -1.97 (-2.99; -0.95) Feature binding condition HC x AC = -0.56 (-1.16; 0.04) HC x MCI = -0.75 (-1.66; 0.16)	Low
Valdéz-Hernández, Clark, Wang, Guazzo, Calia, Pattan, Starr, Della Sala & Parra (2020). Controls and MCI patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	-1. 95%CI upper and lower bounds with different meaning.	No publication bias identified.		Single feature condition HC x MCI = -0.66 (-1.25; -0.06) Feature binding condition HC x MCI (ss2) = -0.82 (-1.43; -0.22) HC x MCI (ss3) = -0.79 (-1.39; -0.18)	Low
Cecchini et al. (2021). Controls, MCI and AD patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	No serious imprecision.	No publication bias identified.	Increased from low to moderate quality based on large effect sizes.	Feature binding condition HC x MCI = -0.63 (-1.23; -0.03) HC x AD = -1.34 (-2.03; -0.65)	Moderate
Martínez-Florez et al. (2021). Controls and MCI patients were compared.								
-1. Observational, case-control.	-1. Impossibility of blinding procedures or lack of allocation concealment	No serious inconsistencies.	No indirectness observed	-1. 95%CI upper and lower bounds with different meaning.	No publication bias identified.		Single feature condition HC x MCI (t1 ss3) = -0.67 (-1.03; -0.32) HC x MCI (t2 ss3) = -1.07 (-1.67; -0.48) Feature binding condition HC x MCI (t1 ss2) = -0.87 (-1.23; -0.51) HC x MCI (t1 ss3) = -0.64 (-1.00; -0.29) HC x MCI (t2 ss2) = -0.64 (-1.22; -0.07) HC x MCI (t2 ss3) = -0.61 (-1.18; -0.03)	Low

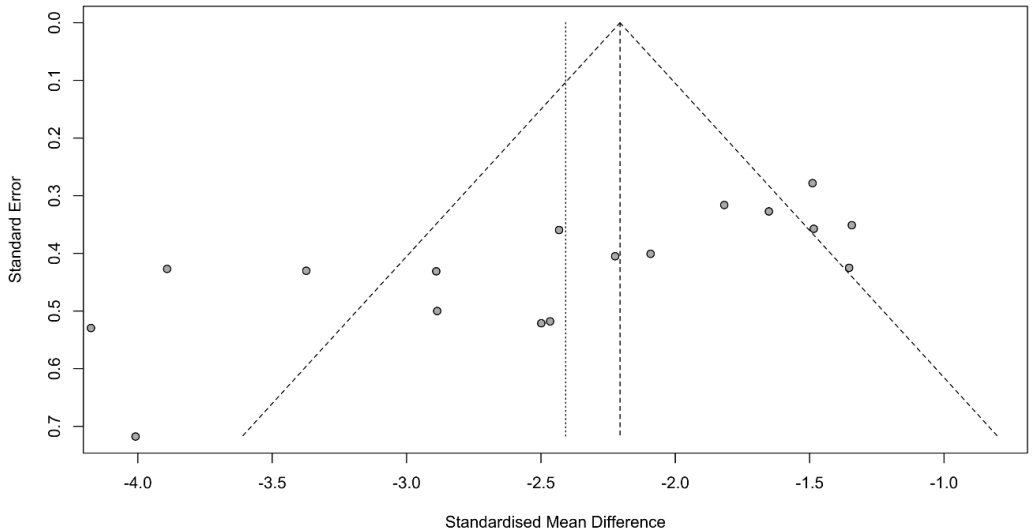
S5. Funnel Plots

S5.1 Performance of people with AD / Familial AD versus Controls, single feature condition.



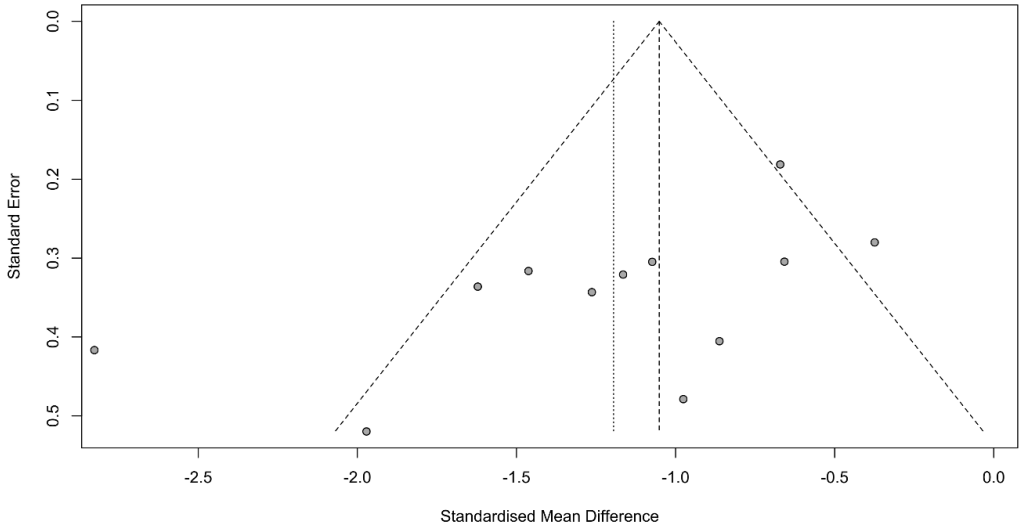
Note. Funnel plot of studies assessing the difference of the single feature condition of the short-term memory binding test between patients with sporadic/familial Alzheimer's disease and controls.

S5.2 Performance of people with AD / Familial AD versus Controls, feature binding condition.



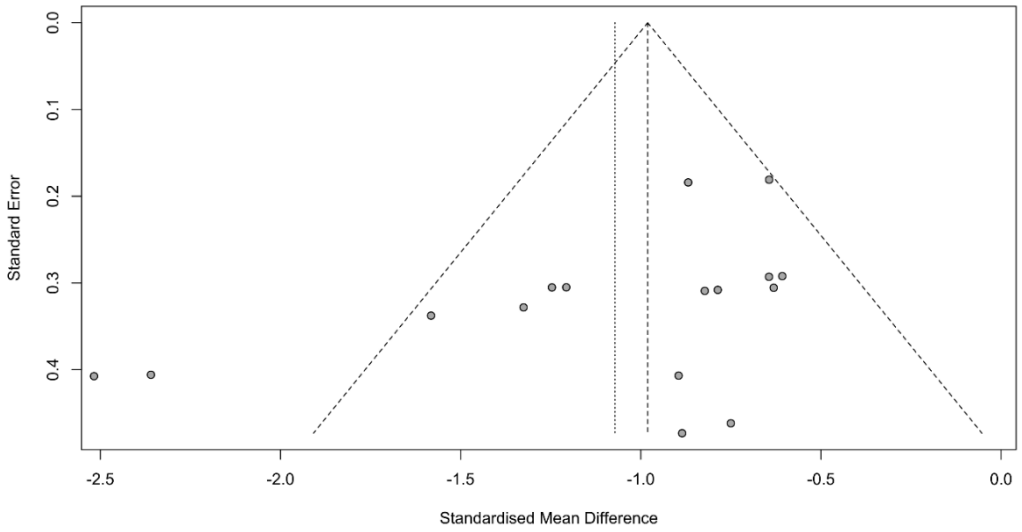
Note. Funnel plot of studies assessing the difference of the feature binding condition of the short-term memory binding test between patients with sporadic/familial Alzheimer's disease and controls.

S5.3 Performance of people with MCI / MCI-FAD versus controls, single feature condition.



Note. Funnel plot of studies assessing the difference of the single feature condition of the short-term memory binding test between people with MCI and MCI-FAD and controls.

S5.4 Performance of people with MCI / MCI-FAD versus controls, feature binding condition.

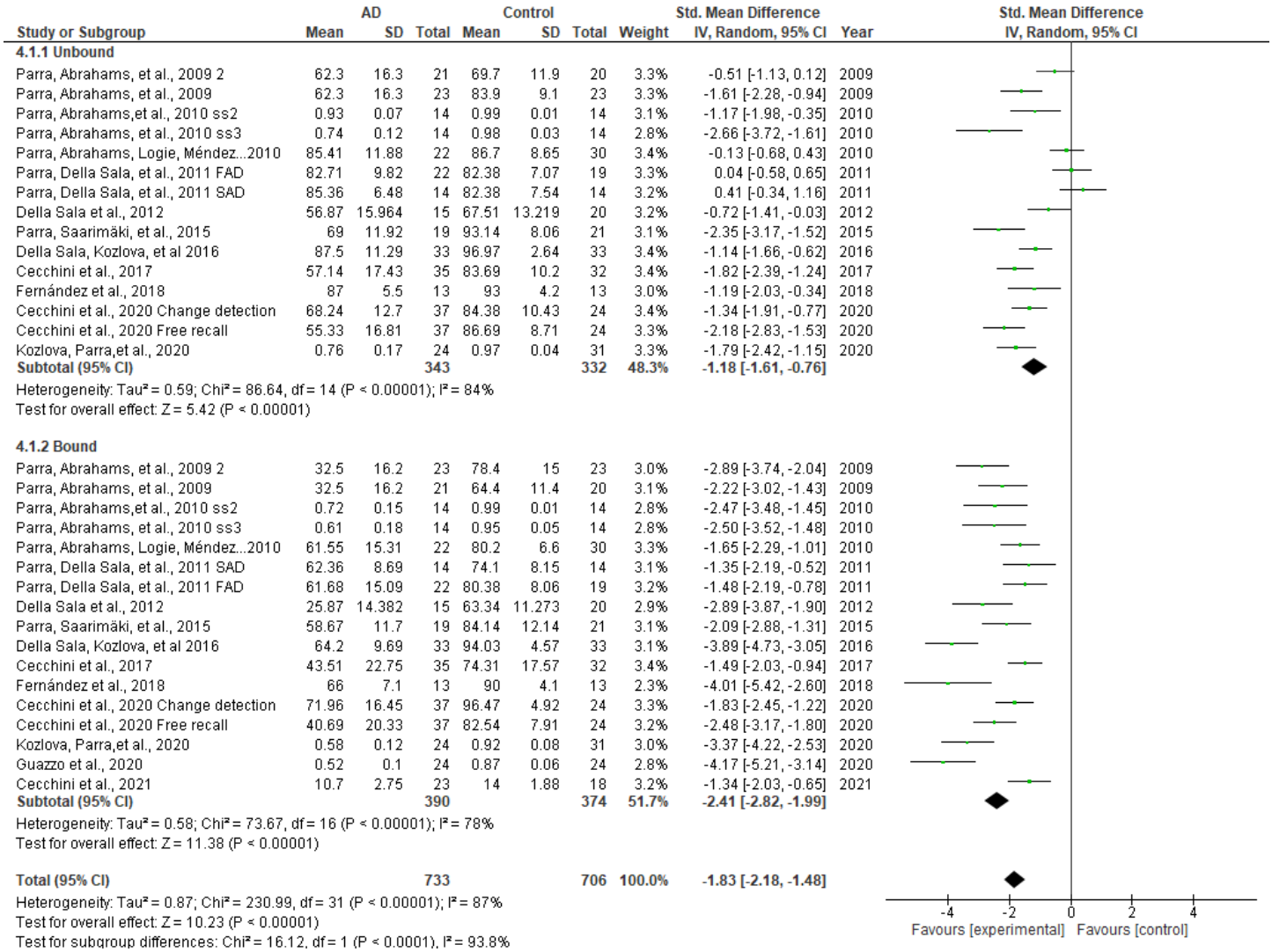


Note. Funnel plot of studies assessing the difference of the feature binding condition of the short-term memory binding test between patients with MCI and MCI-FAD and controls.

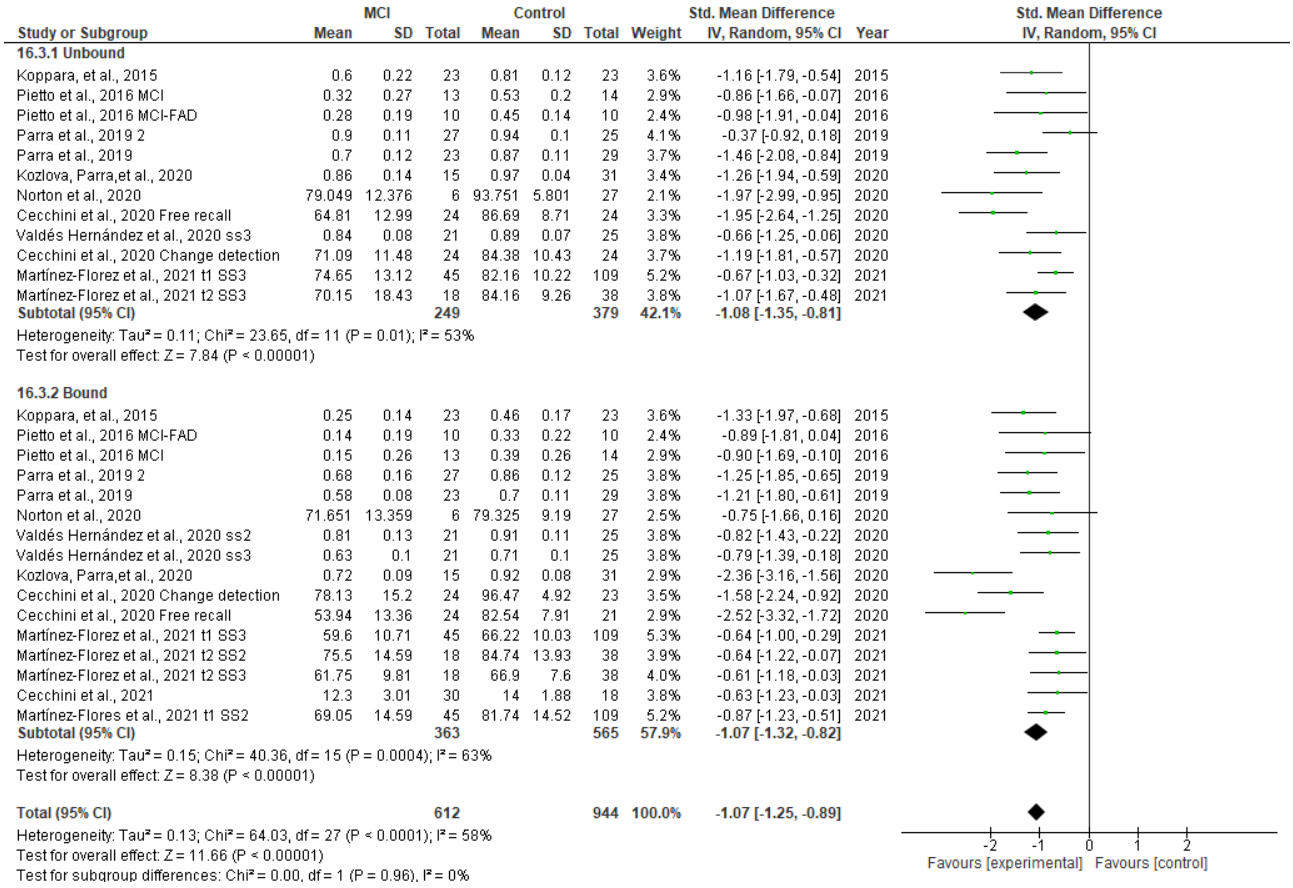
S6. Subgroup analyses

S6.1 Single feature vs. feature binding conditions

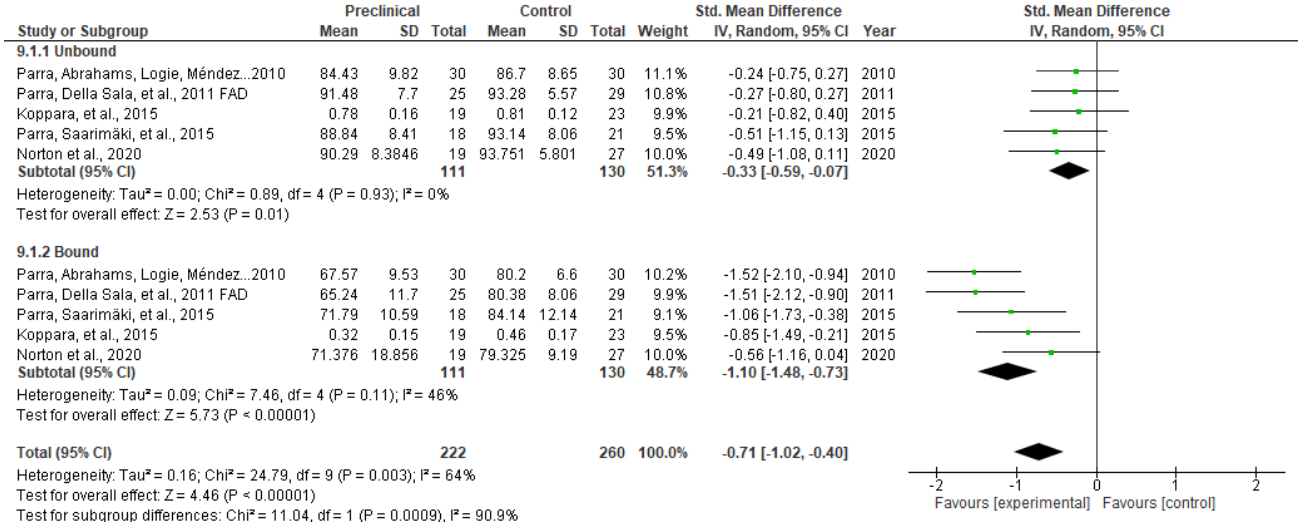
AD


AD
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
4.1.1 Unbound
Parra, Abrahams, et al., 2009 2 62.3 16.3 21 69.7 11.9 20 3.3% -0.51 [-1.13, 0.12] 2009
Parra, Abrahams, et al., 2009 62.3 16.3 23 83.9 9.1 23 3.3% -1.61 [-2.28, -0.94] 2009
Parra, Abrahams,et al., 2010 ss2 0.93 0.07 14 0.99 0.01 14 3.1% -1.17 [-1.98, -0.35] 2010
Parra, Abrahams, et al., 2010 ss3 0.74 0.12 14 0.98 0.03 14 2.8% -2.66 [-3.72, -1.61] 2010
Parra, Abrahams, Logie, Méndez...2010 85.41 11.88 22 86.7 8.65 30 3.4% -0.13 [-0.68, 0.43] 2010
Parra, Della Sala, et al., 2011 FAD 82.71 9.82 22 82.38 7.07 19 3.3% 0.04 [-0.58, 0.65] 2011
Parra, Della Sala, et al., 2011 SAD 85.36 6.48 14 82.38 7.54 14 3.2% 0.41 [-0.34, 1.16] 2011
Della Sala et al., 2012 56.87 15.964 15 67.51 13.219 20 3.2% -0.72 [-1.41, -0.03] 2012
Parra, Saarimäki, et al., 2015 69 11.92 19 93.14 8.06 21 3.1% -2.35 [-3.17, -1.52] 2015
Della Sala, Kozlova, et al 2016 87.5 11.29 33 96.97 2.64 33 3.4% -1.14 [-1.66, -0.62] 2016
Cecchini et al., 2017 57.14 17.43 35 83.69 10.2 32 3.4% -1.82 [-2.39, -1.24] 2017
Fernández et al., 2018 87 5.5 13 93 4.2 13 3.0% -1.19 [-2.03, -0.34] 2018
Cecchini et al., 2020 Change detection 68.24 12.7 37 84.38 10.43 24 3.4% -1.34 [-1.91, -0.77] 2020
Cecchini et al., 2020 Free recall 55.33 16.81 37 86.69 8.71 24 3.3% -2.18 [-2.83, -1.53] 2020
Kozlova, Parra,et al., 2020 0.76 0.17 24 0.97 0.04 31 3.3% -1.79 [-2.42, -1.15] 2020
Subtotal (95% CI) 343 332 48.3% -1.18 [-1.61, -0.76]
Heterogeneity: Tau² = 0.59; Chi² = 86.64, df = 14 (P < 0.00001); I² = 84%
Test for overall effect: Z = 5.42 (P < 0.00001)
4.1.2 Bound
Parra, Abrahams, et al., 2009 2 32.5 16.2 23 78.4 15 23 3.0% -2.89 [-3.74, -2.04] 2009
Parra, Abrahams, et al., 2009 32.5 16.2 21 64.4 11.4 20 3.1% -2.22 [-3.02, -1.43] 2009
Parra, Abrahams,et al., 2010 ss2 0.72 0.15 14 0.99 0.01 14 2.8% -2.47 [-3.48, -1.45] 2010
Parra, Abrahams, et al., 2010 ss3 0.61 0.18 14 0.95 0.05 14 2.8% -2.50 [-3.52, -1.48] 2010
Parra, Abrahams, Logie, Méndez...2010 61.55 15.31 22 80.2 6.6 30 3.3% -1.65 [-2.29, -1.01] 2010
Parra, Della Sala, et al., 2011 SAD 62.36 8.69 14 74.1 8.15 14 3.1% -1.35 [-2.19, -0.52] 2011
Parra, Della Sala, et al., 2011 FAD 61.68 15.09 22 80.38 8.06 19 3.2% -1.48 [-2.19, -0.78] 2011
Della Sala et al., 2012 25.87 14.382 15 63.34 11.273 20 2.9% -2.89 [-3.87, -1.90] 2012
Parra, Saarimäki, et al., 2015 58.67 11.7 19 84.14 12.14 21 3.1% -2.09 [-2.88, -1.31] 2015
Della Sala, Kozlova, et al 2016 64.2 9.69 33 94.03 4.57 33 3.1% -3.89 [-4.73, -3.05] 2016
Cecchini et al., 2017 43.51 22.75 35 74.31 17.57 32 3.4% -1.49 [-2.03, -0.94] 2017
Fernández et al., 2018 66 7.1 13 90 4.1 13 2.3% -4.01 [-5.42, -2.60] 2018
Cecchini et al., 2020 Change detection 71.96 16.45 37 96.47 4.92 24 3.3% -1.83 [-2.45, -1.22] 2020
Cecchini et al., 2020 Free recall 40.69 20.33 37 82.54 7.91 24 3.2% -2.48 [-3.17, -1.80] 2020
Kozlova, Parra,et al., 2020 0.58 0.12 24 0.92 0.08 31 3.0% -3.37 [-4.22, -2.53] 2020
Guazzo et al., 2020 0.52 0.1 24 0.87 0.06 24 2.8% -4.17 [-5.21, -3.14] 2020
Cecchini et al., 2021 10.7 2.75 23 14 1.88 18 3.2% -1.34 [-2.03, -0.65] 2021
Subtotal (95% CI) 390 374 51.7% -2.41 [-2.82, -1.99]
Heterogeneity: Tau² = 0.58; Chi² = 73.67, df = 16 (P < 0.00001); I² = 78%
Test for overall effect: Z = 11.38 (P < 0.00001)
Total (95% CI) 733 706 100.0% -1.83 [-2.18, -1.48]
Heterogeneity: Tau² = 0.87; Chi² = 230.99, df = 31 (P < 0.00001); I² = 87%
Test for overall effect: Z = 10.23 (P < 0.00001)
Test for subgroup differences: Chi² = 16.12, df = 1 (P < 0.0001), I² = 93.8%
-4
-2
0
2
4
Favours [experimental]
Favours [control]

MCI

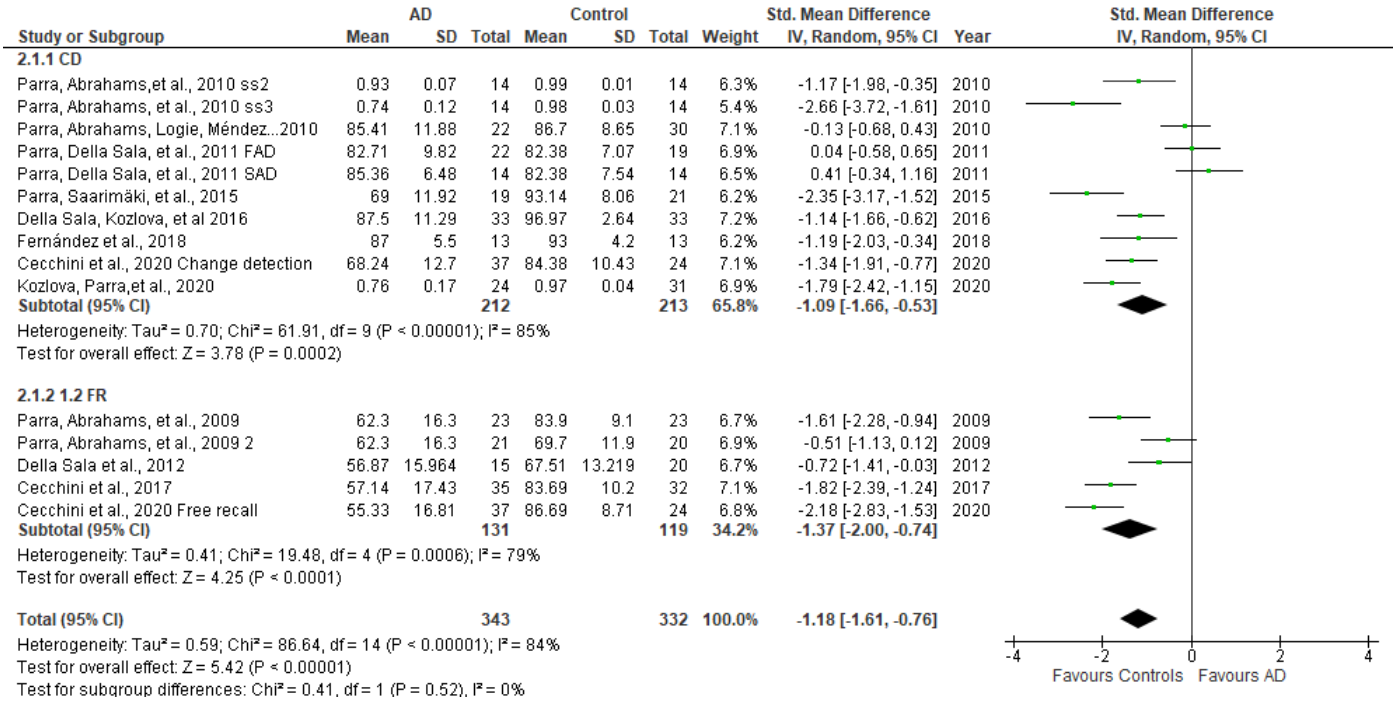


Preclinical

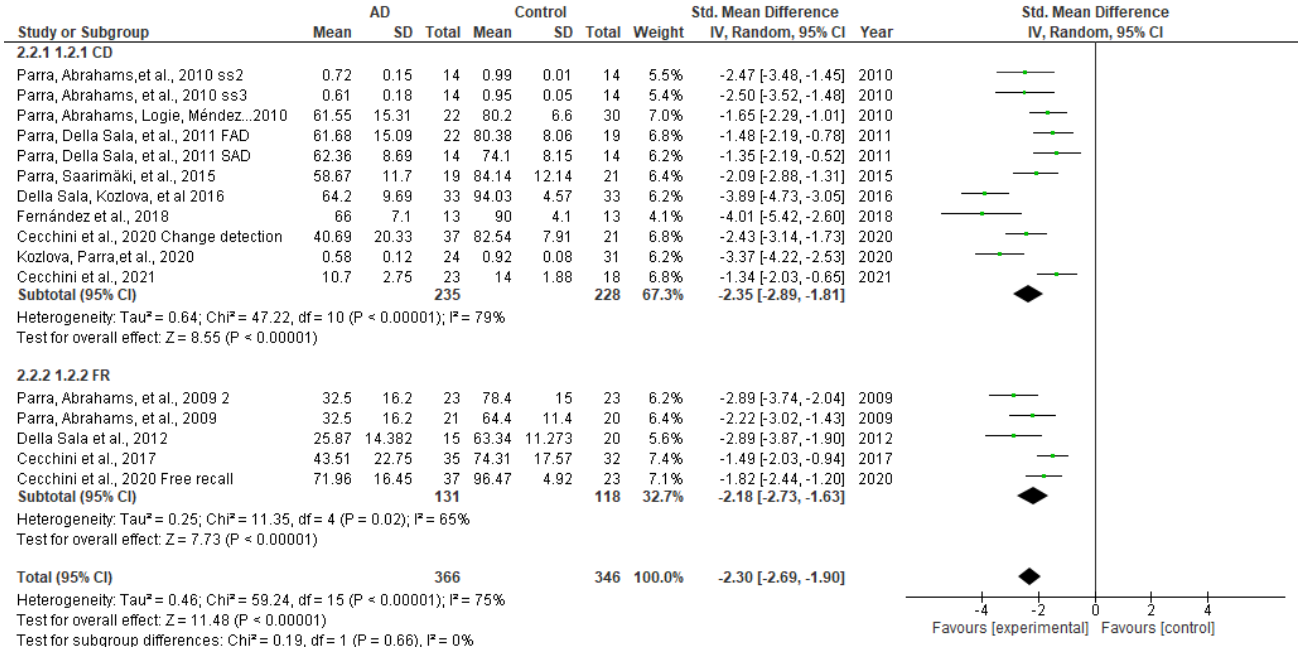


S6.2 Change detection vs. Free recall tasks

AD – Single feature



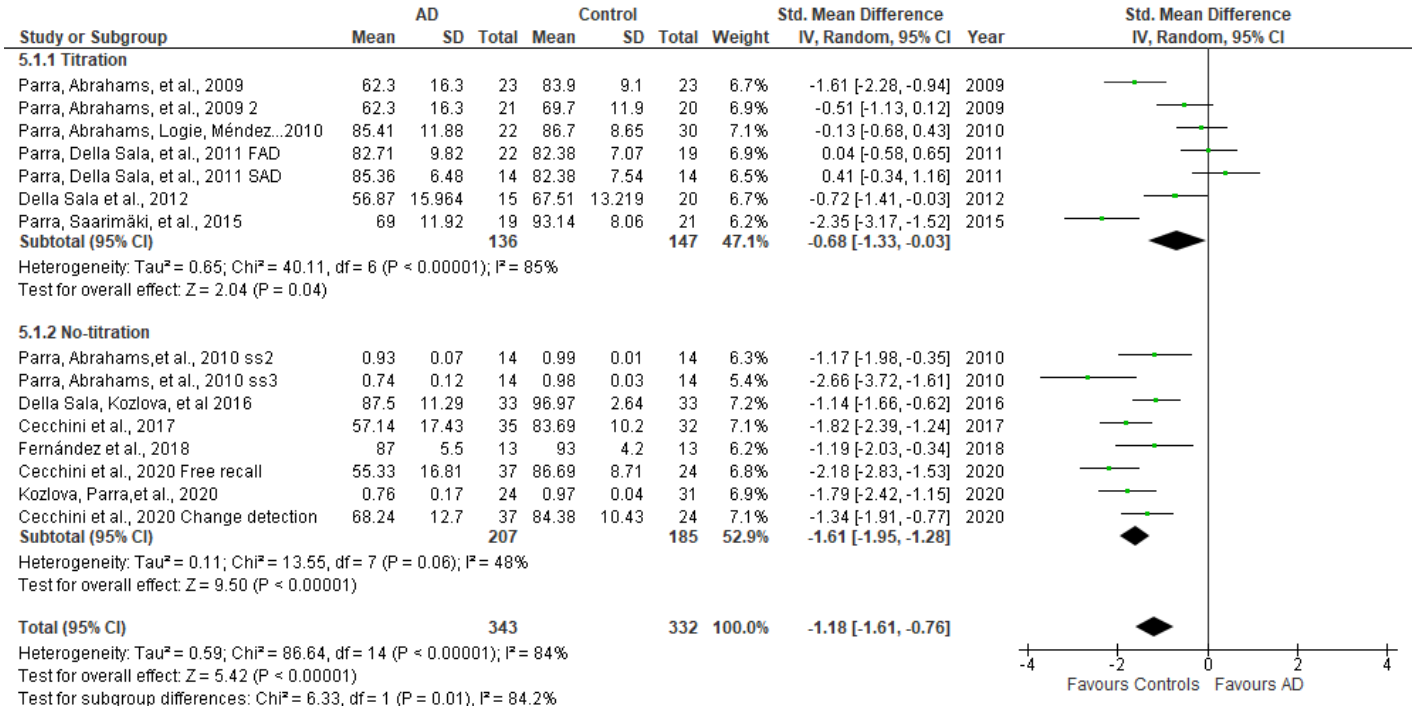
AD – feature binding



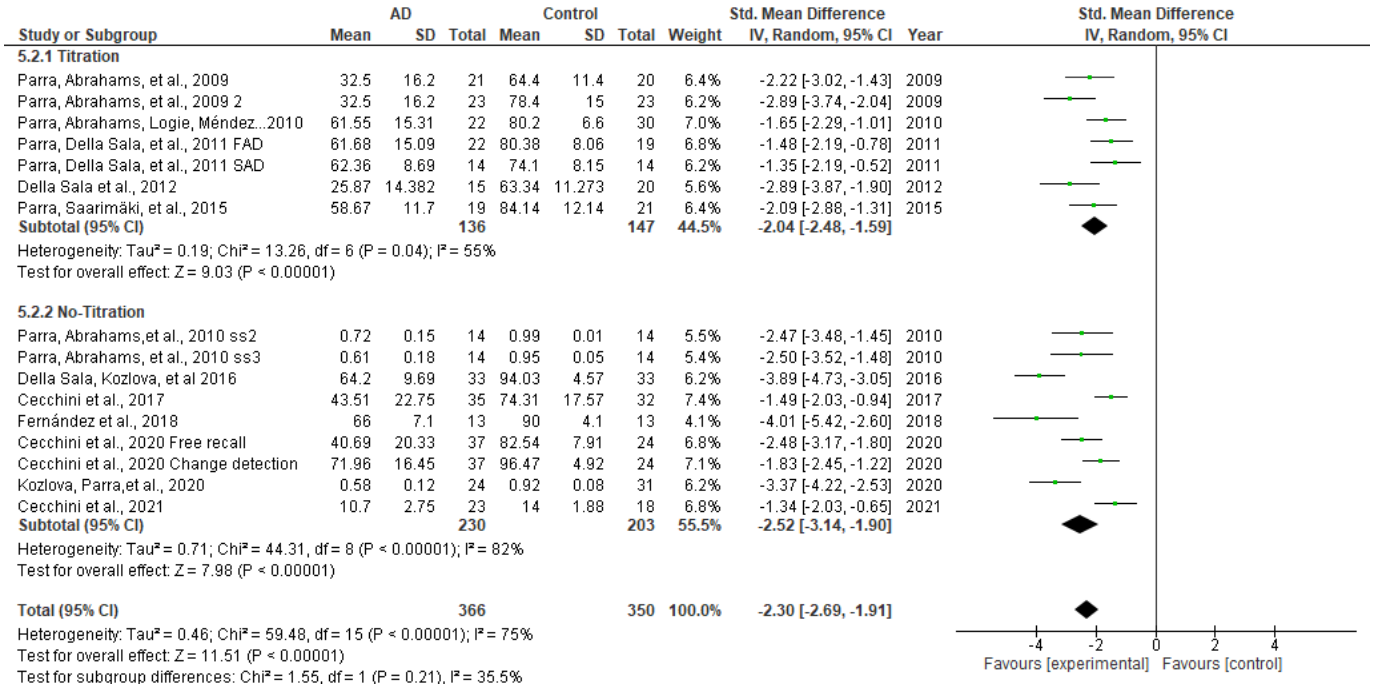
S6.3 Difficulty titration vs. no-titration

AD

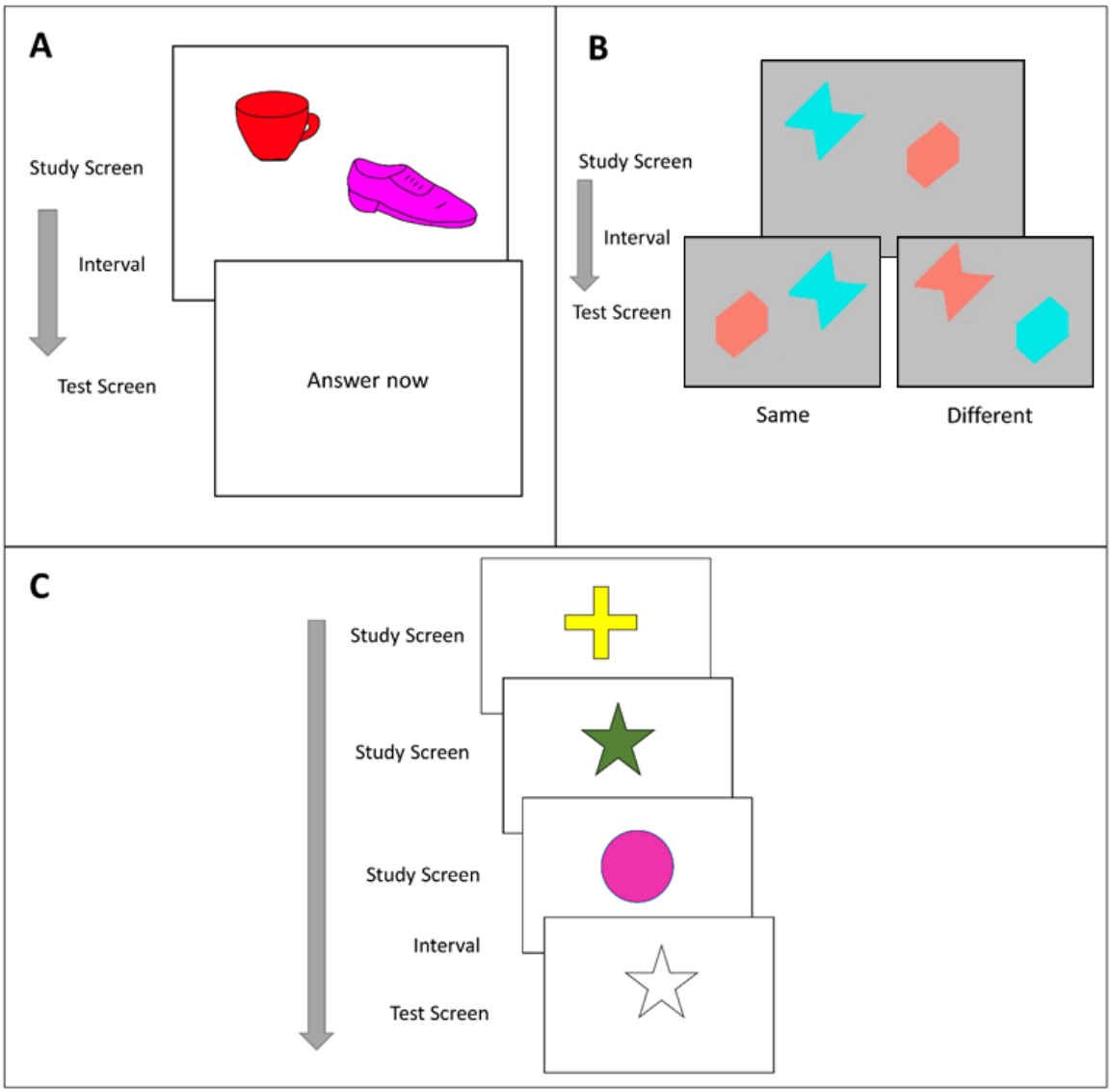
Single feature



Feature binding



S7. Short-Term Memory Conjunctive Binding Tasks Examples



Note. Examples of paradigms used in short-term memory conjunctive binding tasks. **A**: Free recall task, as used in *Della Sala et al., 2012; Parra et al., 2009b; Cecchini et al., 2017a; 2020*. Participants were presented with nameable stimuli (objects and colors) and after a delay they should say aloud the combination of objects and colors previously seen. **B**: Change detection task, as used in *Parra et al., 2010a; 2010b; 2011b; 2015b; 2017a; 2019; Koppara et al., 2015b; Della Sala et al., 2016; Pietto et al., 2016; Fernández et al., 2018; Kozlova et al., 2020; Norton et al., 2020; Valdés Hernández et al., 2020; Cecchini et al., 2020; Martínez-Flores et al., 2021; Cecchini et al., 2021; Fernández & Parra, 2021*. In test phase, participants should recognize if the combinations between shapes and colors are the same or different as shown in the study phase. **C**: Cued recall paradigm, in a continuous presentation method, as used in *Guazzo et al., 2020*. A sequence of shapes was presented, and their colors were presented verbally through headphones. On test phase, participants should recall the missing feature (e.g., in this example, the color green).

Variations in the tasks were found, including: the exposure time at study or test phase, the study-test interval, the activity performed during this interval (e.g., articulatory suppression), the number of stimuli per trial and the type of stimuli on change detection tasks (unnamable shapes-colors binding or color-color binding).