Profiles of cognitive impairment in the continuum from normal cognition to Alzheimer's Clinical Syndrome

Contributions of the Short-term Memory Binding tests

Profiles of cognitive impairment in the continuum from normal cognition to Alzheimer's Clinical Syndrome: contributions of the Short-term Memory Binding tests

Running head: The accuracy of different memory binding tasks to detect MCI and AD

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Abstract

BACKGROUND: Short-term memory binding (STMB) tests assess conjunctive binding, in which participants should remember the integration of features, such as shapes (or objects) and colors, forming a unique representation in memory. In this study, we investigated two STMB paradigms: Change Detection (CD) and Free Recall (FR). OBJECTIVE: To investigate the cognitive profile in the CD and FR tasks of three diagnostic groups: cognitively unimpaired (CU), mild cognitive impairment (MCI) and Alzheimer's Clinical Syndrome (ACS). In addition, we aimed to calculate and compare the accuracy of the CD and FR tasks to identify MCI and ACS. METHODS: Participants were 24 CU, 24 MCI and 37 ACS. The cognitive scores of the clinical groups were compared using ANOVA and ROC analyses were carried out to verify the accuracy of the STMB tasks. RESULTS: In the CD task, CU was different from MCI and ACS (CU > MCI = ACS), while in the FR task all groups were different (CU > MCI > ACS). The ROC analyses showed an AUC of 0.855 comparing CU with MCI for the CD task and 0.975 for the FR. The AUC comparing CU and ACS was 0.924 for the CD and 0.973 for the FR task. The FR task showed better accuracy to identify MCI patients, and the same accuracy to detect ACS. CONCLUSION: The present findings indicate that impairments in CD and FR of bound representations are features of the cognitive profiles of MCI and ACS patients.

Keywords: Mild Cognitive Impairment, Cognitive Aging, Alzheimer’s Disease, Alzheimer's Clinical Syndrome; Short-term memory; Memory binding; Working memory.

Key-points:

- The accuracy to detect mild cognitive impairment and Alzheimer’s clinical syndrome of two modalities of the short-term memory binding test were compared
- Results indicated that both modalities of the short-term memory binding test showed high accuracy to identify these syndromes
- Free Recall modality seemed slightly superior to identify subtle cognitive changes.

Introduction:

Memory binding refers to the ability to integrate features, such as shape and color, to form one unique representational object. The Short-Term Memory Binding (STMB) test[1–3] has been shown to discriminate patients with Alzheimer's disease (AD) from cognitively unimpaired controls (CU)[3–6] and from other dementia sub-types[1,2]. The STMB tests assess conjunctive binding, in which participants should remember the integration of features, forming a unified representation in memory.

Evidence suggests that conjunctive binding is not affected by age[7–12] or repeated testing[13]. These properties match those suggested a good cognitive marker for AD should hold[14].

There are two main paradigms to assess conjunctive STMB. One is the Free Recall (FR) task, in which participants retrieve verbally by saying aloud objects and colors individually (Unbound Features) or object-color integrations (Bound Features) that they have just seen. The other paradigm is the Change Detection (CD) task, in which participants recognize if there is a difference in shapes and colors individually or shape-color integrations between two consecutive screens. Therefore, the CD task relies on recognition of abstract shapes, whereas the FR task relies on free recall of common objects. The two tasks have proved successful in distinguishing healthy older adults from patients with dementia of the Alzheimer's type[1–4,15]. However, the CD but not the FR task has been used to assess patients with mild cognitive impairment (MCI) showing good discriminative power[16,17].

MCI has been described as a heterogeneous syndrome which may represent an intermediate stage between normal cognition and dementia[18,19]. The prevalence of MCI in those older than 65 years ranges from 16 to 20% [20]. Previous criteria define MCI as a condition leading to complaints about cognition (from patient or relatives), measurable impairments in one or more cognitive functions, and still preserved abilities to perform everyday tasks independently[21,22]. It is well established that MCI patients have a higher risk to convert to dementia, either AD or other types [23,24]. Besides, MCI patients could revert to cognitive normality[20,25,26], especially those who do not show biomarkers of AD pathology[26,27]. It is therefore essential to identify cognitive phenotypes of MCI which will accurately predict clinical trajectories.

For more than a decade, impairment on neuropsychological tests has been used as the key criteria to diagnose MCI, but traditional tests do not provide a reliable measure of

underlying AD pathology. Presently, it is necessary to refine neuropsychological tools to better identify patients with the MCI profile who have a higher chance of having positive biomarkers and converting to AD dementia. According to a new biological framework to diagnose AD, MCI is the intermediate stage in the cognitive continuum between the cognitively unimpaired (CU) and patients with dementia, which may or may not have AD, depending on biomarker status. This biological framework proposes that AD should be identified by *in vivo* biomarkers, specifically, beta amyloid deposition, pathologic tau, and neurodegeneration [AT(N)][28–30]. Beta amyloid deposition and pathologic tau are required for the diagnosis. Importantly, neurodegeneration and cognitive impairment are seen as unspecific symptoms and, therefore, are indicated for staging cognitive syndromes.

Notwithstanding the impact that the AT(N) framework can make to improve understanding of AD pathology and selection of candidates for prevention trials, it holds several limitations. Relevant to this study are their low specificity for the clinical stage of patients, high cost, limited availability, lack of standardization, and need of advanced training for use and interpretation[14]. Therefore, novel cognitive tests that can inform about the early stages of AD are still necessary. New tasks that assess different types of memory binding have shown promising results. For instance, Koppara and colleagues (2015) have compared CU older adults with participants with subjective cognitive decline (SCD) and MCI patients, and they showed that the Bound Features of the CD STMB could differentiate SCD and MCI from CU participants[16]. Another study showed that the CD STMB task could differentiate CU volunteers from asymptomatic carriers of the E280A single presenilin-1 mutation, a mutation that eventually leads to AD[31]. In other words, in the pre-clinical stage, before cognitive symptoms were present, the asymptomatic carriers already showed impairment in conjunctive STMB but unimpaired performance in usual neuropsychological tests. Recently, Parra, Calia, García and colleagues (2019) showed that MCI patients with hippocampal atrophy in the MRI (probably in the AD continuum) had binding deficits similar to those observed in AD dementia patients[17]. The CD STMB test, therefore, seems to be a promising tool to identify AD pre-clinically. Yet, as noted above, no study has investigated the usefulness of the FR STMB task to identify patients with MCI profile.

Therefore, the main aim of this study was to contrast the clinical contributions of the two modalities of the STMB test. Specifically, the objective was to investigate the cognitive

profile of three diagnostic groups (CU, syndromal MCI and Alzheimer's Clinical Syndrome (ACS)) in the CD and FR STMB tasks. In addition, we aimed to calculate and compare the accuracy of the CD and FR tasks to identify syndromal MCI and ACS. The comparison of different STMB modalities is novel and hence it may add to our current knowledge regarding their vulnerability to and complementary value in the assessment of patients at different disease stages.

Methods

Participants

Patients were recruited from Neurology outpatient units from the University of São Paulo (USP) and Federal University of Minas Gerais (UFMG). For the CU group, we recruited 24 older adults from community senior centres and University of Third Age programs. To identify the participants with MCI profile, the NIA-AA criteria was used[21]. Using the CU group mean and standard deviation as reference, z-scores were generated for the delayed score of the Rey Auditory Verbal Learning Test[32]. Twenty-one out of 24 (87,5%) MCI patients scored < -1.5 SD in this test, therefore were considered as amnestic MCI. We recruited 37 patients who met criteria for dementia due to probable AD based on the NIA-AA (National Institute on Aging/ Alzheimer's Association)[33]. Data collection for the study preceded the NIA-AA 2018 biological criteria, and due to the lack of CSF and molecular neuroimaging biomarkers, it was not possible to ascertain the presence of AD pathology in the sample, therefore, we opted to use Alzheimer's Clinical Syndrome (ACS) terminology to describe this group. A sub-sample of the MCI and ACS groups (16 MCI and 12 ACS) underwent a structural MRI scan and hippocampal atrophy was used to give some support to the diagnostic strategy utilized.

CU participants, those with MCI profile and caregivers of patients with ACS signed the informed consent form, which was approved by the Ethics Committee from USP (protocol number 16627413.0.0000.0068) and UFMG (protocol number CAA 17850513.2.0000.5149).

Instruments and procedures

Participants were assessed by a neurologist and a neuropsychologist. In neurological care, patients underwent a clinical evaluation which included the Mini Mental State Examination (MMSE)[34,35], the Clinical Dementia Rating (CDR)[36,37] to assess the dementia stage, the Functional Activities Questionnaire (FAQ)[38,39] to measure functional status and a neuropsychological test battery to assist in the identification of MCI and ACS. The latter was comprised of the Dementia Rating Scale (DRS)[40,41], the RAVLT[32,42], and phonemic verbal fluency (FAS)[43]. The Geriatric Depression Scale (GDS)[44] and the Hachinski Ischemic Score[45] were also applied for screening.

First, the participants underwent a neurological evaluation conducted by a neurologist that, when necessary, could refer to a psychiatric evaluation to exclude mental health conditions. Next, all participants completed the neuropsychological assessment. We recruited participants aged 55 years and older. All participants had four years of formal education or more. For the CU group, inclusion criteria required participants to have cognitive scores within the normal range and to be in good self-reported health. The exclusion criteria were significant sensory (visual or auditory) or motor deficits and severe or decompensated clinical conditions; the CU participants should not have a diagnosis of psychiatric or neurologic disorders and use medications with potential cognitive side-effects.

The CU group was defined by the following criteria: MMSE > 24, FAQ < 5, Hachinski Ischemic Score ≤ 4, GDS ≤ 5 and anamnesis not indicative of any concurrent condition that could affect the central nervous system. For the MCI group the criteria were: MMSE > 24, FAQ <5, Hachinski Ischemic Score ≤4, an anamnesis that indicated perception of cognitive change in relation to a pre-existing pattern, and impairment in one or more cognitive domains (-1.5 SD when compared to normative data). Finally, individuals with ACS met the following criteria: MMSE ≤ 24, FAQ ≥5, Hachinski Ischemic Score ≤4, impairment in at least two cognitive domains (-1.5 SD when compared to normative data), and an anamnesis which should not be indicative of any concurrent condition that could affect the central nervous system. After the diagnosis, patients were referred to complete the STMB tests.

The STMB tests took an average of 15 to 20 minutes to be completed. The CD and the FR tasks, as well as the Bound and Unbound Features conditions, were counterbalanced to avoid order bias.

Change Detection STMB task

Stimuli were random polygons and non-primary colors previously used[7,31]. A set of eight polygons and eight colors were used to generate the stimuli which were created by randomly combining polygons and colors.

Trials began with a fixation screen for 500 ms after which a study display was presented for 2000 ms. The test display was then presented after a 900 ms blank retention interval and remained on until the participants responded. On 50% of trials, the study and test displays presented identical items. 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 'same' or 'different' as appropriate. There was then a gap of 1000 ms until the next trial. For the decision of "same or different" the participants were clearly informed that they should pay attention only to the items on the screen and not to their position as items' locations changed randomly from study to test. Participants performed 16 trials with 2 shapes and 2 colors.

The task consisted of two conditions, one assesses shapes and colors separately (Unbound Features) and the other assesses shapes and colors integrated within objects (Bound Features).

Unbound Features: In this condition, two shapes and two colors were simultaneously and separately presented within the same array. No feature was repeated within a given display. In the test display for "different" trials, either two shapes (in 50% of the different trials) or two colors (in the remaining 50% of the different trials) were replaced by new shapes or colors which had not been shown in the study display. Hence, memory for bindings of shape and color in the study display was not required to detect a change.

Bound Features: In this condition, two combinations of shape and color were presented for study. No feature was repeated within a given display. In the test display for "different" trials, two shapes swapped the colors in which they have been shown in the study display. Hence, memory for bindings of shape and color in the study display was required in order to detect this change. Figure 1 presents an illustration of the CD task.

INSERT FIGURE 1 HERE

Previous studies[7,31] used the shape-only condition, in which participants should detect changes in shapes across two consecutives screens. In the present study, we chose to use the Unbound condition with colors and shapes unintegrated. The rationale was to use a version of the task in which conditions (Bound and Unbound Features) were equated by the number of features (as opposed to versions that equated by the number of objects[7,31]). This would also make the baseline condition of the CD task comparable with the baseline condition used in the Free Recall task that we explain next.

Free Recall STMB task

It consisted of displays presenting common objects and primary colors used in previous studies[1–3]. At the beginning of the task, participants were requested to name the colors and objects used in the test to ensure that they had no naming problems.

Unbound Features: The study screen consisted of three colors and three objects presented as separate features. Half of the items were colored squares and the other half were line drawings of common objects. The study screen was presented for 9 seconds in total (1.5 sec per feature). Participants were requested to remember as many colors and objects as they could. After the study time, they were asked to recall by saying aloud all the colors and objects they could remember. Each object and each color correctly recalled added one point to the total score.

Bound Features: The study screen consisted of three objects filled with a different color each (i.e., colored objects), and it was also presented for 9 seconds (1.5 seconds per feature). These colored objects were constructed by randomly combining objects with colors from the two sets in a way that avoided prototypical color-object associations (e.g., red apple). Participants were asked to remember as many colored objects (combination color-object) as possible. We recorded the recalled objects and colors and a response was considered correct when the two features making up each studied object were recalled together, for instance: “red-bed”.

Each condition (Bound and Unbound Features) consisted of 6 trials with 6 features each (3 colors and 3 objects). Figure 2 presents an illustration of this task.

INSERT FIGURE 2 HERE

Magnetic Resonance Imaging (MRI) Image Acquisition and Processing

In the present sample, 16 MCI and 12 ACS patients had a recent structural MRI exam available (less than six months from the cognitive assessment). Hippocampal volume measures from this sample were made available. The images were acquired in a Philips 3 Tesla scanner with a Quasar Dual gradient system using a 3DT1 weighted turbo-field-echo gradient sequence with the following parameters: 2500ms repetition time, 3.2 ms echo time, 7.0 ms time echo spacing, 900 ms inversion time, 1mm isotropic voxel size, 8◦ flip angle, 240 × 240 × 160mm^3 field of view.

A healthy control group composed of 133 subjects, from the NKI-RS database (Nathan Kline Institute - Rockland Sample) were paired by age with the patients from the Clinical Hospital of Ribeirão Preto (USP). For this sample, two types of acquisition were selected, the pilot with 2500 ms repetition time, 3.5 ms echo time, 1200 ms inversion time, 1mm isotropic voxel size, 8◦ flip angle and 256x256x200mm3 field of view and the enhanced with 1900 ms repetition time, 2.5 ms echo time, 900 ms inversion time, 1mm isotropic voxel size, 9◦ flip angle and 250x250x176mm^3 field of view.

Volumetric measures of hippocampus were obtained using the FreeSurfer imaging software, version 5.3 (Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA). This software classifies each voxel with a neuroanatomical label based on probabilistic information automatically estimated and it has accuracy comparable to manual labelling[46]. This software has been more recently validated in elderly subjects, who showed that FreeSurfer volumetry has quality near manual editing[47]. All automatic segmentations were double checked by visual inspection. Volumetric measures were normalized by ICV, intracranial volume obtained from FreeSurfer pipeline processing, and multiplied by 100 to express as a percentage value.

Statistical Analyses

The group means of the cognitive measures were compared using one-way ANOVA analyses, with Bonferroni's correction for multiple comparisons. A 3 x 2 mixed ANOVA

model was used to verify the interactions between the diagnostic groups, as a between-subjects factor, and CD and FR (with Bound and Unbound Features collapsed) as a within-subjects factor. The effect size, as informed by partial eta-squared (η^2), and power by Beta (β), were calculated in these mixed models. To unfold significant interactions, T-tests and effect sizes (Cohen's d) were calculated to compare conditions within and across groups. Significance level was set at 0.05. To interpret the effect size, the thresholds proposed by Cohen (1988) were used (0.2 = small; 0.5 = medium; 0.8 = large).

In addition, receiver-operating characteristics (ROC) analyses were used to assess the diagnostic accuracy (area under the curve - AUC, specificity and sensitivity) of the CD and FR STMB Bound Features to differentiate between the clinical groups. ROC curves for the CD and the FR Bound tasks were compared using the DeLong's test. Analyses were carried out in SPSS v.25 and JASP v.0.11.1.0, and the DeLong's test was run in the pROC package (v. 1.15.3) in R[49].

Results

Table 1 presents descriptive statistics across the clinical groups. The groups had equivalent age and educational levels. FAQ scores showed that CU and MCI participants had statistically equivalent functional performance, and both had better scores than ACS. As expected, CU had higher cognitive performance in general, while the ACS group had the lowest performance and the MCI group was in between. In addition, the groups showed significantly different hippocampal volumes in MRI data (Normative sample > MCI > ACS).

INSERT TABLE 1 HERE

INSERT FIGURE 3 HERE

Results for the CD and FR STMB tests are shown in Figure 3 and Table 2. The results of the mixed ANOVA models showed a significant main effect of the FR [$F(1,79) = 41.144$, $p < 0.001$, $\eta^2 = 0.342$, $\beta = 1.000$] and CD [$F(1,81) = 20.665$, $p < 0.001$, $\eta^2 = 0.203$, $\beta = 0.994$] tasks. There was a significant interaction between diagnostic groups and the FR

conditions (Unbound and Bound Features) [$F(2,79) = 3.294$, $p = 0.042$, $\eta^2 = 0.077$, $\beta = 0.609$], with the pairwise comparisons showing statistically significant difference between the three diagnostic groups (CU > MCI > ACS). In addition, there was no significant interaction with the CD tasks [$F(2,81) = 2.077$, $p = 0.132$, $\eta^2 = 0.049$, $\beta = 0.416$], with pairwise comparisons showing CU with higher performance than the other groups (CU > MCI = ACS). However, the statistical power (β) in both interaction analyses was limited.

Table 2 contains the comparisons between the Bound and Unbound Features within each diagnostic group. For the CD task, there was a significant increase from the Unbound to the Bound Features condition, with a large effect size in the CU group, while in the MCI the effect size was medium, and in the ACS group there was no significant difference and a small effect size. In the FR task, all groups showed statistically significant decrease between Unbound and Bound Features condition. The effect sizes showed increasing values across groups (CU < MCI < ACS) with a medium effect size for the CU and MCI groups, and a large effect size for the ACS group.

INSERT TABLE 2 HERE

ROC analyses with data from the Bound Features (Table 3) indicated that both CD and FR STMB tasks had high accuracy to distinguish CU from MCI, and CU from ACS. However, accuracy was low to separate MCI from ACS. The CD task showed good sensitivity, but low specificity for identifying MCI or ACS, while the FR task showed high sensitivity and specificity values.

INSERT TABLE 3 HERE

When the AUC to identify MCI or AD using CD or FR Bound Features were compared, there was no significant difference between CD for CU x MCI and CU x ACS ($p = 0.298$) and FR for CU x MCI and CU x ACS ($p = 0.670$). When the AUC for CD was compared to the AUC for FR to discriminate CU x MCI, results were significant ($p = 0.016$), but that was not observed for CU x ACS ($p = 0.132$). There was no significant difference

when we compared the ROC curves for CD and FR to discriminate MCI x ACS (p = 0.339).

Discussion

The first aim of the present study was to investigate the contribution of STMB tasks to the identification of cognitive profiles in a sample of older adults with different cognitive status. STMB assessed via CD clearly distinguished between CU and both MCI and ACS, but not between the last two groups (CU > MCI = ACS). STMB assessed via FR showed a gradient whereby CU > MCI > ACS. These findings suggest that impairments of STMB functions, assessed via FR and CD, can be observed among individuals from pre-dementia to the dementia stages of the ACS.

The second aim was to calculate and compare the diagnostic accuracy for the CD and FR tasks. The results suggest that the CD and the FR STMB tasks can identify with high accuracy those participants with MCI and dementia profiles, according to the syndromal staging framework proposed by Jack et al. (2018)[30]. However, the Bound FR task showed significantly higher accuracy than the Bound CD task to detect MCI.

To our knowledge, this is the first study to report that the FR STMB task can also identify significant impairments in MCI patients. Our results using the CD STMB task are in line with previous findings[16,17], in which the MCI groups showed significantly worse performance than CU participants in the CD Bound condition. In addition, our results support previous findings which suggested that STMB impairments can be identified in ACS using CD and FR[1–3,31,50]. We now proceed to discuss our key findings in more details.

Effects of binding in CD and FR tasks

As shown in Table 2 and Figure 3, the CD task revealed that the CU group had higher performance on the Bound condition with a large effect size when compared to the Unbound condition (binding gain). That did not occur among MCI and ACS patients, who showed medium and small effect sizes, respectively. The clinical groups did not benefit from binding, as the CU did. In the present, study we used a version of the CD which equated memory load across conditions according to the number of features.

Previous studies have argued that such testing conditions allow assessment of the "weak-object hypothesis" of visual STM capacity. The hypothesis suggests that visual STM is limited by both the number of objects and the feature composition of those objects [51]. Based on this hypothesis, equating conditions by the number of features should result in higher performance level for the Bound Features than the Unbound Features condition. This would reflect the benefit that feature integration (i.e., binding) would offer to visual STM, which would increase its capacity. Contrary to previous CD tasks which have focused on the binding cost (when conditions are equated by the number of objects[31,52], the CD task used in this study allows assessment of the binding gain. Such a gain can be experienced if binding functions supporting feature integration are available. Here we have demonstrated that impairments of such binding abilities characterise MCI patients and those with the ACS.

In the FR tasks, on the other hand, the Bound Features yielded a drop in performance in the three groups (binding cost), with an increasing effect size from CU to ACS. The binding cost was significantly larger in ACS patients, in line with previous findings[1,2]. Such binding cost may be explained by the fact that participants needed to freely recall each feature and the binding between features. It has been acknowledged that retrieving information via recall is more challenging for older adults than via recognition[53,54].

This evidence is novel and further supports the notion that STMB impairments do characterise the cognitive profile of ACS regardless of the task used to assess such a function. We have demonstrated for the first time that patients at risk of this type of dementia and those in the dementing stages of the disease are less able to benefit from binding functions, which alleviate memory load via feature integration in recognition tasks, and exhibit a greater cost when more taxing retrieval functions are used (i.e., FR).

Diagnostic accuracy analyses for the CD and FR tasks

The ROC analyses indicated that the CD and the FR Bound Features showed high accuracy to identify MCI and ACS, and very low accuracy to discriminate MCI from ACS. The FR task showed statistically better accuracy than CD task to diagnose MCI patients, but similar accuracy to diagnose ACS. In addition, the FR task showed high sensitivity and specificity values, while the CD task showed high sensitivity, but low specificity for MCI and ACS. It could be argued that interactions between disease severity

and memory load could have played a role in this discrepancy. The Bound condition of the FR task presented 6 features/3 objects whereas in the CD task it presented 4 features/2 objects.

Parra et al. (2019)[17] recently investigated optimal settings of STMB CD tasks to detect impairments in MCI patients. In their study, they found that a task presenting 2 objects was optimal at revealing specific binding deficits in such patients. They noted that such specificity decreased when memory load increased seemingly due to a performance drop in the control group. They suggested that to identify impairments in patients in the early stages of ACS (i.e., pre-symptomatic or early prodromal stages) assessment should include 3 items, while for patients in more advanced stages it should include 2 items. The background measures from patients studied by Parra and colleagues (2019)[17] and those assessed here seem to indicate that the former group was in more advanced stages than the latter, as informed by the MMSE and functional scales. Parra and colleagues (2019)[17] suggested that to address this potential limitation, a task that combines the two set sizes (2 and 3 objects) may be a more feasible approach. Our current data lend support to this proposal.

It is worth noting that at the group level, a subsample of our MCI patients showed reduced volume of the hippocampus. Although hippocampal atrophy characterises ACS dementia from the early stages, such a finding in MCI does not guarantee that our patients will develop such type of dementia[30]. Longitudinal assessments involving the versions of the STMB tasks above suggested (i.e., STMB tasks combining 2 and 3 items) would help identify cognitive profiles of MCI patients that will eventually convert to ACS dementia.

Final remarks

Based on these results, it would be plausible to suggest that STMB tasks can be a useful tool to screen for the ACS profile among MCI patients, as they clearly differ from CU. The usefulness of such tests as monitoring tools for dementia progression remains less clear. For instance, Logie, Parra, and Della Sala (2015)[14] suggested that by tailoring task difficulty to the changing abilities of affected patients, the STMB tasks may become effective to assess progression and response to treatments (see also Parra et al., 2019[17]). Although both STMB tasks achieved high level of accuracy in distinguishing MCI and ACS patients from UC, they displayed different classification power. The CD task

discriminated the MCI and ACS group from CU group but could not distinguish between the first two. The FR task, however, revealed a graded impairment which followed the disease severity. It might be that STMB functions supporting recognition in CD tasks decline dramatically in the very early stages of ACS while those supporting FR continue to decline as the disease progresses. Should this hypothesis holds true, CD and FR STMB may offer tools for early detection and follow up assessment of people embarked on the AD continuum.

A limitation of the current study worth highlighting is the lack of beta-amyloid or tau biomarker data, which precluded the possibility of adhering to the new framework supporting the biological definition of ACS. However, we analysed the MRI data available from sizeable subsamples of our MCI and ACS groups. These analyses showed that hippocampal atrophy would be a likely feature of MCI and ACS patients, identified via our assessment protocols. In fact, we found that the severity of such atrophy followed the disease course (Normative Sample > MCI > ACS). Although deemed non-specific by recent consensus[30], hippocampal atrophy has been shown to be a predictor of the progression from MCI to AD and it is a hallmark of AD dementia[30,33,55–57]. Taken together, the MRI findings coupled with the observed deficits in the neuropsychological measures suggested that our MCI patients were likely in the prodromal stages of AD[58].

In sum, present findings indicated that the CD and the FR STMB tasks can identify MCI and ACS with adequate accuracy. To test if the STMB is specific to diagnose ACS pathology, future studies should verify the relationship between STMB tasks and ACS biomarkers (beta amyloid and tau).

Data Availability Statement: Author elects to not share data.

References

1. Cecchini MA, Yassuda MS, Bahia VS, et al. Recalling feature bindings differentiates Alzheimer's disease from frontotemporal dementia. *J Neurol*. 2017;264(10):2162-2169. doi:10.1007/s00415-017-8614-9

2. Della Sala S, Parra MA, Fabi K, Luzzi S, Abrahams S. Short-term memory binding is impaired in AD but not in non-AD dementias. *Neuropsychologia*.

2012;50(5):833-840. doi:10.1016/j.neuropsychologia.2012.01.018

3. Parra MA, Abrahams S, Fabi K, Logie R, Luzzi S, Della Sala S. Short-term memory binding deficits in Alzheimers disease. *Brain*. 2009;132(4):1057-1066. doi:10.1093/brain/awp036

4. Della Sala S, Kozlova I, Stamate A, Parra MA. A transcultural cognitive marker of Alzheimer's Disease. *Int J Geriatr Psychiatry*. November 2016. doi:10.1002/gps.4610

5. Smith K, Azami H, Escudero J, Parra MA, Starr JM. 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)*. IEEE; 2015:2207-2210. doi:10.1109/EMBC.2015.7318829

6. Liang Y, Pertzov Y, Nicholas JJM, et al. Visual short-term memory binding deficit in familial Alzheimer's disease. *Cortex*. 2016;78:150-164. doi:10.1016/j.cortex.2016.01.015

7. Brockmole JR, Parra MA, Della Sala SD, Logie RH. Do binding deficits account for age-related decline in visual working memory? *Psychon Bull Rev*. 2008;15(3):543-547. doi:10.3758/PBR.15.3.543

8. Brockmole JR, Logie RH. Age-Related Change in Visual Working Memory: A Study of 55,753 Participants Aged 8–75. *Front Psychol*. 2013;4(JAN):1-5. doi:10.3389/fpsyg.2013.00012

9. Hoefeijzers S, González Hernández A, Magnolia Rios A, Parra MA. Feature Binding of Common Everyday Items Is Not Affected by Age. *Front Aging Neurosci*. 2017;9(MAY):1-12. doi:10.3389/fnagi.2017.00122

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

11. Kirmsse A, Zimmer HD, Ecker UKH. Age-related changes in working memory: Age affects relational but not conjunctive feature binding. *Psychol Aging*. 2018;33(3):512-526. doi:10.1037/pag0000249

12. Yassuda MS, Carthery-Goulart MT, Cecchini MA, et al. Free Recall of Bound Information Held in Short-Term Memory is Unimpaired by Age and Education. *Arch Clin Neuropsychol*. April 2019. doi:10.1093/arclin/acz015

13. Logie RH, Brockmole JRJ, Vandenbroucke AREA. Bound feature combinations in visual short-term memory are fragile but influence long-term learning. *Vis cogn*. 2009;17(1-2):160-179. doi:10.1080/13506280802228411

14. Logie R, Parra MA, Della Sala S. From Cognitive Science to Dementia Assessment. *Policy Insights from Behav Brain Sci*. 2015;2(1):81-91. doi:10.1177/2372732215601370

15. Parra MA, Abrahams S, Logie RH, Della Sala S. Visual short-term memory binding in Alzheimer's disease and depression. *J Neurol*. 2010;257(7):1160-1169. doi:10.1007/s00415-010-5484-9

16. Koppara A, Frommann I, Polcher A, et al. Feature Binding Deficits in Subjective Cognitive Decline and in Mild Cognitive Impairment. *J Alzheimer's Dis*. 2015;48(S1):S161-S170. doi:10.3233/JAD-150105

17. Parra MA, Calia C, García AF, et al. Refining memory assessment of elderly people with cognitive impairment: Insights from the short-term memory binding test. *Arch Gerontol Geriatr*. 2019;83:114-120. doi:10.1016/j.archger.2019.03.025

18. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 2001;56(3):303-308. doi:10.1001/archneur.56.3.303

19. Petersen RC. Mild Cognitive Impairment. *N Engl J Med*. 2011;364(23):2227-2234. doi:10.1056/NEJMcp0910237

20. Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med*. 2013;29(4):753-772.

21. Albert MS, DeKosky ST, Dickson D, et al. 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 Dement*. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008

22. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194. doi:10.1111/j.1365-2796.2004.01388.x

23. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia - meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*. 2009;119(4):252-265. doi:10.1111/j.1600-0447.2008.01326.x

24. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58(12):1985-1992.

25. Grande G, Cucumo V, Cova I, et al. Reversible Mild Cognitive Impairment: The Role of Comorbidities at Baseline Evaluation. Gallucci M, ed. *J Alzheimer's Dis*. 2016;51(1):57-67. doi:10.3233/JAD-150786

26. Galluzzi S, Geroldi C, Amicucci G, et al. Supporting evidence for using biomarkers in the diagnosis of MCI due to AD. *J Neurol*. 2013;260(2):640-650. doi:10.1007/s00415-012-6694-0

27. Park MH, Han C. Is there an MCI reversion to cognitively normal? Analysis of Alzheimer's disease biomarkers profiles. *Int Psychogeriatrics*. 2015;27(03):429-437. doi:10.1017/S1041610214002129

28. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. *Alzheimer's Dement*. 2018;14(3):367-429. doi:10.1016/j.jalz.2018.02.001

29. Knopman DS, Haeberlein SB, Carrillo MC, et al. The National Institute on Aging and the Alzheimer's Association Research Framework for Alzheimer's disease: Perspectives from the Research Roundtable. *Alzheimer's Dement*. 2018;14(4):563-575. doi:10.1016/j.jalz.2018.03.002

30. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018

31. Parra MA, Abrahams S, Logie RH, Méndez LG, Lopera F, Della Sala S. Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain*. 2010;133(9):2702-2713. doi:10.1093/brain/awq148

32. Malloy-Diniz LF, Lasmar VAP, Gazinelli L de SR, Fuentes D, Salgado JV. The Rey Auditory-Verbal Learning Test: applicability for the Brazilian elderly

population. *Rev Bras Psiquiatr*. 2007;29(4):324-329. doi:10.1590/S1516-44462006005000053

33. McKhann GM, Knopman DS, Chertkow H, et al. 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 Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005

34. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

35. Brucki SMD, Nitrini R, Caramelli P, Bertolucci PHF, Okamoto IH. Sugestões para o uso do mini-exame do estado mental no Brasil. *Arq Neuropsiquiatr*. 2003;61(3 B):777-781. doi:10.1590/S0004-282X2003000500014

36. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology*. 1993;43(11):2412-2412. doi:10.1212/WNL.43.11.2412-a

37. Chaves MLF, Camozzato AL AL, Godinho C, et al. Validity of the clinical dementia rating scale for the detection and staging of dementia in Brazilian patients. *Alzheimer Dis Assoc Disord*. 2007;21(3):210-217. doi:10.1097/WAD.0b013e31811ff2b4

38. Pfeffer RI, Kurosaki T, Harrah CH, et al. Measurement of Functional Activities in Older Adults in the Community. *J Gerontol*. 1982;37(3):323-329. doi:10.1093/geronj/37.3.323

39. Sanchez MAS, Correa PCR, Lourenço RA. Cross-cultural Adaptation of the "Functional Activities Questionnaire - FAQ" for use in Brazil. *Dement Neuropsychol*. 2011;5(4):322-327. doi:10.1590/S1980-57642011DN05040010

40. Porto CS, Fichman HC, Caramelli P, Bahia VS, Nitrini R. Brazilian version of the Mattis dementia rating scale: diagnosis of mild dementia in Alzheimer's disease. *Arq Neuropsiquiatr*. 2003;61(2B):339-345. doi:10.1590/S0004-282X2003000300004

41. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: *Geriatric Psychiatry: A Handbook for Psychiatrists and Primary*

Care Physicians. ; 1976. http://ci.nii.ac.jp/naid/10017615871/. Accessed July 31, 2017.

42. Rey A. *L'examen Clinique En Psychologie.* Oxford: Presses Universitaries De France; 1958. http://psycnet.apa.org/psycinfo/1959-03776-000. Accessed August 27, 2017.

43. Machado TH, Fichman HC, Santos EL, et al. Normative data for healthy elderly on the phonemic verbal fluency task - FAS. *Dement Neuropsychol*. 2009;3(1):55-60. doi:10.1590/S1980-57642009DN30100011

44. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. *J Psychiatr Res*. 1982;17(1):37-49. doi:10.1016/0022-3956(82)90033-4

45. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral Blood Flow in Dementia. *Arch Neurol*. 1975;32(9):632-637. doi:10.1001/archneur.1975.00490510088009

46. Fischl B, Salat DH, Busa E, et al. Whole Brain Segmentation. *Neuron*. 2002;33(3):341-355. doi:10.1016/S0896-6273(02)00569-X

47. Wenger E, Mårtensson J, Noack H, et al. Comparing manual and automatic segmentation of hippocampal volumes: Reliability and validity issues in younger and older brains. *Hum Brain Mapp*. 2014;35(8):4236-4248. doi:10.1002/hbm.22473

48. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. New York: Hillsdale; 1988.

49. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12(1):77. doi:10.1186/1471-2105-12-77

50. Parra MA, Della Sala S, Logie RH, Abrahams S. Selective impairment in visual short-term memory binding. *Cogn Neuropsychol*. 2009;26(7):583-605. doi:10.1080/02643290903523286

51. Olson IR, Jiang Y. Is visual short-term memory object based? Rejection of the "strong-object" hypothesis. *Percept Psychophys*. 2002;64(7):1055-1067. doi:10.3758/BF03194756

52. Wheeler ME, Treisman AM. Binding in short-term visual memory. *J Exp Psychol Gen*. 2002;131(1):48-64. doi:10.1037//0096-3445.131.1.48

53. Danckert SL, Craik FIM. Does aging affect recall more than recognition memory? *Psychol Aging*. 2013;28(4):902-909. doi:10.1037/a0033263

54. Rhodes S, Greene NR, Naveh-Benjamin M. Age-related differences in recall and recognition: a meta-analysis. *Psychon Bull Rev*. August 2019. doi:10.3758/s13423-019-01649-y

55. Platero C, Lin L, Tobar MC. Longitudinal Neuroimaging Hippocampal Markers for Diagnosing Alzheimer's Disease. *Neuroinformatics*. 2018:1-19.

56. Frisoni GB, Fox NC, Jack Jr CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol*. 2010;6(2):67.

57. Risacher S, Saykin A, Wes J, Shen L, Firpi H, McDonald B. Baseline MRI Predictors of Conversion from MCI to Probable AD in the ADNI Cohort. *Curr Alzheimer Res*. 2009;6(4):347-361. doi:10.2174/156720509788929273

58. Halliday G. Pathology and hippocampal atrophy in Alzheimer's disease. *Lancet Neurol*. 2017;16(11):862-864. doi:10.1016/S1474-4422(17)30343-5

Tables

Table 1. Sociodemographic, cognitive characteristics and hippocampal volume across clinical groups (n=85).

	CU (n = 24)	**MCI** (n = 24)	**ACS** (n = 37)	p-value
Age	67.83(6.06)	70.33(6.89)	71.14(7.58)	0.195
Education	12.83(4.06)	9.54(5.82)	10.05(5.23)	0.055
MMSE	28.29(1.16)^{c}	26.64(1.92)^{c}	23.23(3.74)^{ab}	<0.001
CDR†	(22, 2, 0, 0)^{bc}	(3, 18, 0, 0)^{ac}	(0, 15, 20, 1)^{ab}	<0.001
FAQ	1.09(1.51)^{c}	2.71(2.67)^{c}	9.44(5.77)^{ab}	<0.001
FAS	40.67(13.79)^{bc}	27.54(7.59)^{a}	21.15(10.36)^{a}	<0.001
RAVLT (A1-A5)	49.96(7.54)^{bc}	34.71(10.47)^{ac}	24.68(6.14)^{ab}	<0.001
RAVLT Delayed	10.75(2.21)^{bc}	4.96(2.63)^{ac}	1.24(1.66)^{ab}	<0.001
DRS Total	139.86(3.85)^{bc}	130.33(6.55)^{ac}	119.19(9.24)^{ab}	<0.001
HV left‡	3698.30(414.77)^{bc}	3387.05(537.03)^{ac}	2689.54(378.06)^{ab}	<0.001

Note. Mean (SD). † = Number of participants who scored 0, 0.5, 1.0 and 2.0, respectively, in CDR; the proportions of CDR scores were compared using the chi-squared test; p value refers to ANOVA, with Bonferroni post hoc comparisons. ‡ to assess the hippocampal volume data, a subsample of 16 MCI and 12 ACS patients were compared to a normative sample of 133 controls. In the present sample, 16 MCI and 12 ACS patients had a recent available image, ; CU = Cognitively Unimpaired; MCI = Mild Cognitive Impairment; ACS = Alzheimer's Clinical Syndrome; MMSE = Mini Mental State Examination; DRS = Dementia Rating Scale; FAQ = Functional Activities Questionnaire; FAS = phonemic verbal fluency task; RAVLT = Rey Auditory Verbal Learning Test; RAVLT (A1-A5) = sum of the first five trials of the RAVLT; HV = Hippocampal volume (left hemisphere) taken from the subsample described above. a = differ from CU ($p < 0.05$); b = differ from MCI ($p < 0.05$); c = differ from ACS ($p < 0.05$). There were missing cases for MMSE (2 in MCI group and 2 in ACS), FAS (4 cases in ACS group), CDR (3 cases for MCI group, 1 case for ACS), FAQ (2 cases for CU group, 3 cases for MCI and 1 for ACS) and DRS (6 in ACS group).

Table 2. Results for the comparisons between the Unbound and Bound Features across diagnostic groups.

	CD Unbound	CD Bound	p-value	Effect Size	FR Unbound	FR Bound	p-value	Effect Size
CU	84.38(10.43)	96.47(4.92)	<0.001	0.989	86.69(8.71)	82.54(7.91)	0.040	0.480
MCI	71.09(11.48)	78.13(15.20)	0.047	0.428	64.81(12.99)	53.94(13.36)	0.005	0.631
ACS	68.24(12.70)	71.96(16.45)	0.146	0.244	55.33(16.81)	40.69(20.33)	<0.001	1.102

Note. CU = Cognitively Unimpaired; MCI = Mild Cognitive Impairment; ACS = Alzheimer's Clinical Syndrome. CD = Change Detection; FR = Free Recall. Effect Size was calculated using the Cohen's d method. There were three missing cases for FR bound and one for CD bound, both in the CU group.

Table 3. ROC analyses for the diagnostic accuracy of the short-term memory binding tasks

Variable	Groups	Cut off (%)	AUC	95% CI	Sensitivity	Specificity	p-value
CD Bound	CU x MCI	90.63	0.855	0.741 – 0.970	0.900	0.708	<0.001
	CU x ACS	90.63	0.924	0.858 – 0.991	0.900	0.784	<0.001
	MCI x ACS	71.88	0.612	0.469 – 0.755	0.625	0.514	0.142
FR Bound	CU x MCI	75.00	0.975	0.937 – 1.000	0.905	0.958	<0.001
	CU x ACS	75.00	0.973	0.939 – 1.000	0.900	0.919	<0.001
	MCI x ACS	47.22	0.697	0.567 – 0.827	0.667	0.676	0.010

Note. CD = Change Detection task; FR = Free Recall task; CU = Cognitively Unimpaired; MCI = Mild Cognitive Impairment; ACS = Alzheimer's Clinical Syndrome; AUC = Area Under the Curve; CI = Confidence Interval.

Figure Legends

Figure 1. Change Detection short-term memory binding test (Unbound and Bound Features)

Figure 2. Free Recall Short-term Memory Binding Task (Unbound and Bound Features)

Figure 3. Change Detection (CD) and Free Recall (FR) modalities of the short-term memory binding test. CU = Cognitively Unimpaired; MCI = Mild Cognitive Impairment; ACS = Alzheimer's Clinical Syndrome. Error bars = SEM.