Tracing brain amyloid-β in asymptomatic older adults relying on a memory marker for Alzheimer's disease

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Research in context

Evidence before this study

A recent systematic review and meta-analysis suggested that a memory marker for Alzheimer's disease (AD) called the Visual Short-Term Memory Binding (VSTMB) Test shows large effect sizes in all stages of the disease. The authors acknowledged that more work is needed in earlier stages of the disease to boost the strength of the evidence. Earlier evidence from asymptomatic carriers of the mutation E280A-PSEN1 suggested that this function declines before any other ability assessed via traditional neuropsychological tests. Similar findings were drawn from a study that investigated older adults with Subjective Cognitive Complaints. Two recent neuroimaging studies that followed the new recommendations toward the biological definition of AD highlighted that decline of this memory function is associated to the accumulation of brain Amyloid-β (Aβ) in those at risk of AD prior to neurodegeneration. No study to date had explored such an association in completely asymptomatic healthy older adults.

Added value of this study

The results here reported have significant implications for theories of cognitive aging and for the preclinical detection of AD. Regarding the former, we have demonstrated that VSTMB remains preserved throughout the lifespan. Such a property renders this function unique to aid in the detection of departures from healthy ageing. This leads to the latter

contribution inasmuch as tests that tax such a memory function are proving markers for the preclinical detection of AD.

Implications of all the available evidence

The shift from cure to prevention of AD has significant challenges. Prevention entails early detection and effective treatments, and both are lacking. Prevention trials for AD rely on Aβ-PET for screening purposes. It has been recently reported that the fail rate of this highly expensive methodology is 71%, with 3.39 individuals screened to identify one Aβ+ individual. Having available a test that selectively indexes amyloid deposition from the very early stages of the disease continuum will greatly support AD prevention initiatives.

Abstract

Recent approaches to the early diagnosis of Alzheimer's disease (AD) are aimed at detecting neuropathological signatures of this type of dementia in still healthy older adults. Should these efforts prove fruitful, strategies then focus on identifying the cognitive and functional decline that ensue. These approaches have proved both little effective and costly. In the present study, we investigated the hypothesis that effective cognitive markers for AD could help detect among still healthy older adults who would have likely started to accumulate the neuropathological changes pursued by costly neuroimaging procedures. A sample of 39 healthy older adults was recruited and assessed with an extensive neuropsychological and neuroimaging protocol. As the memory marker, we used the Visual Short-Term Memory Binding Task. Using existing data, participants were divided in two groups depending on whether or not they displayed the typical binding profile seen in AD subjects (i.e., strong binders – SB and weak binders - WB). The results show that in addition to the increased binding cost seen in WB, SB and WB could only be differentiated by the amount of Amyloid-β accumulated in brain regions known to be involved in this cognitive function. No other neuropsychological tests proved informative, and neither volumetric nor cortical thickness metrics provided meaningful neuropathological signals. Our findings have significant implications for our understanding of the transition from normal ageing to preclinical AD and methodological approaches currently used to ascertain it. These are discussed at length.

Introduction

Assessment of memory in people with suspected Alzheimer's disease (AD) has long focused on episodic memory, being its associative forms the most commonly targeted [1]. This practice stems from the shared view that early AD pathology affects the hippocampus, a medial temporal lobe region known to support the formation of episodic memory via associative representations [2]. Our understanding of memory decline in AD has increased considerably since traditional memory tests used to aid its diagnosis were developed. A hypothetical model of memory decline in AD rooted in Braak's pathological stages [3] suggests that hippocampal atrophy, resulting from the accumulation of neurofibrillary tangles, appears rather late in the disease continuum. There is first a sub-hippocampal stage during which, regions of the anterior temporal lobe network are targeted by the disease. Such regions (e.g., entorhinal and perirhinal cortex) are involved in context-free memory functions such as familiarity-based recognition. Regions of this network are affected by AD earlier than the hippocampus [4], spared in normal ageing [5], and involved in context-free memory [3]. Therefore, tests that tax the functional integrity of this network will more likely detect AD-related impairments in its preclinical stages.

A promising function is Visual Short-Term Memory Binding (VSTMB [6]). VSTMB supports the integration and temporary retention of object's features such as shape and color into unified representations. The function does not rely on the integrity of the hippocampus [7], is affected by AD prior to its hippocampal stages [8], and has proved insensitive to normal ageing [9,10]. The VSTMB task (VSTMBT) is seemingly indexing very early neuropathological changes associated to the AD continuum. For instance, VSTMB correlates with Amyloid-β (Aβ) deposits in individuals who are in the preclinical stages of familial AD (i.e., E280A-PSEN1 mutation [11]) and in those expressing the early prodromal stages of sporadic AD [12] before any overt neurodegeneration is observed. The ability of memory tests to index AD pathology is a topic of ongoing research [13].

There is an urgent need for cognitive tests that can help detect the transition from normal to abnormal ageing and monitor disease progression. Meeting such needs is proving challenging. Based on traditional neuropsychological and clinical assessments we have been allocating older adults who do not provide signals of AD (or other dementias) to control groups. Evidence has accrued suggesting that older adults who are still asymptomatic may be accumulating AD-related pathology and some show significant resilience to such changes [14]. It will be ideal to identify memory tests which (1) are sensitive and specific to AD, (2) correlate with the accumulation of abnormal proteins in the brain linked to the development of AD dementia, and (3) are not sensitive to the brain changes that accompany normal ageing. The VSTMB test seems to hold these properties. However, such a test has never been used to investigate if among those still healthy older adults there are individuals who show VSTMB decline that can be accounted for by the accumulation of AD related brain pathology. This was the aim of the present study. Based on the above reviewed evidence we predicted that

older adults with selective VSTMB impairment would also display a significant increase of Aβ in their brains.

Materials and Methods

Participants

Subjects were recruited primarily by randomized market mailing. An initial telephone screening determined whether participants met basic inclusion criteria (i.e., right-handed, English speaking, no psychiatric or neurological disorders, and normal or corrected-to-normal vision). Potentially eligible participants were further screened in person with structured medical and neuropsychological evaluations to ensure that they had no neurological or psychiatric conditions, cognitive impairment, or contraindication for MRI scanning. Global cognitive functioning was assessed with the Mattis Dementia Rating Scale, on which a minimum score of 130 was required for retention in the study. In addition, participants who met diagnostic criteria for Mild Cognitive Impairment (MCI) were excluded. A group of 39 healthy older adults [Age: 65.38 (3.06); Education in years: 16 (2.01); Gender M/F: 23/17] entered the study. The studies were approved by the Internal Review Board of the College of Physicians and Surgeons of Columbia University.

Assessments

Neuropsychological test battery

A battery of neuropsychological tests was administered to all participants. These included tests of premorbid IQ (Wechsler Test of Adult Reading (WTAR), WAIS-III Vocabulary subtest, memory and learning (Selective Reminding Test), processing speed (Trail Making Test Part A, WAIS-III Digit Symbol subtest), executive functions (Trail Making Test Part B), revision and monitoring (WAIS-III Letter-Number Sequencing), and language (Category Fluency Test - Animals).

The Visual Short-Term Memory Binding Task (VSTMBT)

The VSTMBT presented visual arrays of three stimuli each on a flat screen controlled by a PC. At the beginning of each trial, a fixation screen was presented for 500 msec. This was followed by the study display presented for 2000 msec. After a blank retention interval of 900 msec, the test display was presented. On 50% of trials, the study and test displays were identical. On the other 50%, there were changes between the study and test display. The task for the participant was to detect when a change had occurred and to respond orally ‘same’ or ‘different’ as appropriate. Items randomly changed locations across study and test display to

avoid the use of location as a memory cue. There was then a gap of 1000 msec until the next trial (Figure 1).

The Shape only and Color Only conditions assessed VSTM for single features. The study arrays consisted of black shapes or colors (Figure 1). In the test display for the different trials, two shapes or colors from the study array were replaced by new shapes or new colors. In the shape-color binding condition, the arrays consisted of combinations of shapes and colors. In the test display for different trials, two shapes swapped the colors in which they had been shown in the study display. For each condition there was a practice session using flashcards. This was followed by 16 test trials. Trials were fully randomized across participants and conditions were blocked and delivered in a counterbalanced order. Participants had to pass a perceptual screening test in order to perform the VSTM binding task [15].

Insert Figure 1 about here

MRI and PET assessment

PET scans were acquired on a Siemens Biograph64 mCT/PET scanner in dynamic, 3D imaging mode beginning 50 min after injection. Brain images were acquired in 4 X 5-minute frames over a period of 20 minutes. The images were immediately assessed for technical validity. If considered inadequate, the participant had an additional 20 minutes of continuous imaging. Transmission scans were done prior to the scan. If there was a repeat scan, transmission was done after the scan. We used a recently published, state-of-the-art automatic quantification technique to reconstruct Amyloid PET scans. The process started by aligning four dynamic PET frames to the first frame using rigid-body registration and generating a static PET image by averaging the four registered frames. The static PET volume was then registered with the CT and merged to generate a composite image. Each individual's structural T1 scan, after being reconstructed with FreeSurfer, was registered directly to the static Tau PET volume using an inter-modal and intra-subject registration technique (rigid-body registration: 6 degree of freedom, mutual information). FreeSurfer regional masks were then used to extract regional uptake values. Regional and voxelwise amyloid SUVRs were obtained by normalizing the regional and voxelwise uptake value with the average uptake value in the cerebellum gray matter region and were used in many analyses.

Magnetic Resonance Imaging data

All MR images were acquired on a 3.0T Philips Achieva Magnet. There were two 2-hour MR imaging sessions to accommodate the twelve fMRI tasks as well as the additional imaging modalities. Relevant to the current study, T1-weighted MPRAGE scan was acquired to determine cortical thickness, with a TE/TR of 3/6.5 ms and Flip Angle of 8°, in-plane resolution of 256 x 256, field of view of 25.4 × 25.4 cm, and 165–180 slices in axial direction with slice-

thickness/gap of 1/0 mm. In addition, BOLD fMRI for twelve tasks, FLAIR, DTI, ASL and a 7-minute resting BOLD scan were acquired but not reported in the current study. A neuroradiologist reviewed each subject's scans. Any significant findings were conveyed to the subject's primary care physician.

Each subject's structural T1 scans were reconstructed using FreeSurfer v5.1 (http://surfer.nmr.mgh.harvard.edu/). The accuracy of FreeSurfer's subcortical segmentation and cortical parcellation has been reported to be comparable to manual labeling. Each subject's white and gray matter boundaries as well as gray matter and cerebral spinal fluid boundaries were visually inspected slice by slice, manual control points were added when any visible discrepancy was found, and reconstruction was repeated until we reached satisfactory results within every subject. The subcortical structure borders were plotted by FreeView visualization tools and compared against the actual brain regions. In case of discrepancy, they were corrected manually. Finally, we computed the mean cortical thickness for each participant to be used in group-level analyses.

Statistical Analysis

Behavioral data

Based on previous studies [10,16] we defined a cut-off score for the Cost of Binding (20%). The Cost of Binding was calculated as follows.

Binding Cost = ((Score on Single Shape – Score on Shape-Color Binding)/ Score on Single Shape)) *100.

Healthy older adults whose cost was greater than 20% were allocated to the group Weak Binders (WB) while those below the cut-off were allocated to the Strong Binders (SB) group. For the analysis of data drawn from the VSTMBT, we used a mixed model with Group (SB vs WB) as the between-subjects factor and Condition (Color Only vs Shape Only, vs Shape-Color Binding) as the within-subjects factor. For the analysis of neuropsychological data we relied on FDR corrected t-tests. All the results we report were corrected for multiple comparisons.

Neuroimaging data

Amyloid SUVR were tested in regions of interest (ROI) and voxelwise. In ROIs, mean normalized amyloid SUVRs were obtained from 68 regions. We selected a subset of brain regions which, based on previous neuroimaging and EEG studies, have proved relevant to VSTMB. These include regions from frontal [17], parietal [18], occipital [18] and temporal lobes [2]. PET regional uptake values entered between-group contrasts (i.e., SB vs WB) across brain regions. Volumetric and cortical thickness data were also contrasted across groups (SB vs WB). Voxelwise, we explored correlations between amyloid SUVR and binding cost across participants, restricted to voxels with at least 50% probability of being gray matter. The ROI analyses were corrected for lobar volume and both ROI and voxelwise results were corrected for multiple comparisons (False Discovery Rate, FDR).

Results

Behavioral outcomes

VSTMB

After applying the cut-off for the Cost of Binding, 21 asymptomatic older adults were classified as SB and 18 were classified as WB. A mixed ANOVA model was used to test if our classification of participants in SB and WB would yield a Group x Condition interaction confirming that binding impairments observed in the latter group would be accompanied by preserved memory for individual features. This is the dissociation previously observed in people with or at risk of AD [8,15,16]. Our data confirmed this prediction (see Figure 2). Although the effect of Group failed to reach significance [$F(1,39) = 1.93$; $p = 0.173$; $\eta2 = 0.05$; $\beta=0.23$] the Group x Condition Interaction was significant [$F(2,78) = 24.88$; $p < 0.001$; $\eta2 = 0.39$; $\beta=1.0$]. Bonferroni corrected post-hoc tests confirmed that neither Shape Only nor Color Only yielded significant differences between SB and WB [$t(39) = 0.92$, $p = 0.363$ and $t(39) = 1.24$, $p = 0.225$, respectively. In fact, performance of WB on these baseline conditions was numerically superior, which our manipulation would not predict. That is, our manipulation did anticipate that relative to SB, WB would show significantly poorer performance on the Shape-Color Binding Condition but this would warrant neither equivalent performance on single feature conditions nor a significant Group x Condition Interaction. These findings therefore grant us confidence that WB did present with the typical binding profile previously identified in population with or at risk of AD dementia.

Finally, relative to WB, SB had a numerically though not statistically higher level of Education [16.55±2.02 vs 15.45±1.79, p = 0.071], Premorbid IQ (WTAR, [41.11±7.19 vs 38.53±9.55, p = 0.36]) and Vocabulary (WAIS-III Vocabulary subtest [58.21±8.05 vs 57.28±9.43 p = 0.77]). We therefore decided to run the above model controlling for the effects of these variables. That did not remove the key Group x Condition Interaction [$F(2,78) = 12.57$; $p < 0.001$; $\eta2 = 0.32$; $\beta=0.98$].

Insert Figure 2 about here

Traditional neuropsychological tests

Strong and Weak Binders could not be distinguished based on their performance on standard neuropsychological tests (see Figure 3).

Insert Figure 3 about here

Aβ and VSTM

Comparing WB to SB across ROIs, areas where Aβ deposits were significantly greater in WB relative to SB were mainly located in posterior regions of the brain. Bilateral involvement was found in the superior parietal lobe, superior and middle temporal gyrus, pericalcarine cortex and lingual gyrus. Interhemispheric discrepancies were found for the inferior parietal lobe (only left) and for the lateral-occipital cortex, entorhinal cortex, fusiform gyrus, and cuneus (only right). Figure 4.A shows that group discrepancies in these regions survived FDR correction. Voxelwise correlation analyses revealed significant positive correlations between Aβ deposits and the cost of binding in all the regions where between-group discrepancies were found (Figure 4.B and see Table 1 in Supplementary Material).

Insert Figure 4 A and B

Volume, Cortical Thickness and VSTMB

Neither volumetric nor cortical thickness measures differed between SB and WB. Only the right lateral-occipital cortex reached marginal FDR corrected values (see Figure 5).

Insert Figure 5 about here

Discussion

The present study was set out to investigate the hypothesis that asymptomatic older adults who present with VSTMB impairments would display increased brain Aβ deposits relative to those whose VSTMB remain preserved. This hypothesis proved valid. We also found that such an association occurred when neither measures of grey matter integrity nor standard neuropsychological tests could identify differences between these groups. These findings have important implications for our understanding of the boundaries between normal and pathological cognitive ageing and for the preclinical detection of Alzheimer's disease. We discuss such implications in turn.

VSTMB has been found to remain preserved across the lifespan [9,10,19] and to be unaffected by the level of education of those assessed [20]. The hypothesis that VSTMB impairments in asymptomatic older adults would reflect early Aβ pathology stemmed from recent studies in individuals at high risk of AD. VSTMB impairments have been found in middle-age adults who would inevitably develop familial AD due to the mutation E280A-PSEN1 [8] and who were otherwise completely asymptomatic. Aβ deposits in such carriers reach a plateau at the mean age of 35 [21], which when VSTMB impairments were first observed [8]. The association between Aβ and VSTMB impairments in asymptomatic carriers of the mutation E280A-PSEN1 becomes apparent before evidence of tau pathology or neurodegeneration [11]. Interestingly, such an

association also characterizes individuals at risk of late-onset sporadic AD (i.e., mild cognitive impairment) [12]. The still scarce yet converging evidence suggests that VSTMB deficits might be associated to the earliest pathological changes that underpin the transition from normal ageing to AD, that is, β-amyloidopathy.

Disentangling normal and pathological cognitive ageing is a challenge that neuropsychological tests are currently facing [22]. There is growing concern about the reliability of norms or control groups as the available neuropsychological tests currently used to ascertain normality are outdated and do not detect the earliest cognitive deficits caused by neurodegenerative disease. The traditional neuropsychological tests used in our study proved insensitive to the increased Aβ observed in older adults with poor VSTMB functions. In fact, participants enrolled in this study were recruited relying on strict inclusion criteria for normal cognitive ageing. Yet, almost half of them presented with a behavioral VSTMB profile compatible with that consistently observed in individuals with or at risk of AD [8,23,24] (Figure 2). It is worth noting that our neuropsychological assessment battery included the Selective Reminding Test, which has been considered a preclinical cognitive marker for AD [1]. The differential sensitivity of the forms of memory binding assessed by the VSTMBT and SRT to the transition from normal ageing to AD has been recently noted [22]. The observation that VSTMB impairments were associated to increased deposits of Aβ in brain regions known to support visual object processing and memory contributes novel insights into the earliest neurocognitive changes that will likely characterize such a transition. We discuss such links next.

VSTMB appears to be linked to the functions of the visual ventral stream [25]. Cortico-cortical connections along this pathway support object unitization and identity formation. However, the occipitotemporo-medialtemporal pathway plays a key role in memory [25]. This pathway consists of projections from the cortical components to various structures within the medial temporal lobe including the perirhinal cortex, which projects in turn to both the entorhinal cortex and to regions of the hippocampus. These regions of the anterior temporal network are thought to support familiarity-based recognition, a function known to support performance on change detection tasks such as the VSTMBT. VSTMB remains preserved in patients with hippocampal damage [7], and is affected in patients at risk of AD who still perform normally on memory tests that tax the function of the hippocampus [8,15,26]. This suggests that pathology during the transentorhinal stage of AD, which appears prior to the hippocampal stage [3], might be the one the VSTMBT is detecting. Accrued evidence seems to support this notion. While the hippocampus undergoes substantial atrophy as we grow older, the volume of the perirhinal and entorhinal appears to be unaffected by age [5]. Interestingly, these regions are targeted by AD before the hippocampus [4,27]. This would explain why VSTMB has been consistently found to be insensitive to normal ageing and sensitive to AD in its subhippocampal transentorhinal stage.

Evidence gathered to date suggests that the above sequence of neuropathological events is seemingly driven by tau pathology i.e., deposits of neuro-fibrillary tangles (NFT) in regions of the anterior network of the medial temporal lobe. In fact, a hypothetical model that maps the earliest memory impairments detectable in AD to the underlying neuropathology [3] suggests that NFT in the sub-hippocampal stages of AD may account for the type of deficit we find with the VSTMBT (context-free memory impairments). Our data suggests that increased Aβ in the

same regions of such a network can also disrupt such a memory function. Taking together, the evidence above reviewed and that drawn from our own study we feel compelled to suggest that the VSTMBT appears to be indexing Aβ pathology in the very early stages of the AD continuum, seemingly before tau pathology becomes apparent. Studies using animal models have confirmed that tau is not necessary for Aβ to induce memory impairments [28]. In fact, tau pathology in humans seems to account for stages where the abnormal brain structure–function relationships become detectable. Accrued wisdom suggests that this may be too late when it comes to dementia prevention.

The findings here reported come from a relatively small cross-sectional sample of healthy older adults. Future studies will be needed to validate these results in larger longitudinal samples. Lending support to this suggestion, recently observed that the VSTMBT is a reliable predictor of progression from normal to pathological ageing, as defined by the very early stages of MCI. The authors suggested that it is at this stage when the test stands the best chance to identify those will progress to AD dementia [22]. Taken together these and our results suggest that the novel memory marker here investigated could help identify those presymptomatic older adults who are currently missed by available cognitive screening procedures.

In fact, evidence from CSF/PET Amyloid findings in asymptomatic adults suggests that preclinical and prodromal AD may be more prevalent than previously estimated [29]. This might have important implications for clinical trial recruitment strategies and for the development of normative samples. Regarding the latter, some have already suggested the need of biomarker adjusted normative data to reliably separate normal and pathological ageing trajectories [30]. An alternative would be to rely on theory-driven function-specific cognitive tests capable of unveiling the earliest manifestation of AD. The VSTMBT seems to be a promising candidate. Dementia prevention entails both early detection and effective treatments, and both are currently lacking [22]. The results here presented grant us confidence to suggest that the VSTMBT can be considered a promising screening tool to help identify individuals who can be good candidates for AD prevention trials.

Data sharing

The data linked to this study can be accessed upon requests sent to Mario A Parra mario.parra-rodriguez@strath.ac.uk and Yunglin Gazes yl2107@cumc.columbia.edu

Declaration of interests

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Figures Caption

Figure 1. An example trial for each condition of the VSTMBT.

Figure 2. Mean performance from SB and WB across the three conditions of the VSTMB Task. Bonferroni-corrected post-hoc tests showed that the Group x Condition interaction was driven by the discrepancy between SB and WB only in the Shape-Color Binding Condition.

Figure 3. Data from SB and WB on an extensive neuropsychological test battery. The graph shows uncorrected (blue diamond) and corrected (orange square) p-values for each test.

Figure 4. (A) Between-groups contrasts for Aβ SUVRs in WB relative to SB across the investigated brain regions drawn from whole-brain voxelwise analysis (Blue diamond = Uncorrected tests, Orange Square = FDR correction for multiple comparisons). **(B)** Correlations and whole-brain voxel-wise analyses illustrating brain regions where Aβ deposits significantly correlated with the cost of binding (all corrected for multiple comparisons).

Figure 5. Volume (blue diamond) and cortical thickness (orange square) from SB and WB across the investigated brain regions (all corrected for multiple comparisons).

Figures

Figure 1.

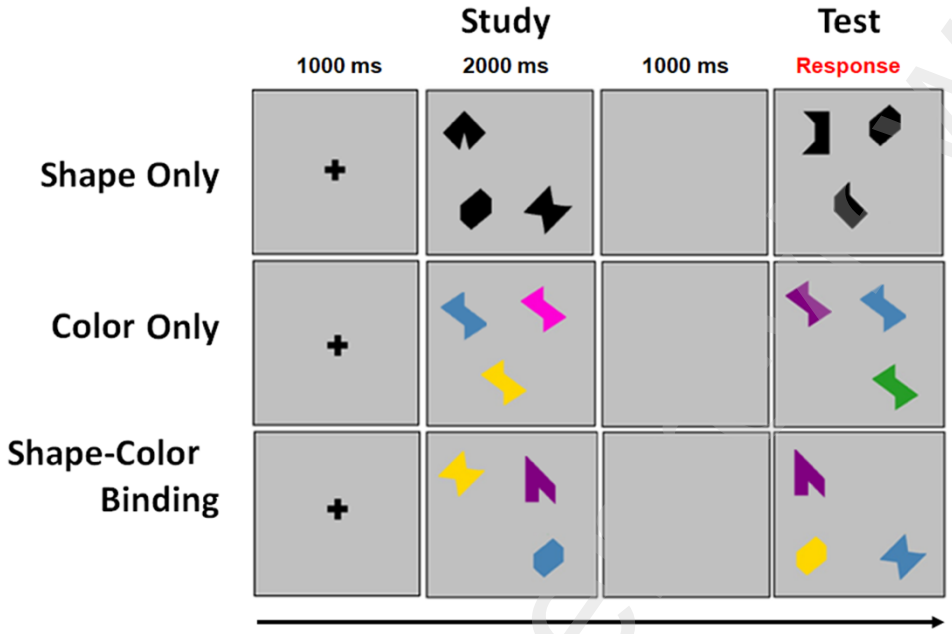

Figure 2.

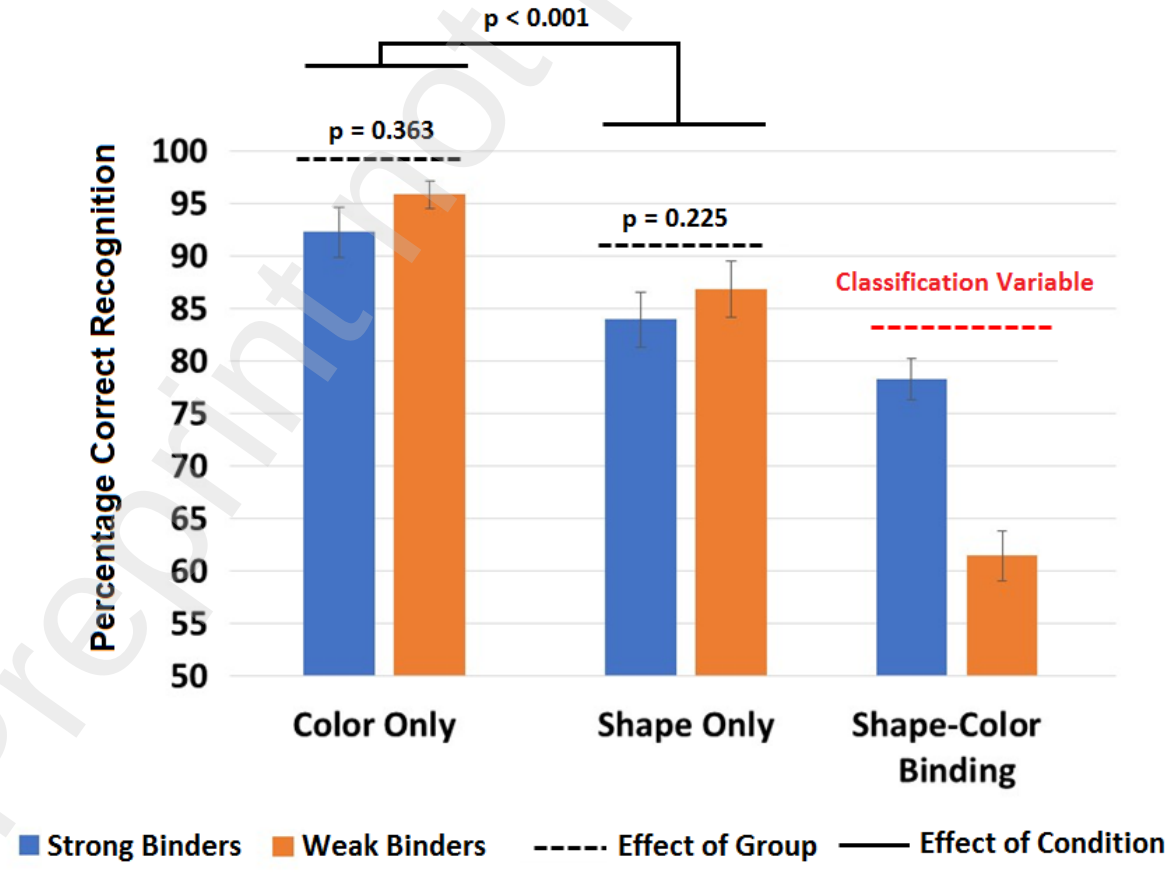

Figure 3.

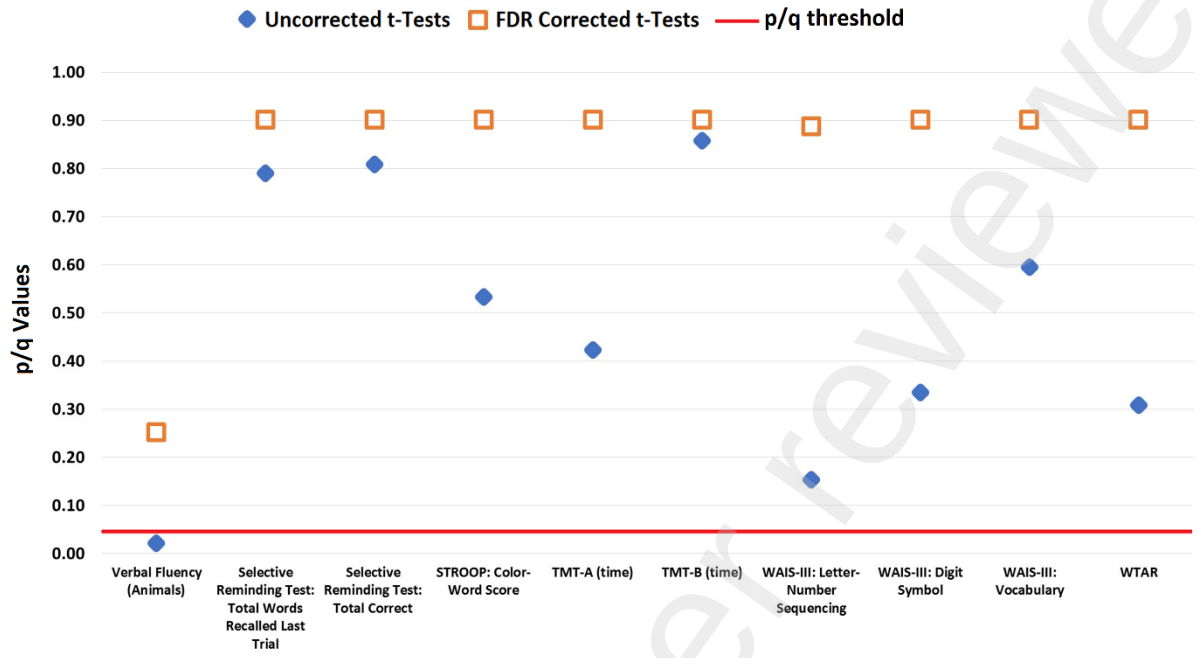

Figure 4.

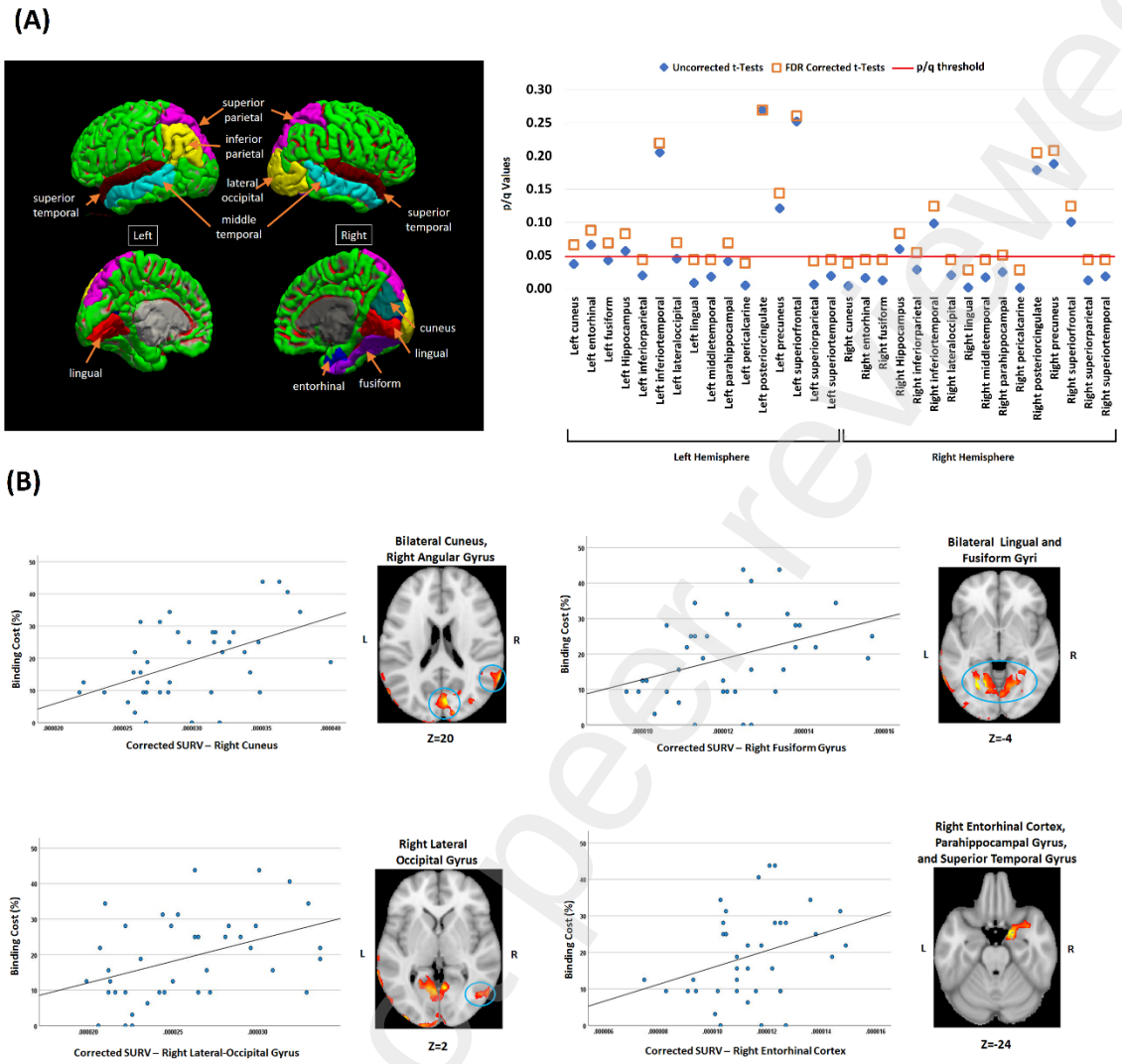

Figure 5.