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Repeatable Battery for the Assessment of Neuropsychological Status and its relationship to biomarkers of Alzheimer's disease

Kevin Duff[1], **Kayla R. Suhrie**[1], **Dustin B. Hammers**[1], **Ava M. Dixon**[1], **Jace B. King**[2], **Vincent Koppelmans**[3], **John M. Hoffman**[4]

[1]Center for Alzheimer's Care, Imaging and Research, Department of Neurology, University of Utah

[2]Department of Radiology and Imaging Sciences, University of Utah, United States

[3]Department of Psychiatry, University of Utah, United States

[4]Center for Quantitative Cancer Imaging, Huntsman Cancer Institute, University of Utah

Abstract

Background: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) has been associated with commonly used biomarkers of Alzheimer's disease (AD). However, prior studies have typically utilized small and poorly characterized samples, and they have not analyzed the subtests of the RBANS. The current study sought to expand on prior work by examining the relationship between the Indexes and subtest scores of the RBANS and three AD biomarkers: amyloid deposition via positron emission tomography, hippocampal volume via magnetic resonance imaging, and APOE ε4 status.

Method: One-hundred twenty-one older adults across the AD continuum (intact, amnestic Mild Cognitive Impairment, mild AD), who were mostly Caucasian and well-educated,underwent assessment with the RBANSand collection of the three biomarkers.

Results: Greater amyloid deposition was significantly related to lower scores on all five Indexes and the Total Scale score of the RBANS, as well as 11 of 12 subtests. For bilateral hippocampal volume, significant correlations were observed for 4 of the 5 Indexes, Total Scale score, and 9 of 12 subtests, with smaller hippocampi being related to lower RBANS scores. Participants with at least one APOE ε4 allele had significantly lower scores on 3 of the 5 Indexes, Total Scale score, and 8 of the 12 subtests.

Conclusions: In this sample of participants across the dementia spectrum, most RBANSIndexes and subtests showed relationships with the amyloid deposition, hippocampal volumes, and APOE status, with poorer performance on the RBANS being associated with biomarker positivity. Although memory scores on the RBANS have traditionally been linked to biomarkers in AD, other Index and subtest scores also hold promise as indicators of AD. Replication in a more diverse sample is needed.

Corresponding author: Kevin Duff, PhD, Center for Alzheimer's Care, Imaging and Research, University of Utah, Department of Neurology, 650 Komas Drive #106-A, Salt Lake City, UT 84108. Tel: 801-585-9983. Fax: 801-581-2483. kevin.duff@hsc.utah.edu.

INTRODUCTION

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; (Randolph, 2012) is a widely-used collection of brief subtests that assess immediate and delayed memory, visuospatial/constructional skills, language, and attention in adults. It has been validated in multiple samples of older adults, including those with intact cognition (Cooley et al., 2015; Duff & Ramezani, 2015; Phillips et al., 2015; Thaler, Hill, Duff, Mold, & Scott, 2015), Mild Cognitive Impairment,(MCI)(Clark, Hobson, & O'Bryant, 2010; Duff, Hobson, Beglinger, & O'Bryant, 2010; Hobson, Hall, Humphreys-Clark, Schrimsher, & O'Bryant, 2010; Karantzoulis, Novitski, Gold, & Randolph, 2013; O'Mahar et al., 2012), and Alzheimer's disease(AD) (Burton, Enright, O'Connell, Lanting, & Morgan, 2015; Duff et al., 2008; Enright, O'Connell, MacKinnon, & Morgan, 2015; Heyanka, Scott, & Adams, 2015; McDermott & DeFilippis, 2010; Morgan, Linck, Scott, Adams, & Mold, 2010; Schmitt et al., 2010). Various metrics for change across time on the RBANS have been developed and validated for geriatric cohorts(Duff et al., 2005; Duff et al., 2004; Hammers, Suhrie, Porter, Dixon, & Duff, 2020a, 2020b; O'Connell, Gould, Ursenbach, Enright, & Morgan, 2019). Scores on the RBANS have also been linked to daily functioning in older adults with intact and impaired cognition (Duff, Porter, Dixon, Suhrie, & Hammers, 2020; Freilich & Hyer, 2007; O'Bryant et al., 2011). As such, the RBANS provides valuable information about diagnosis, prognosis, and daily functioning in late life cognitive disorders.

Several studies have also examined the relationship between scores on the RBANS and various biomarkers associated with AD. For example, the Total Scalescore, the Delayed Memory Index, and the Immediate Memory Index of the RBANS have been shown to positively correlate with hippocampal and whole brain volumes in older adults with and without cognitive impairment (England, Gillis, & Hampstead, 2014; Jiang et al., 2014; Ottoy et al., 2019; Paul et al., 2011), with better scores being associated with larger brain volumes. Furthermore, cerebral amyloid levels have typically been negatively correlated with Total Scale score and various memory scores from the RBANS (e.g., Delayed Memory Index, Immediate Memory Index) across the dementia spectrum(Duff et al., 2013; Hammers, Atkinson, Dalley, Suhrie, Beardmore, et al., 2017; Hammers, Atkinson, Dalley, Suhrie, Horn, et al., 2017; Ottoy et al., 2019; Teng et al., 2019), with better scores being associated with less brain amyloid. To our knowledge, no studies have examined the relationship between the RBANS and APOE ε4 allele carrier status in older adults, which is another biomarker of AD (Holtzman, Herz, & Bu, 2012; Mayeux et al., 1993; Petersen et al., 1995).

Despite the multiple studies that have assessed this association between the RBANS and AD biomarkers, notable gaps in our knowledge remain. First, as mentioned above, no studies have specifically analyzed the effects of APOE on the RBANS. Second, some studies utilized vaguely characterized samples (e.g., "non-demented" subjects in Duff et al., 2013; "non-clinical" subjects in Paul et al., 2011). Third, most studies used small cohorts (e.g., average across all studies <60 subjects; citations for all studies reviewed). Fourth, those using clearly-defined clinical groups (England et al., 2014; Ottoy et al., 2019; Teng et al., 2019) were even smaller (e.g., averaged 44 with MCI and 25 with AD). These smaller samples raise concern about the generalizability of prior results, so replication is necessary. Finally, whereas multiple studies have examined the Total Scale, Delayed Memory Index, and Immediate Memory Index, no studies have examined how all of the subtests of the RBANS relate to biomarkers. Therefore, the current study sought to examine the relationship between the RBANS Indexes and subtests and three biomarkers of AD (hippocampal volumes, cerebral amyloid deposition, APOE ε4) in a cohort of older adults who span the AD continuum (intact, MCI, AD). Based on existing literature, it was hypothesized that RBANS scores, especially those tapping memory, would positively correlate with hippocampal volumes, negatively correlate with cerebral amyloid, and be smaller in those with at least one APOE ε4 allele. Further support for the use of the RBANS as a cognitive marker in AD might allow for enrichment of samples prone to AD pathology in related clinical trials, as well as give clinicians more confidence in a diagnosis of AD with certain cognitive impairments on the RBANS.

METHODS

Participants

One hundred twenty-oneolder adults were recruited from a cognitive disorders clinic (48.8%) or through the community (51.2%) to participate in a larger study of brain imaging and neuropsychological testing across the dementia spectrum. Their mean age was 74.2 (SD=5.7) years and their mean education was 16.1 (SD=2.4) years. Most were Caucasian (98.3%) and 58.7% were female. Mean premorbid intellectual functioning – as measured by the Reading subtest of the Wide Range Achievement Test – 4 (WRAT-4; (Wilkinson & Robertson, 2006)– was in the average range (M=109.7, SD=8.5), and self-rating of depression symptoms were minimal on the 15-item Geriatric Depression Scale (M=1.2, SD=1.2; (Yesavage et al., 1982).

Participants from the cognitive disorders' clinic were recruited with a clinical diagnosis of either amnestic MCI (single or multi-domain) or AD based on a neurological visit, neuropsychological evaluation, and brain imaging. Participants from the community were largely recruited as cognitively intact controls; however, a minority of amnestic MCI cases (~15%) were identified in the community. Confirmation of group assignment was made with the Alzheimer's Disease Neuroimaging Initiative (ADNI2, 2020) classification battery, which included the Mini Mental Status Examination (Folstein, Folstein, & McHugh, 1975), the Clinical Dementia Rating Scale (Morris, 1993), and the Wechsler Memory Scale –Revised (Wechsler, 1987)Logical Memory II Paragraph A.Fifty-fourparticipants were classified as cognitively intact, thirty-fiveas amnestic MCI (single or multidomain), and thirty-two as mild AD.

Participants were included if they were 65 years of age or older and had a knowledgeable collateral source available to comment on their cognition and daily functioning. Participants were excluded for medical comorbidities likely to affect cognition (including neurological conditions, current severe depression, substance abuse, and major psychiatric conditions), the inability to complete MRI or PET, the inability to complete cognitive assessments due to inadequate vision, hearing, or manual dexterity, and being enrolled in a clinical drug trial related to anti-amyloid agents. Additional exclusion criteria included elevated depression as indicated by a score of greater than 5 on the 15-item Geriatric Depression Scale, and moderate or severe dementia as indicated by aClinical Dementia Rating score of 2 or greater or a Mini Mental Status Examination score of less than 20.

Procedure

Procedures were approved by the local Institutional Review Board before participants enrolled. Following informed consent/assent, participants underwent testing with the ADNI battery and other neuropsychological testing, including the RBANS, at a baseline visit. They returned about a week and a half later (M=10.7 days, SD=19.2) foran MRI of the brain. Within a few weeks (M= 19.5 days, SD=16.9) they returned to receive anamyloidPET scanof the brain using ^{18}F-Flutemetamol and a blood draw to determine APOE ε4 status.

Neuropsychological Measures

The RBANS (Randolph, 2012) is a brief neuropsychological testing battery comprised of 12 subtests used to calculate five Index scores: Immediate Memory Index (comprised of List Learning and Story Memorysubtests), Visuospatial/Constructional Index (Figure Copy and Line Orientation subtests), Attention Index (Digit Span and Coding subtests), Language Index (Picture Naming and Semantic Fluency subtests), and Delayed Memory Index (List Recall, List Recognition, Story Recall, and Figure Recall subtests), and a Total Scale score (comprised of all 12 subtests). Using normative data from the test manual, these Index scores are age-corrected standard scores (M=100, SD=15), with higher scores indicating better cognition. Subtest scores are raw scores, again with higher scores indicating better cognition.The RBANS was not part of either the clinical evaluation of individuals nor part of the research classification that confirmed group assignment (i.e., it was independent of the any diagnosis).

The WRAT-4 Reading subtest(Wilkinson & Robertson, 2006), in which a participant reads irregular words, was administered to assess premorbid intellect. Usingnormative data, age-corrected standard scoresare generated (M=100, SD=15), with higher scores indicating higher premorbid intellect.

MRI

MRI was acquired on a 3.0-T Siemens Prisma scanner with a 64-channel head coil. Structural data were acquired using an MP2RAGE sequence (TR = 5000, TE = 2.93, acquired sagittally, resolution=1 x 1 x 1 mm) to obtain high quality whole brain 1mm isotropic T1 images with improved signal homogeneity in ~7 minutes. All MRI scans were examined for the presence of common artifacts, including motion, susceptibility, and distortion, and were determined to be of sufficient quality for quantitative analysis. All data were processed on the same workstation using FreeSurfer image analysis suite v6.0 (http://surfer.nmr.mgh.harvard.edu/) to estimate total estimated intracranial and hippocampal volumes. Technical details are described previously (Fischl & Dale, 2000; Fischl et al., 2002; Fischl et al., 2004). To address head size differences, hippocampal volumes have been adjusted by estimated total intracranial volume. Left and right hemispheric volumes were summed to create total hippocampal volume adjusted by total intracranial volume.

Amyloid Imaging

Amyloid imaging was performed using ^{18}F-Flutemetamol which is a radioactive diagnostic agent indicated for PET imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment. ^{18}F-Flutemetamol was produced under PET cGMP standards and conducted under an approved FDA Investigational New Drug application (IND). Twenty minutes of emission imaging was performed 90 minutes after the injection of approximately 185 mBq (5 mCi) of ^{18}F-Flutemetamol. A GE Discovery PET/CT 710(GE Healthcare) was used in this study. This PET/CT scanner has full width at half-maximum spatial resolution of 5.0 mm and excellent performance characteristics (Sunderland & Christian, 2015; Yester, Al-Senan, & White, 2014). Volumes of interest were automatically generated by using the CortexID Suite analysis software (GE Healthcare). ^{18}F-Flutemetamol binding was analyzed using a regional semi-quantitative technique described byVandenberghe et al. (2010)and refined byThurfjell et al. (2014). The CortexID Suite software generates, semi-quantitative regional (prefrontal, anterior cingulate, precuneus/posterior cingulate, parietal, mesial temporal, lateral temporal, occipital, sensorimotor, cerebellar grey matter, and whole cerebellum) standardized uptake value ratios (SUVRs) normalized to the pons. A composite standardized uptake value ratio (SUVR) in the cerebral cortex was generated automatically and normalized to the pons using the CortexID Suite software(Lundqvist et al., 2013).

APOE Genotyping

Polymerase Chain Reaction and Fluorescence Monitoring using hybridization probes for APOE genotyping was conducted using whole blood samples. Results were dichotomized as being APOE ε4 allele carriers (both hetero- and homozygous) or non-carriers.

Data Analysis

For the entire sample of 121 participants, continuous biomarker data (hippocampal volumes and amyloid SUVR) were correlated (via Pearson correlations)with RBANS Indexes and subtests. For dichotomous/ordinal data (APOE ε4 status), biserial correlations were calculated between those with at least one ε4 allele and those with no ε4 alleles and RBANS Indexes and subtests. To protect against multiple comparisons, a false discovery rate (Benjamin & Hochberg, 1995) was calculated for each biomarker analysis at .05.As an additional exploration of the unique impact of the various biomarkers on RBANS performance, we conducted a stepwise regression, which included RBANS Total Scale score as the dependent variable and age, education, and the three biomarkers as the predictor variables.

RESULTS

As can be seen in Table 1, of the 121 participants in this study, 52 were classified as cognitively intact, 37 were classified as amnestic MCI, and 32 were classified as AD. Demographically, those with AD were significantly older than the other two groups, and the intact individuals had significantly more years of education than those with MCI. Otherwise, there were no differences between the groups on any demographic information (e.g., age, education, sex, or race). There were no differences between the three groups on premorbid intellect or depression.

As seen in Table 1, on the RBANS, all three groups were significantly different on the Total Scale score, Immediate Memory Index, Language Index, and Delayed Memory Index, with the cognitively intact participants having the highest scores, followed by the MCI participants, and then the AD participants. For the Visuospatial/Constructional and Attention Indexes, the cognitively intact participants outperformed the MCI and AD participants, who were comparable. The group differences on the twelve subtests of the RBANS are also presented in Table 1.

For the three biomarkers, there were also group differences. All three groups were significantly different on hippocampal volumes (intact>MCI>AD). For cerebral amyloid, the intact group possessed significantly lower SUVRs compared to the MCI and AD participants (who were comparable). For APOE, the AD and MCI groups had higher percentages of individuals with one or more ε4 alleles than the cognitively intact group.

Although there were differences between groups on age and education,many RBANS scores, and biomarkers, these differences were not considered in the correlational analyses and t-tests, as the groups were pooled. However, when age was considered as covariate, the correlations between the RBANS scores and the biomarkers were very similar. The interested reader can contact the first author for these results.

Hippocampal Volumes

For the entire sample, using a false discovery rateadjusted p-value of 0.007, total hippocampal volumes were significantly correlated with RBANS Total Scale, 4 of the 5 Indexes, and 9 of the 12 subtests (see Table 2). All significant correlations werein the expected direction, with larger hippocampal volumes being associated with better scores on the RBANS.

Cerebral Amyloid

Cerebral amyloid (SUVR) was significantly correlated with RBANS Total Scale, all five of the Indexes, and 11 of the 12 subtests in the full sample (see Table 2). All correlations werein the expected direction, with greater amyloid deposition being associated with worse RBANS scores.Although our analyses combined intact, MCI, and AD participants into one group for these correlations, Figure 1 shows the relationship between cerebral amyloid (SUVR) and the RBANS Total Scale score in a scatterplot, with participants in each group individually presented. The interested reader can contact the first author for additional biomarker by RBANS score scatterplots.

APOE ε4

When individuals were dichotomized as having either no ε4 alleles or having one/two copies of ε4, then these two groups were statistically significantly different on the RBANS Total Scale, 3 of the 5 Indexes, and 8 of the 12 subtests (see Table 2). For each statistically significant difference, those with no ε4 alleles performed better on the RBANS than those with one/two ε4 alleles.

Although no within-group correlations (e.g., correlation between cerebral amyloid and Immediate Memory Index in just the MCI group) are reported to minimize the number of statistical tests, the interested reader can contact the first author for the results of these analyses.

All Three Biomarkers

When age, education, and the three biomarkers were examined as predictors of the RBANS Total Scale score in a stepwise regression, the initial step included amyloid deposition on PET ($R2=0.32$, $F[1,110]=51.5$, $p<0.001$). In a second step, hippocampal volumes on MRI statistically added to this model ($R2=0.39$, $F[2,110]=35.2$, $p<0.001$). In the final step in the model, education statistically added to the model ($R2=0.42$, $F[3,110]=25.8$, $p<0.001$). In that final model, neither age nor APOE e4 statistically added variance (ps=0.70 and 0.13, respectively). The interested reader can contact the first author for the results of the regression models for the remaining Indexes and subtests of the RBANS.

DISCUSSION

The current study sought to examine the relationship between the Indexes and subtests of the RBANS and three biomarkers associated with AD (hippocampal volumes, cerebral β-amyloid, APOE ε4 allele carrier status) in a sample of older adults along the AD continuum (cognitively intact, amnestic MCI, mild AD).Although past research has found associations between RBANS Indexes and some of these biomarkers, very few studies have reported on any of the subtests of the RBANS as they relate to AD biomarkers. Such associations would aid in the interpretation of RBANS scores in older adults at risk of dementia due to AD. Additionally, such information might allow for the more efficient identification of individuals appropriate for screening for AD clinical trials that require biomarker positivity.

Consistent with prior work(England et al., 2014; Hammers, Atkinson, Dalley, Suhrie, Beardmore, et al., 2017; Hammers, Atkinson, Dalley, Suhrie, Horn, et al., 2017; Jiang et al., 2014; Paul et al., 2011; Teng et al., 2019), the Total Scale score of the RBANS was cerebral amyloid (and hippocampal volume), with better performance on this overall composite of the RBANS being associated with more brain amyloid (and smaller hippocampi). As depicted in Figure 1, the vast majority of intact participants had higher scores on the RBANS Total score and sub-cutoff amyloid values, whereas the MCI and AD participants tended to have lower RBANS Total scores and amyloid values above the cutoff for positivity.Furthermore, to our knowledge, this is the first study to examine the impact of the ε4 allele of APOE on the RBANS in those across the dementia spectrum. Consistent with prior studies on other neuropsychological tests(Caldwell et al., 2018; Ge et al., 2018; Lim, Mormino, & Alzheimer's Disease Neuroimaging, 2017; Mormino et al., 2014), those with one or more copies of APOE ε4 performed significantly below those with no copies on the RBANS Total Scale. Finally, in our exploratory regression analysis, cerebral amyloid, hippocampal volumes, and education all significantly predicted the RBANS Total Scale score. Although this regression result would need to be replicated in larger and more diverse samples, it suggests that two of the biomarkers independently predict this global composite measure, and that one demographic variable further predicts this neuropsychological test score.Such findings continue to suggest that this global composite of the RBANS is an important cognitive variable in clinical assessments.

Similar to the Total Scale score, the Delayed Memory Index and the Immediate Memory Index were related to all three biomarkers in this study. One or both of these memory indices of the RBANS have been previously implicated with brain atrophy (England et al., 2014; Jiang et al., 2014; Ottoy et al., 2019) and amyloid (Duff et al., 2013; Hammers, Atkinson, Dalley, Suhrie, Beardmore, et al., 2017; Hammers, Atkinson, Dalley, Suhrie, Horn, et al., 2017; Ottoy et al., 2019). Although many prior studies have focused on the Delayed Memory Index, the relationship between the biomarkers and the Immediate Memory Index were nearly as strong (see *r* values in Table 2). Given that the Immediate Memory Index is made up of fewer subtests than the Delayed Memory Index and it could be given without the extra time of the delay, it may also be an attractive option for a screening measure of clinical trials in AD. Nonetheless, these memory Indexes of the RBANS continue to hold promise as critical cognitive characterization scores for those recruiting for AD clinical trials(Randolph, 2019).

Somewhat surprisingly, very few studies have examined the non-memory Indexes of the RBANS as they relate to biomarkers. Only Ottoy et al. (2019) reported a relationship between the Visuospatial/Constructional Index and hippocampal volumes in their sample that ranged from intact to AD. The current study also found an association with this Index (which includes the copy of a complex figure and a line orientation task) and hippocampal volumes, as well as between this Index and cerebral amyloid. Furthermore, in the present cohort, the Language Index of the RBANS, which contains a brief confrontational naming test and a semantic fluency task, showed significant relationships with 2 of the 3biomarkers(hippocampal volumes and cerebral amyloid). Finally, the Attention Index, which includes a simple auditory attention task and a graphomotor divided attention test, was only related to cerebral amyloid in this sample. Although the Total Scale and memory Indexes of the RBANS have received the most attention in studies involving AD biomarkers, these results would suggest that there are other cognitive targets that appear sensitive to AD pathology.

Perhaps even more surprising is the lack of studies examining the relationship between subtests of the RBANS and AD biomarkers. In fact, only England et al. (2014) and Ottoy et al. (2019) have reported onthe RBANS subtests. These studies, which only seemed to analyze the memory subtests, found that some of the delayed recall and recognition subtests were related to hippocampal volumes and brain amyloid on PET. In our larger sample, we also found that all of the memory subtests –List Learning, Story Memory, List Recall, List Recognition, Story Recall, and Figure Recall – were significantly related to all three biomarkers in this study. For example, the mean correlation between these six memory subtests of the RBANS and SUVR was −0.61, and hippocampal volume was 0.45, and with APOE e4 was −0.39. Therefore, these brief measures of learning and memory were sensitive to brain imaging and genetic markers of AD, which also adds to their clinical value and potential utility in clinical trials (either as screening or outcome measures).

Of the non-memory subtests of the RBANS, some of the results might have been predictable, but others seemed less intuitive. For example, that Semantic Fluency was related to all three biomarkers might be expected by most, as various semantic fluency tests have been found to be reduced in AD (Giffard et al., 2001; Rascovsky et al., 2007). Additionally, the Semantic Fluency subtest was as strongly related to all three biomarkers as the six memory subtests of the RBANS (e.g., modified Fisher r to z transformation between these correlations was non-significant). The Coding subtest was also related to all three biomarkers, which might be slightly less anticipated, as this divided attention task has been less clearly noted to be abnormal in MCI and AD(Park et al., 2020; Skinner et al., 2012; Tsatali et al., 2021). This speeded test of psychomotor abilities was also as strongly related to 2 of the 3 biomarkers (hippocampal volume and APOE e4) as the six memory subtests were. Figure Copy, which is a simplified version of the Rey-Osterrieth Complex Figure Test, was also related to hippocampal volumes and cerebral amyloid (but not APOE ε4). Figure Copy was also as strongly related to hippocampal volume and APOE e4 (but not cerebral amyloid) as the six memory subtests.Such a finding may be consistent with Melrose et al. (2013), who found that the copy trial of the Rey-Osterrieth Complex Figure Test was related to brain hypometabolism in patients with AD. Of the remaining subtests of the RBANS, Line Orientation and Picture Naming was each related to only one biomarker, cerebral amyloid. Digit Span was the only subtest that was not related to any biomarker. In some ways, this might not be so unexpected either, as intact simple attention is typical in AD(De Tollis et al., 2021; Olson et al., 2021; Silva et al., 2012). Similar to the non-memory Indexes from which they are derived, some of the non-memory subtests of this brief battery also appear to hold promise as indicators of AD pathology.

Although there was a difference in the magnitude of correlations between both RBANS Index and subtest scores with the different AD-related biomarkers, the overall pattern of these correlations for the three different biomarkers was remarkably similar (see Figure 2). SUVR showed the strongest correlations across the RBANS, followed by hippocampal volume, with APOE e4 allele status showing the weakest correlations. One reason for the relatively weaker associations of APOE ε4 with RBANS scores could be the limited variation in the number of e4 alleles, which was dichotomized as no ε4 alleles or one or more ε4 alleles. Conversely, SUVR and hippocampal volumes were continuous variables. Another reason for this discrepancy could be due to the nature of these three biomarkers. Whereas APOE is a genetic marker that is present since birth and does not change over time, amyloid deposition and hippocampal volumes do change over time, which appear to more closely track with cognition, which also changes over time. Finally, these different biomarkers might have significance at different points along the path towards AD. For example, as noted earlier, one’s APOE status maintains a relatively constant level of significance as one ages. Conversely, the significance of amyloid positivity and hippocampal atrophy increases from intact to MCI to AD, as they provide additional evidence of diagnostic and etiological specificity along this continuum.

This study is not without limitations. First, the current sample was limited in its demographic and diagnostic diversity, being largely white and well-educated, which could limit the generalizability of these findings to more diverse populations.Additionally, our intact group performed around the 75th percentile on measures of premorbid intellect and RBANS Total Scale score, which may have influenced the results. Second, the range on the 15-item Geriatric Depression Scale was restricted to 0-5 to reduce the influence of depression-related cognitive impairment. Since depression can cause cognitive dysfunction(Ahern & Semkovska, 2017; Peters et al., 2017), it is unclear if these results would remain in a depressed sample. Third, the current sampleonly included individuals with normal cognition, amnestic MCI, and mild AD, as initially diagnosed in a clinical setting and then confirmed by the ADNI criteria. There is some concern about how accurately the ADNI criteria identify AD-specific cases(Bondi et al., 2014; Edmonds et al., 2015). Additionally, these results may not necessarily be generalizable to individuals with more advanced AD or non-AD neurodegenerative conditions (e.g. Lewy Body Dementia, vascular dementia). Future research should address these generalizability concerns and seek to include individuals who are more diverse in race, education, levels of depression, and neurogenerative conditions. Finally, although the current study examined three widely-used biomarkers in AD, it did not include a measure of tau. Research suggests that tau may have a mediating effect on the relationship between amyloid and cognition (Teng et al., 2019). As tau PET imaging technology becomes more widespread, future researchshould examine its relationship with the RBANS.Despite these limitations, the current results provide additional support for using the RBANS in clinical evaluations of older adults with suspected AD, as well as a key measure in clinical trials of AD.

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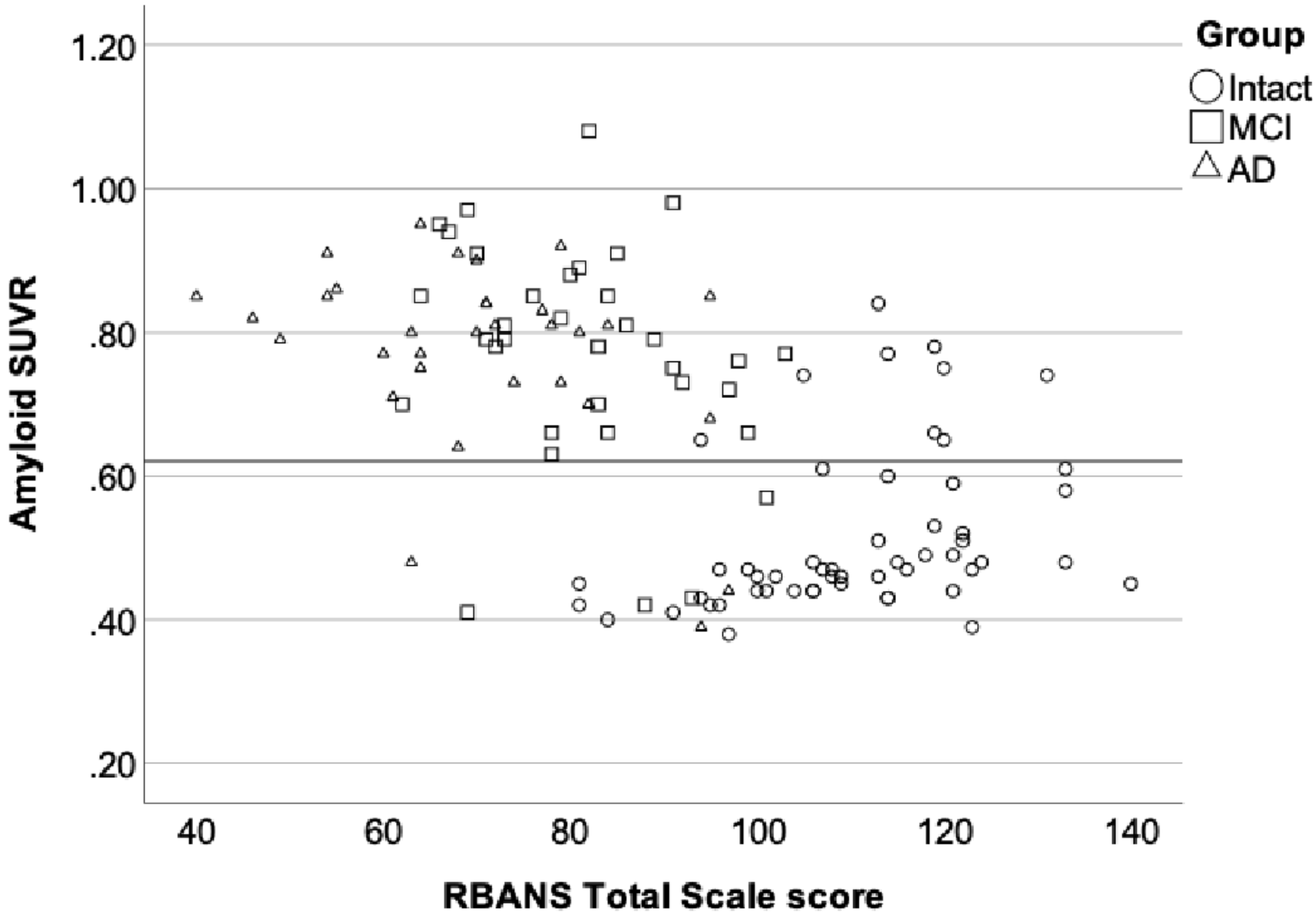

Figure 1.

Scatterplot of amyloid SUVR and RBANS Total Scale score.

Note. AD = Alzheimer's disease. MCI = Mild Cognitive Impairment. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. SUVR = standardized uptake value ratio. The horizontal line (just above .60) reflects the boundary between amyloid positivity (above the line) and negativity (below the line).

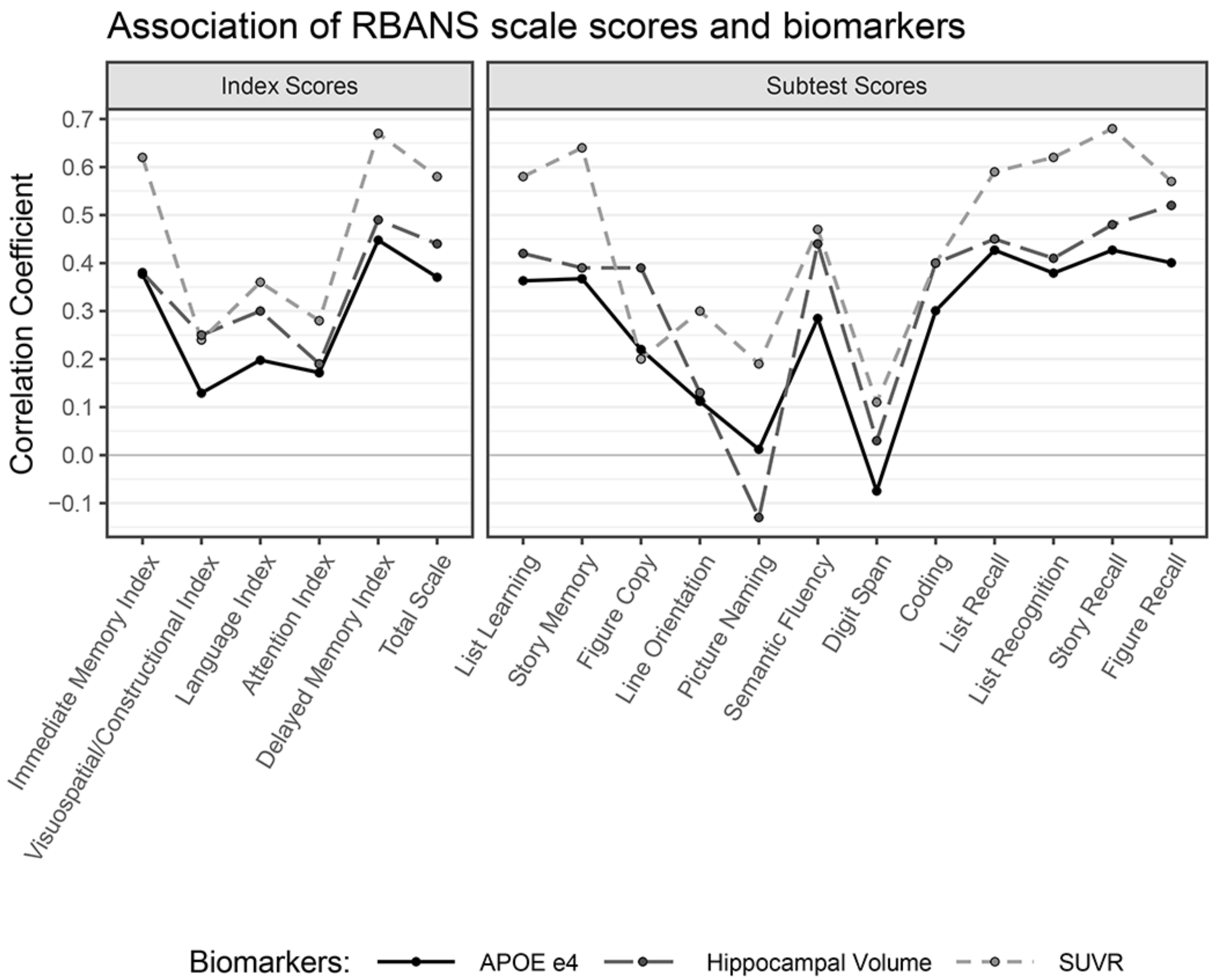

Figure 2.
Association of RBANS scores and biomarkers.

Table 1.

Sample Information

Variable	Cognitively Intact	MCI	Mild AD	Group Differences	Total Sample
N	54	35	32		121
Age (years)	72.5 (4.8)	73.4 (5.1)	77.8 (6.2)	10.4, p<0.001 c>a,b	74.2 (5.7)
Education (years)	16.7 (2.1)	15.1 (2.6)	16.2 (2.3)	5.3, p=0.006 a,c>b	16.1 (2.4)
WRAT-4 (*SS*)	110.5 (7.3)	107.2 (10.2)	110.9 (8.2)	n.s.	109.7 (8.5)
GDS (raw)	0.9 (1.1)	1.5 (1.4)	1.2 (1.2)	n.s.	1.2 (1.2)
Sex (% female)	61.1%	57.1%	56.3%	n.s.	58.7%
Race (% Caucasian)	100.0%	94.3%	100.0%	n.s.	98.3%
RBANS					
Immediate Memory Index	107.4 (13.2)	77.7 (14.8)	67.8 (14.0)	96.3, p<0.001 a>b>c	88.4 (22.3)
List Learning	28.5 (4.8)	20.1 (5.4)	16.7 (3.3)	72.1, p<0.001 a>b>c	23.1 (6.9)
Story Memory	18.7 (3.2)	11.9 (3.8)	8.3 (3.8)	95.4, p<0.001 a>b>c	14.0 (5.6)
Visuospatial/Constructional Index	106.8 (13.6)	95.0 (16.0)	91.5 (19.9)	10.9, p<0.001 a>b,c	99.3 (17.4)
Figure Copy	18.3 (1.7)	17.3 (1.8)	16.0 (2.7)	13.0, p=0.001 a>b>c	17.4 (2.2)
Line Orientation	17.6 (2.3)	15.7 (3.2)	15.9 (3.2)	7.0, p=0.001 a>b,c	16.4 (3.5)
Language Index	104.1 (11.5)	91.3 (11.1)	84.2 (12.8)	31.6, p<0.001 a>b>c	95.2 (14.4)
Picture Naming	9.7 (0.5)	9.6 (0.7)	9.4 (0.9)	n.s	9.6 (0.7)
Semantic Fluency	21.7 (5.4)	15.9 (4.6)	11.3 (3.7)	50.2, p<0.001 a>b>c	17.3 (6.4)
Attention Index	108.3 (13.4)	96.3 (14.6)	89.9 (16.3)	17.7, p<0.001 a>b,c	100.0 (16.4)
Digit Span	10.7 (2.1)	9.9 (2.4)	9.0 (2.3)	6.0, p=003 a>c	10.0 (2.3)
Coding	46.8 (8.4)	39.5 (8.9)	30.5 (11.5)	30.1, p<0.001 a>b>c	40.4 (11.5)

Variable	Cognitively Intact	MCI	Mild AD	Group Differences	Total Sample
Delayed Memory Index	110.4 (12.0)	67.5 (18.6)	52.2 (11.4)	200.4, p<0.001 a>b>c	82.6 (29.3)
List Recall	6.1 (2.9)	1.4 (2.0)	0.6 (1.8)	67.2, p<0.001 a>b,c	3.3 (3.5)
List Recognition	19.6 (0.7)	16.9 (2.2)	14.4 (2.4)	88.1, p<0.001 a>b>c	17.5 (2.8)
Story Recall	10.3 (1.6)	3.4 (3.0)	1.5 (1.3)	222.3, p<0.001 a>b>c	6.0 (4.5)
Figure Recall	14.5 (3.4)	5.2 (5.8)	1.6 (2.3)	117.9, p<0.001 a>b>c	8.4 (6.9)
Total Scale	110.6 (13.3)	81.6 (11.1)	70.1 (14.3)	112.0, p<0.001 a>b>c	91.5 (22.0)
Biomarkers					
APOE ε4 (% with one or more alleles)	29.6%	65.7%	75%	$X^2(2)=20.2$, p<0.001, a<b,c	52.1%
SUVR	0.51 (0.11)	0.77 (0.15)	0.77 (0.13)	57.9, p<0.001 a<b,c	0.66 (0.18)
Hippocampal Volume (cm^3)	4.25 (0.76)	3.60 (0.50)	3.20 (0.90)	19.8, p<0.001 a>b>c	3.81 (0.84)

Note: MCI = Mild Cognitive Impairment, AD = Alzheimer's disease, WRAT-4 = Wide Range Achievement Test – 4 Word Reading subtest, GDS= Geriatric Depression Scale 15-item version, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SUVR = ^{18}F-Flutemetamol PET scan global composite standardized uptake value ratio, APOE ε4 = Apolipoprotein E ε4 allele. For Group Differences, F-values with 2,188 degrees of freedom reported unless otherwise specified, and post-hoc comparisons were a=intact, b=MCI, and c=AD. All values are Mean (Standard Deviation) unless listed otherwise. RBANS Indexes and WRAT-4 are standard scores (M=100, SD=15). RBANS subtests (indented under their respective Indexes) and GDS are raw scores.

Table 2.

Associations of RBANS scores and biomarkers.

RBANS Variable	SUVR	Hippocampal volume	APOE ε4
Immediate Memory Index	−0.62 *	0.38 *	−0.38 *
List Learning	−0.58 *	0.42 *	−0.36 *
Story Memory	−0.64 *	0.39 *	−0.37 *
Visuospatial/Constructional Index	−0.24 *	0.25 *	−0.13
Figure Copy	−0.20 *	0.39 *	−0.22
Line Orientation	−0.30 *	0.13	−0.11
Language Index	−0.36 *	0.30 *	−0.20
Picture Naming	−0.19 *	−0.13	−0.01
Semantic Fluency	−0.47 *	0.44 *	−0.29 *
Attention Index	−0.28 *	0.19	−0.17
Digit Span	−0.11	0.03	0.07
Coding	−0.40 *	0.40 *	−0.30 *
Delayed Memory Index	−0.67 *	0.49 *	−0.45 *
List Recall	−0.59 *	0.45 *	−0.43 *
List Recognition	−0.62 *	0.41 *	−0.37 *
Story Recall	−0.68 *	0.48 *	−0.43 *
Figure Recall	−0.57 *	0.52 *	−0.40 *
Total Scale	−0.58 *	0.44 *	−0.37 *

Note. For SUVR and Hippocampal volume, Pearson correlations are reported. For APOE ε4, biserial correlations are reported.

* = statistically significant after false discovery rate.