Neuropsychologia 69 (2015) 1–8

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

A study on the specificity of the association between hippocampal volume and delayed primacy performance in cognitively intact elderly individuals

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ARTICLE INFO

Article history:
Received 3 September 2014
Received in revised form
15 January 2015
Accepted 17 January 2015
Available online 19 January 2015

Keywords:
Serial position
Primacy
Hippocampus
Structural MRI

ABSTRACT

Delayed recall at the primacy position (first few items on a list) has been shown to predict cognitive decline in cognitively intact elderly participants, with poorer delayed primacy performance associated with more pronounced generalized cognitive decline during follow-up. We have previously suggested that this association is due to delayed primacy performance indexing memory consolidation, which in turn is thought to depend upon hippocampal function. Here, we test the hypothesis that hippocampal size is associated with delayed primacy performance in cognitively intact elderly individuals.

Data were analyzed from a group ($N=81$) of cognitively intact participants, aged 60 or above. Serial position performance was measured with the Buschke selective reminding test (BSRT). Hippocampal size was automatically measured via MRI, and unbiased voxel-based analyses were also conducted to explore further regional specificity of memory performance. We conducted regression analyses of hippocampus volumes on serial position performance; other predictors included age, family history of Alzheimer's disease (AD), *APOE* ε4 status, education, and total intracranial volume.

Our results collectively suggest that there is a preferential association between hippocampal volume and delayed primacy performance. These findings are consistent with the hypothesis that delayed primacy consolidation is associated with hippocampal size, and shed light on the relationship between delayed primacy performance and generalized cognitive decline in cognitively intact individuals, suggesting that delayed primacy consolidation may serve as a sensitive marker of hippocampal health in these individuals.

1. Introduction

A decline in episodic memory performance is an early key symptom in Alzheimer's disease (AD) and is considered critical for the prediction of the disease (e.g., McKhann et al., 2011; Sperling et al., 2011), especially when memory is tested after a delay (Gomar et al., 2011). Recently, Bruno et al. (2013) have shown that a detailed analysis of serial position performance in delayed recall tests is more sensitive to the prediction of subsequent cognitive decline in healthy elderly subjects compared to total delayed recall performance. Serial position refers to the pattern in free recall whereby early-list items (primacy) and late-list items (recency) are remembered better than items learned in the middle (Murdock, 1962; Glanzer, 1972). Bruno et al. (2013), using a verbal memory task, tested a group of cognitively intact individuals over a span of up to seven years and showed that delayed recall at the primacy position was a better predictor of generalized cognitive decline than total memory performance, or performance anywhere else on the list (e.g., recency). Poorer delayed primacy recall was associated with greater subsequent decline.

Bruno et al. (2013) argued that the predictive advantage of delayed primacy performance over the other memory indices,

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http://dx.doi.org/10.1016/j.neuropsychologia.2015.01.025
0028-3932/

including immediate primacy performance, was due to its reliance upon memory consolidation (McGaugh, 2000). Primacy effects are typically explained as a consequence of increased opportunities for rehearsal of early list items as compared to items learned later (Rundus, 1971; Tan and Ward, 2000). More rehearsal is expected to lead to better encoding of the information and, consequently, stronger memories, although alternative interpretations have also been put forward (e.g., Brown et al., 2007). If the value of primacy performance in predicting cognitive decline were due to its ability to index effective use of rehearsal strategies, then little predictive difference would be expected between immediate and delayed primacy. However, since Bruno et al. (2013) isolated *delayed* primacy performance as the best predictor of subsequent generalized cognitive ability, it is arguable that a process of consolidation, requiring time and structural changes to stabilize memory traces and render them more resistant to interference, is required.

Consolidation is thought to depend upon hippocampal function (Wixted, 2004; Wixted and Cai, 2013) and Bruno et al. (2013) have suggested that the assessment of delayed primacy performance could work as a proxy measure for hippocampal integrity. Associations between the hippocampus and primacy have been reported in the literature, albeit with mixed methods and results. Hermann et al. (1996) conducted a study to examine serial position performance in participants who underwent anterior temporal lobectomy, including resection of the hippocampus. Hermann et al. (1996) measured memory over five learning trials with the California Verbal Learning Test (CVLT), and observed a drop in primacy performance (first four words), which they interpreted as a loss of consolidation ability, only in those participants who underwent resection of the left hippocampus when this was not sclerotic prior to the surgery. In other words, only the removal of a relatively healthy left hippocampus caused a drop in primacy recall performance in the participants. In contrast, Albuquerque et al. (2008), also using the CVLT, reported that only participants with focal frontal lesions, but not participants with mesotemporal lesions, showed reduced primacy performance.

In a study using functional magnetic resonance imaging (fMRI), Strange et al. (2002) tested 14 healthy participants, aged 19–32. Participants were asked to learn a set of 12 words and then free recall the words; this procedure was repeated over 30 consecutive trials. Strange et al. (2002) found that retrieval of early list items (first two items were classed as primacy) was associated with activation of the right anterior hippocampus, the posterior fusiform, and parahippocampal areas (bilaterally), but that these areas were not engaged with retrieval of later words. In contrast, Talmi et al. (2005), who also tested young adults ($n=10$) with fMRI, found that primacy items were associated with left hippocampal activation in a series of recognition memory tasks.

Despite some inconsistencies, there is evidence that hippocampal integrity is associated with successful retrieval of primacy items. Therefore, following Bruno et al. (2013), we hypothesize that hippocampal size should predict the likelihood of successful retrieval of primacy words in a delayed memory task in a group of cognitively intact elderly volunteers. Moreover, considering the prominence of delayed performance, we hypothesize that hippocampal volume should be a better predictor of primacy performance after a delay as compared to primacy performance immediately after study (consolidation hypothesis). Finally, we also hypothesize (primacy specificity hypothesis) that there should be a special relationship between the hippocampus and delayed primacy performance, but not between the former and delayed recall performance for items learned afterwards (non-primacy).

To test our hypotheses, we examined the relationship between hippocampal gray matter volume and delayed primacy performance in two groups of participants who were cognitively intact and at least 60 years of age. The first group comprised 54 individuals, originally enrolled as controls for a study on Major Depressive Disorder (MDD), whereas the second group consisted of 28 volunteers recruited for a study on the effects of benzodiazepines on cognition (all tested prior to drug/placebo administration). These two groups were merged for the purpose of the present study. To estimate the specificity of the relationship between delayed primacy performance and hippocampal size, we employed a number of relevant control variables in our analyses, and also explored separately the potential impact on memory of potential indicators of AD-related pathology (see Section 2), such as *APOE* ε4 status (e.g., Corder et al., 1993).

Memory performance was measured with the Buschke Selective Reminding Test (BSRT; Buschke and Fuld, 1974). The BSRT (see Section 2.4), despite some minor differences, is analogous to the test used in Bruno et al. (2013; i.e., Rey Auditory Verbal Learning Test). Primacy was defined as the first four words on the study list, and the delayed task occurred roughly 15–20 min after the end of the learning trials. The study prediction was that larger hippocampal volumes would be associated with more primacy words retrieved in the delayed task.

2. Methods

2.1. Subjects

Participants in the first group were recruited via advertisements in local newspapers and flyers, or from the Memory Education and Research Initiative (MERI) program at the Nathan Kline Institute for Psychiatric Research; participants' recruitment was part of a study on late-life MDD (Bruno et al., 2012a, 2012b; Pillai et al., 2012; Pomara et al., 2012). All participants provided formal consent prior to testing and received compensation for up to $450.00 for their time and efforts. A total of 133 participants were recruited for the study. In order to maintain a cognitively intact sample without major indication of cerebrovascular disease, we excluded participants who presented MRI evidence of confluent deep or periventricular white matter hyperintensities, defined as one or more hyperintense lesions measuring at least 10 mm in any direction on the FLAIR scan (see Section 2.2), or had a Mini-Mental State Examination (MMSE) score below 28. Excluding participants with MDD left us with a total of 54.

For the second group, a total of 76 participants were recruited originally through advertisement. All participants formally and in writing consented prior to testing and were paid $200 for their time and efforts. Participants' recruitment was for a study on the combined effects of Lorazepam and APOE variants on cognition (Pomara et al., 2005, 2006), but all data analyzed here was taken from baseline performance on week 1 (i.e., prior to drug/placebo administration). Participants did not show any cognitive impairment, and were free of significant neurological or medical illnesses, as determined by laboratory tests and medical examination; they were not currently using any psychotropic medication, as determined by a urine toxicology exam; and did not meet the DSM-IV criteria for a psychiatric disorder after evaluation. Participants also had an MMSE score of 28 or higher and a Clinical Dementia Rating of 0. A total of 28 participants received an MRI scan of the head and are included in the present analysis. Table 1 reports the population demographics split by cohort. Both studies received ethical approval by the institutional review boards of the Nathan Kline Institute for Psychiatric Research and the New York University School of Medicine, and were conducted at these institutions.