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The relationship between cerebrospinal fluid tau markers, hippocampal volume, and delayed primacy performance in cognitively intact elderly individuals

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Abstract

Background: Primacy performance in recall has been shown to predict cognitive decline in cognitively intact elderly and conversion from mild cognitive impairment to Alzheimer's disease (AD). Delayed primacy performance, but not delayed nonprimacy performance, has been shown to be associated with hippocampal volume in cognitively intact older individuals. Because presence of neurofibrillary tangles is an early sign of AD-related pathology, we set out to test whether cerebrospinal fluid (CSF) levels of tau had an effect on delayed primacy performance, while controlling for hippocampal volume and CSF amyloid-β 1-42 levels.

Methods: Forty-seven individuals, aged 60 years or older and cognitively intact, underwent a multisession study including lumbar puncture, a magnetic resonance imaging (MRI) scan of the head, and memory testing.

Results: Our regression analyses show that CSF levels of hyperphosphorylated (P) tau are only associated with reduced delayed primacy performance when hippocampal volumes are smaller.

Conclusion: Our findings suggest that hippocampal size may play a protective role against the negative effects of P tau on memory.

Keywords: Serial position; Primacy; Memory; Amyloid β 1-42; Tau; Hippocampus; Alzheimer's disease; CSF biomarkers

1. Background

The identification of individuals at risk of Alzheimer's disease (AD) during preclinical stages is critical for the implementation of early intervention strategies [1]. Recently, episodic memory performance for primacy items (i.e., first few items on a study list) has been shown to provide predictive value for cognitive decline in both cognitively intact elderly [2] and conversion from mild cognitive impairment (MCI) to AD [3]. Primacy performance, especially in delayed memory tasks (e.g., after 20 minutes), is thought to reflect consolidation ability [4], a critical target function for prediction of subsequent neurodegeneration [5]. Importantly, consolidation is thought to rely on the hippocampal formation [6], whose integrity has also been examined in studies of AD prediction (e.g., [7–9]). Finally, we have

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shown that hippocampal gray matter volume predicts delayed primacy performance, but not memory performance for other regions of the study list, in cognitively intact older individuals, thus confirming the link between hippocampus and memory for early list items [10].

A key component of AD neuropathology is the presence of neurofibrillary tangles, which are typically observed in the medial temporal lobe (MTL) first, and in the hippocampus in particular [11]. The degree of neurofibrillary tangle burden has been associated with levels of total (T) and hyperphosphorylated (P) tau in clinical-postmortem comparison studies ([12–14] but see [15]), suggesting that in vivo cerebrospinal fluid (CSF) levels of T and P tau may serve as surrogate measures for the degree of hippocampal and cortical neurofibrillary pathology. CSF levels of T and P tau have been found to associate with short-term memory performance in AD [16] and to correlate negatively with hippocampal volume both in individuals with AD [17] and MCI [18]. Moreover, P tau is considered a key factor in entorhinal cortex degeneration in cognitively intact participants [19].

For the reasons mentioned previously, we set out to test whether delayed primacy performance—defined as the first four words on the study list to maintain consistency with [2]—in cognitively intact individuals is associated with CSF levels of T and P tau. In particular, we expect that higher levels of P tau, which may reflect tangle pathology [20] affecting the hippocampus and cortical brain areas, will be associated with poorer primacy performance. Moreover, we explore whether the relationship between hippocampal size and delayed primacy performance [10] is moderated by CSF tau levels, while controlling also for CSF levels of amyloid-β (Aβ) 1-42, which provide an index of amyloid pathology (e.g., [14]).

2. Methods

2.1. Subjects

Participants for the study were recruited from either the Memory Education and Research Initiative (MERI) program at the Nathan Kline Institute for Psychiatric Research (NKI) or via advertisements; recruitment was originally for a study on major depression disorder (MDD) in old age (see [21]). The study was approved by the institutional review boards of the NKI and the New York University (NYU) School of Medicine. All participants were paid up to $450.00 for their participation in the study and provided formal consent before testing. A total of 133 participants were recruited for the study, although only 51 received a lumbar puncture from which CSF could be extracted. To maintain a cognitively intact sample, we excluded participants whose Mini-Mental State Examination (MMSE) score was below 28 and/or presented magnetic resonance imaging (MRI) evidence of confluent deep or periventricular white matter hyperintensities. These exclusion criteria left us with a total of 47 participants, 28 of whom received a diagnosis of MDD from a board-certified psychiatrist (N.P.) and 19 were controls.

2.2. CSF measurements

$A\beta_{1\text{-}42}$ CSF levels were analyzed with electrochemiluminescence technology using the MS6000 Human Ab Ultra-Sensitive Kit (Meso Scale Discovery, Gaithersburg, MD, USA). Both T and P tau concentrations were determined using a sandwich ELISA (Innotest hTAU-Ag, Innogenetics, Ghent, Belgium) specifically constructed for all tau isoforms, irrespective of phosphorylation status.

2.3. MRI acquisition

The acquisition was performed on a 1.5-T Siemens Vision system (Erlangen, Germany) at the NKI. Images were acquired using a sagittal magnetization prepared rapid gradient-echo sequence (repetition time [TR]/echo time [TE] = 11.4/11.9 ms, 1 excitation [NEX], matrix = 256 × 256, field of view [FOV] = 307 mm, 1.2 mm^3 isotropic voxel, 172 slices, no gap). Evaluation of white matter hyperintensities was performed using a fluid-attenuated inversion recovery sequence (TR/TE = 9000/119 ms, inversion time = 2400 ms, NEX = 1, matrix 256 × 256, FOV = 240 mm, slice thickness = 4 mm, 1 mm gap).

2.4. MRI preprocessing and analysis

MRI data processing followed procedures described previously [22,23]. Fig. 1 illustrates the hippocampal regions of interest. The total intracranial volume (TIV) was used in the statistical model to account for differences in head size (see *Study design and analysis* below) and was calculated as the sum of the total segmented gray matter, white matter, and CSF volumes in native space.

2.5. Procedure

The study was conducted at the NKI and at the Clinical and Translational Science Institute, NYU, over multiple visits. On the first visit, after informed consent was provided, volunteers were administered a general medical intake questionnaire and had their vital signs measured; the MMSE score and the Hamilton Depression Rating (HAM-D) score, which measures severity of current depressive symptoms, were obtained during this visit. On a second visit, participants received an MRI scan of the head. Neuropsychological testing took place on a third visit, and memory performance was assessed at this stage with the Buschke Selective Reminding Test (BSRT) [24]. This test comprises a list of 16 unrelated nouns, presented orally to the participant at a rate of 2 seconds each. After presentation, participants were asked to freely recall as many items as possible, stopping once they feel no more items can be retrieved. In the delayed trial, which is the focus of our current examination (cf., 2), the free recall task occurs roughly after a 20-minute delay from the initial presentation.

During a fourth and final session, a lumbar puncture was performed under guided fluoroscopy. Participants were