The recency ratio is related to CSF Amyloid Beta 1-42 levels in MCI

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Recency ratio and ABeta42

Abstract

As anti-amyloid therapeutic interventions shift from enrolling patients with Alzheimer's disease (AD) dementia to individuals with pre-clinical disease, the need for sensitive measures that allow for non-invasive, fast, disseminable and cost-effective identification of preclinical status increases in importance. The recency ratio (Rr) is a memory measure that relies on analysis of serial position performance, which has been found to predict cognitive decline and conversion to early MCI. The aim of this study was to test Rr's sensitivity to cerebrospinal fluid (CSF) levels of the core AD biomarkers in individuals with MCI and controls. Baseline data from 126 (110 controls and 16 MCI) participants from the Wisconsin Alzheimer's Disease Research Center were analysed. Partial correlations were carried out between CSF Aβ42, T-tau and P-tau, and memory measures (Rr, delayed recall and total recall) derived from the Rey's Auditory Verbal Learning Test. Results indicated that Rr was the most sensitive memory score to Aβ42 levels in MCI, while no memory score correlated significantly with any biomarker in controls. This study confirms the value of Rr as a screening tool for AD risk.

Commented [HZ1]: I am a little bit confused by this sentence. In the MCI stage, people already have or do not have AD depending on their Abeta status. The way I understand the data is that Rr may be a sensitive test for Abeta-related memory dysfunction in MCI. But I may have misunderstood… ☺

Keywords: A/T/N biomarkers; Amyloid Beta; Alzheimer's disease; Recency ratio.

Word count: 1895

Introduction

The recency ratio (Rr) [1-3] is a novel measure of memory performance that aims to identify individuals at risk of Alzheimer's disease (AD) and neurodegeneration. Sensitivity of Rr is based on the observations that when individuals with AD are asked to learn and recall information, a) immediate recall of the most recently presented information (i.e., recency words – last few learned) tends to be higher relative to earlier presented information, and to controls, whereas b) the delayed recall of recency words is usually very poor [4]. Therefore, we postulated that the ratio between immediate and delayed recency would be higher in individuals at risk of AD than controls. Consistent with this assertion, we have shown that higher (i.e., worse) Rr scores predict subsequent cognitive decline [1], and are linked with greater risk of preclinical (early) mild cognitive impairment (MCI) [3]. Moreover, initial, unpublished evidence suggests Rr scores are substantially higher in AD than in other types of dementia, such as dementia with Lewy bodies [5]. However, we have yet to examine the relationship between Rr and AD biomarkers.

In the current study, we set out to test the hypothesis that Rr is sensitive to conventional biomarkers of AD by assessing the relationship between Rr and CSF levels of Amyloid Beta 1-42 (Aβ42), total tau (T-tau), and phosphorylated tau (P-tau). These biomarkers provide the basis for the objective, biomarker-based (A/T/N; 6) classification of AD cases. Disturbances in Aβ42 dynamics emerge early in the pathophysiology of AD and decades before the appearance of cognitive decline [7]. Aβ42 plays a central role in the formation of senile plaques resulting from the peptide's misfolding to form oligomers and fibrils. In contrast, alterations in T-tau and P-tau have been reported to be more proximal to clinical symptoms, and generally thought to reflect later neuropathology associated with AD [8], including increases in neurofibrillary tangles formation, and synaptic and neuronal degeneration. Unlike with tau, CSF Aβ42 levels are reduced when the amyloid burden is higher in the brain [9], probably due to reduced clearance. Therefore, we would expect a cognitive marker sensitive to early AD pathology would be associated with lower CSF Aβ42 levels, indicating increased amyloid load in the brain. In contrast, a cognitive marker sensitive to progressed disease burden would measure neuronal dysfunction and tau dysmetabolism that may relate to

neurodegeneration and tangle formation~~tau pathology and neurodegeneration~~, *i.e.*, CSF T-tau and P-tau levels.

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To test whether Rr was sensitive to AD biomarkers, we carried out secondary cross-sectional analyses on data obtained from the University of Wisconsin – Madison's Wisconsin Alzheimer's Disease Research Center (ADRC). As individuals with MCI and cognitively healthy controls are distinct clinical entities, we conducted separate analyses within each group. Individuals with MCI are at greater risk of AD than controls, but conversion to dementia is not inevitable. Discerning those likely to convert from those whose impairment is stable would allow for targeted and cost-effective interventions. Presently, methods to assess likelihood of conversion are invasive and resource intense, e.g., CSF collection from lumbar puncture or PET imaging of amyloid and tau. It is critical, therefore, to develop measures that allow a non-invasive, disseminable, and cost-effective identification of who is most likely to progress to ~~convert to~~the dementia stage of AD, especially in at-risk cohorts.

Methods

Participants. Participants were recruited from Wisconsin ADRC. All participants provided informed consent for participation and use of their data for research. The study was approved by the University of Wisconsin – Madison IRB, and by Liverpool John Moores University Ethics panel. Data were analysed cross-sectionally (baseline) from 126 participants fulfilling the following criteria: a) diagnosis of MCI or classification as cognitively normal; b) complete Rey Auditory Verbal Learning Test data; and c) available CSF Aβ42, T-tau and P-tau levels collected within 12 months of cognitive data. The cognitive status (MCI, cognitively healthy) was determined via a consensus conference, during which cognitive data, Clinical Dementia Rating collateral reports, and medical history were reviewed by a team of neuropsychologists, neurologists, geriatricians and the nurse practitioners. MCI here refers to participant characteristics consistent with National Institute on Aging-Alzheimer's Association (NIA-AA) criteria of early cognitive deficits on path to AD, without reaching the threshold for a full diagnosis of dementia [10]. Overall, 110 individuals were controls, and 16 participants had MCI.

Aβ42 and Tau. Aβ and Tau levels were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) methods (INNOTEST assays, Fuji~~i~~rebio, Ghent, Belgium). CSF Aβ42

levels were measured using the MSD Multiplex Soluble APP assay (Meso Scale Discovery, Rockville, MD), as described by the manufacturer by board-certified laboratory technicians blinded to clinical information.

Procedure. Lumbar punctures for CSF collection were performed by trained clinicians using Sprotte 25-gauge spinal needles, inserted between L4 and L5, after administration of 1% lidocaine s.c.. Polypropylene tubes were used for both collection and storage. Approximately 22ml of CSF were collected, immediately processed, divided into 0.5 ml aliquots and stored at -80°C for future assays. Samples were then shipped to the University of Gothenburg, Sweden, for determination. Average time between CSF collection and neuropsychological assessment was 0.19 years (SD=0.18) for controls, and 0.20 years (SD=0.13) for individuals with MCI.

The Rey's Auditory Verbal Learning Test (AVLT) was used to assess learning and memory performance. In the AVLT, a list of 15 semantically unrelated words is presented verbally to the participants once, after which they are asked to free recall as many words as possible. Subsequently, this presentation-test routine (learning trials) is repeated four more times. A total recall score is determined by adding the number of recalled items for the five learning trials. After presentation of a distractor list and a delay of approximately 20 minutes, participants are asked to freely recall items from the original word list. A delayed recall score is then derived from this test. The verbatim recall was recorded for all learning and delayed recall trials.

Recency ratio. Recency was defined as the last four items presented in the AVLT word list. Rr was calculated by dividing the recency scores in the first recall test (trial 1 of the AVLT), by the corresponding scores in the very last recall test (delayed trial). An Rr score was calculated for each participant. As customary [3], a correction was applied ((immediate recency score + 1) / (delayed recency score + 1)) to avoid missing data due to zero scores.

Design and Analysis. Partial Bivariate Pearson's correlations, controlling for age and gender, were carried out separately for the controls and individuals with MCI. Correlated variables were (natural log) transformed Rr, the AVLT total recall score, the AVLT delayed recall score, Aβ42, and (natural log) transformed T- and P-tau, all of which distributed normally. Bootstrapping (1000 samples) was also performed, and Steiger's Z tests were used to compare coefficients.

Results

Table reports demographics data for the study participants. Participants with MCI were generally older and performed more poorly at memory tests. CSF Aβ42 levels were lower in individuals with MCI, suggesting increased brain amyloid load, and were on average below the critical threshold of 550 pg/mL (for ELISA methods) that is considered pathological. However, although T-tau was higher in individuals with MCI, P-tau was not, despite high correlations between T- and P-tau in both participants groups ($R \geq 0.890$).

As anticipated, Rr was negatively correlated with CSF Aβ42 in individuals with MCI, R=-0.687, p=0.007, and bootstrapped 95% confidence intervals were both negative, ranging from -0.039 to -0.908. This result suggests that higher Rr scores were associated with increased brain amyloid load. In contrast, total (R=0.442, p=0.113, -0.166 to 0.828) and delayed recall (R=0.555, p=0.039, -0.071 to 0.869) were correlated more weakly with CSF Aβ42 levels in MCI, and yielded only bootstrapped coefficients of the same sign when evaluating the correlation with CSF Aβ42 levels. Of note, a Steiger's Z test to compare the correlation coefficients between Rr and delayed recall indicated that Rr is a stronger predictor than delayed recall of the AVLT word list (Z=|2.913|, p=0.002). None of the memory scores appeared to be sensitive to T- or P-tau levels. Coefficients with T-tau were 0.275 for Rr (p=0.341, -0.336 to 0.688), -0.310 for delayed recall (p=0.281, -0.761 to 0.333), and -0.236 for total recall (p=0.416, -0.669 to 0.392). Coefficients with P-tau were 0.242 for Rr (p=0.404, -0.332 to 0.659), -0.404 for delayed recall (p=0.152, -0.760 to 0.219), and -0.410 for total recall (p=0.146, -0.732 to 0.227).

In cognitively normal subjects, correlation coefficients were much lower than in the MCI group, and none were significant. With Aβ42, coefficients were -0.010 for Rr (p=0.917, -0.204 to 0.184), 0.047 for delayed recall (p=0.631, -0.166 to 0.235), and 0.022 for total recall (p=0.820, -0.186 to 0.199). With T-tau, coefficients were 0.098 for Rr (p=0.313, -0.096 to 0.265), -0.084 for delayed recall (p=0.388, -0.250 to 0.081), and 0.004 for total recall (p=0.971, -0.174 to 0.167). Finally, with P-tau, coefficients were 0.135 for Rr (p=0.163, -0.065 to 0.329), -0.096 for delayed recall (p=0.321, -0.269 to 0.074), and 0.023 for total recall (p=0.814, -0.161 to 0.207).

Figure depicts the correlations between CSF Aβ42 (regressed over age and sex) and log-transformed Rr in MCI and controls. Notably, MCI subjects tend to cluster around higher Rr scores and lower CSF Aβ42 levels, respectively, consistent with the differences reported in Table.

Discussion

The results of the cross-sectional analysis on baseline data, collected from participants enrolled in the Wisconsin ADRC Clinical Core, show that Rr is a sensitive measure of CSF Aβ42 levels in individuals with MCI, performing significantly better than standard neuropsychological measures of memory, such as AVLT total and delayed recall. In contrast, no memory score was sensitive to CSF Aβ42 levels in controls, nor any score correlated significantly with T- or P-Tau levels in either cohort.

The basis for the association between Rr and CSF Aβ42 is not known. Increased amyloid burden in AD tends to develop first in default mode network (DMN) areas, leading to reduced connectivity within these areas, and between the DMN and the frontoparietal network [11]. In contrast, early tau pathology has been detected primarily in the medial temporal lobe [12]. Therefore, it is possible that Rr may be sensitive to the adverse effects of early brain amyloid deposition, and specifically as it affects connectivity in and around the DMN. It is also to note that increases in Amyloid β oligomers and deposition in the neocortex have been associated with widespread abnormal increases in neuronal activity, which can extend to the hippocampus [13, 14]. Hippocampal neuronal hyperactivity has been reported in MCI, and is implicated in cognitive dysfunction [15]. Therefore, future studies with appropriate neuroimaging techniques including PET indices of Amyloid burden and fMRI should be conducted to determine the role, if any, that these factors may have in the modulation of Rr.

A clear limitation of this study is the low sample size in the MCI group, which totalled at 16 individuals. Additionally, brain AD biomarkers were not examined. Nonetheless, further research is needed to confirm these findings.

Rr represents a non-invasive, cost-effective, rapid and accessible test, which can be easily calculated from common neuropsychological test batteries of recall performance, including the AVLT, as long as learning items are not semantically related. Due to its sensitivity to CSF Aβ42 leves

in MCI, as well we its usefulness to predict pre-clinical MCI (3), we recommend that it is considered as part of screening batteries for early-stage therapeutic trials in AD. Moreover, as we have argued in the past, we recommend that serial position data for recall tests are included in databases for the study of AD and neurodegeneration.

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Table 1. *Demographics. N = number of participants included in the analysis who were either cognitively normal or had a diagnosis of MCI-AD; Age in years (mean, standard deviation, and range); Gender (number of females and percentage); Aβ42, total tau (T-tau) and hyperphosphorylated tau (P-tau) (means and standard deviations in pg/mL); AVLT total recall score (mean and standard deviation); AVLT delayed recall score (mean and standard deviation); and Rr score (mean and standard deviation). The last column reports p values for t-tests or Fisher's exact test (Females).*

	Cognitively Normal	MCI	
N (%)	110 (87%)	16 (13%)	Significance
Age at baseline	62.5 (9.2; 45-85)	72.7 (7.1; 60-83)	p<0.001
Females	79 (72%)	4 (25%)	p<0.001
CSF Aβ42	724.9 (198.2)	488.5 (171.6)	p<0.001
CSF T-tau	326.9 (178.4)	471.4 (263.6)	p=0.007[a]
CSF P-tau	43.6 (16.8)	51.9 (28.1)	p=0.186[a]
AVLT total recall	48.5 (8.8)	32.8 (5.5)	p<0.001
AVLT del. recall	2.2 (1.2)	0.6 (0.6)	p<0.001
Rr	1.2 (0.7)	2.3 (0.9)	p<0.001[a]

a: The analyses were carried out using natural log-transformed scores

Recency ratio and ABeta42

Figure. Plot of CSF Aβ42 unstandardized residuals (age and sex; X-axis) by log-transformed Rr (Y-axis). Black represents individuals with MCI, and grey represents healthy controls.

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