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Subjective memory complaints are associated with brain activation supporting successful memory encoding

Jessica M. Hayes [a], Lingfei Tang [a,b,c], Raymond P. Viviano [a,b], Sanneke van Rooden [d], Noa Ofen [a,b,c], Jessica S. Damoiseaux [a,b,e,*]

[a] Institute of Gerontology, Wayne State University, Detroit, MI, USA
[b] Department of Psychology, Wayne State University, Detroit, MI, USA
[c] Merrill Palmer Skillman Institute, Wayne State University, Detroit, MI, USA
[d] Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands
[e] Institute of Psychology, Leiden University, Leiden, the Netherlands

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ABSTRACT

Subjective memory complaints, the perceived decline in cognitive abilities in the absence of clinical deficits, may precede Alzheimer's disease. Individuals with subjective memory complaints show differential brain activation during memory encoding; however, whether such differences contribute to successful memory formation remains unclear. Here, we investigated how subsequent memory effects, activation which is greater for hits than misses during an encoding task, differed between healthy older adults aged 50 to 85 years with ($n = 23$) and without ($n = 41$) memory complaints. Older adults with memory complaints, compared to those without, showed lower subsequent memory effects in the occipital lobe, superior parietal lobe, and posterior cingulate cortex. In addition, older adults with more memory complaints showed a more negative subsequent memory effects in areas of the default mode network, including the posterior cingulate cortex, precuneus, and ventromedial prefrontal cortex. Our findings suggest that for successful memory formation, older adults with subjective memory complaints rely on distinct neural mechanisms which may reflect an overall decreased task-directed attention.

1. Introduction

Alzheimer's disease (AD) pathology starts to form in the brain years before the onset of clinical symptoms (Villemagne et al., 2013). In order for preventative or therapeutic interventions to be administered early in the disease course, when they are more likely to be effective, it is essential to identify individuals who are likely to develop AD early on (DeKosky, 2003). Subjective memory complaints (also known as subjective memory impairment or subjective cognitive impairment) refer to the perceived decline in cognitive abilities in the absence of deficits on clinical assessments (Jessen et al., 2014a). It has been proposed that subjective memory complaints may precede amnestic mild cognitive impairments (MCIs), which in turn often progress to AD (Reisberg et al., 2008). Longitudinal studies of individuals with subjective memory complaints support this position, as they show greater risk for future cognitive decline (Dik et al., 2001; Glodzik-Sobanska et al., 2007; Reisberg et al., 2010), cognitive impairment, and dementia (Jessen et al., 2014b; Kaup et al., 2015; Mitchell et al., 2014). The risk for individuals with subjective memory complaints to convert to MCI or AD is 4.5–6.5 times greater than it is for individuals without subjective memory complaints (Jessen et al., 2010; Reisberg et al., 2010). Autopsy studies have shown that otherwise healthy older adults with subjective memory complaints show early signs of AD pathology, as indicated by the presence of higher levels of amyloid-β deposits and tau tangles in these individuals compared to healthy older adults without subjective memory complaints (Barnes et al., 2006). Neuroimaging studies have identified other AD-associated changes, such as whole-brain gray matter (Hafkemeijer et al., 2013) and hippocampal volume loss (Stewart et al., 2011; Striepens et al., 2010; van der Flier et al., 2004) that also occur in those with subjective memory complaints before cognitive deficits are apparent.

Behaviorally, deficits in episodic memory, or memory for personal events and situations (Tulving, 1972), are one of the first noticeable signs of cognitive decline in AD (Dubois et al., 2007; Ringman, 2005). The neural mechanism of such deficits in episodic memory can be investigated with functional magnetic resonance imaging (fMRI) techniques while participants encode

* Corresponding author at: Institute of Gerontology, Wayne State University, 87 E. Ferry Street, Detroit, MI 48202, USA. Tel.: 313 664-2642; fax: 313 664-2666.
E-mail address: damoiseaux@wayne.edu (J.S. Damoiseaux).

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novel information. Previous research has identified differences in brain activation of the cingulate cortex, precuneus, superior parietal lobule, and medial temporal lobe during encoding in patients with AD and amnestic MCI compared to controls (Hämäläinen et al., 2007; Machulda et al., 2003; Schwindt and Black, 2009). Similarly, differences in functional connectivity (Hafkemeijer et al., 2013) and task-related activations (Erk et al., 2011; Rodda et al., 2011, 2009) have been found between those with and without subjective memory complaints. For example, individuals with subjective memory complaints have shown increased activation in the prefrontal cortex during the encoding of novel words (Rodda et al., 2009). Findings such as these have led to the proposal that these differences in brain function represent a compensatory mechanism that could help explain the disparity between subjective and objective memory functioning in individuals with subjective memory complaints, given their unimpaired memory performance. However, it remains unclear whether these differences are specific for successful memory encoding or related to general cognitive processes.

To address this, we applied a subsequent memory paradigm in which participants preformed memory encoding during fMRI and a postscan recognition test. This paradigm allows for the encoded items to be back sorted and labeled as either remembered or forgotten, which provides direct comparisons between later remembered and later forgotten trials, the subsequent memory effect. This paradigm has been used to investigate the neural correlates of successful memory encoding in the aging population, especially those with cognitive impairment (Duverne et al., 2009; Gutchess et al., 2005; Kircher et al., 2007). Previous research has found that older adults compared to young adults show less activation in the medial temporal and fusiform regions, but more activation in the precuneus, posterior cingulate cortex, and prefrontal cortex (Duverne et al., 2009; Gutchess et al., 2005; Maillet and Rajah, 2014; Miller et al., 2008; Spreng et al., 2010). Among participants with MCI, Trivedi et al. (2008) identified higher medial temporal lobe activation during successful memory encoding. While differences in the subsequent memory effect have been identified with healthy aging and MCI, the subsequent memory effect has not been characterized in those with subjective memory complaints.

The purpose of the present study was to examine potential differences in the subsequent memory effect between healthy older adults with and without subjective memory complaints. Previous studies have predominately examined memory encoding rather than the subsequent memory effect and have found functional differences in the cingulate cortex, precuneus, superior parietal lobule, medial temporal lobe, or prefrontal cortex. Based on these findings, we hypothesized that we would find similar functional differences when comparing healthy older adults with and without subjective memory complaints using a subsequent memory task paradigm. In addition, we aimed to explore the association between frequency of memory complaints and the magnitude of the subsequent memory effect. This is of interest because a majority of older adults report some level of memory complaints, even those who are not actively concerned about their cognitive abilities.

2. Methods

2.1. Participants

Data were collected in 2 locations (Detroit, MI, USA, and Leiden, Netherlands) on a total of 79 healthy older adults between the ages of 50 and 85 years. Of these participants, 15 were excluded due to either incomplete data ($n = 12$), or having a Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score <25 ($n = 3$). The remaining 64 participants, mean age = 67.96, standard deviation (SD) = 8.71, with ($n = 23$) and without ($n = 41$) subjective memory complaints were included in the present analysis. Participants were recruited from memory clinics, senior centers, and communities surrounding both cities. Participants with subjective memory complaints were defined as those who had noticed a worrisome decline in their memory that was unrelated to any other ongoing health or situational factors. Only participants who felt this change was worrisome were included because previous research suggests that mainly individuals who are concerned about the presence of subjective memory complaints have an increased risk for dementia (Jessen et al., 2014b). The majority of the participants with memory complaints (21 out of 23) sought advice from a medical professional before participation and was informed that they did not have any objective cognitive impairment. Interested individuals were screened and excluded if they had a history of neurological disorders, psychiatric disorders, brain injury, or radiation or chemotherapy for cancer treatment. Current use of psychotropic medications, uncontrolled medical conditions, and presence of MRI contraindications also served as exclusion criteria. All participants provided informed consent as approved by the local ethics committees.

2.2. Neuropsychological assessments

A battery of neuropsychological tests was administered to all the participants to assess cognitive function. Participant IQ was assessed with the Wechsler Abbreviated Scale of Intelligence II (Wechsler, 2011) for participants recruited in Detroit, and by using the 4 corresponding subtests (block design, vocabulary, matrix reasoning, and similarities) of the Dutch language version of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) in the Netherlands. IQ scores were age normed. To evaluate long-term memory function, participants completed the Rey Auditory Verbal Learning Task (Rey, 1964) and the adult battery of the Wechsler Memory Scale IV (Wechsler, 2009). Cognitive functioning was further assessed through the Trail Making Test (Reitan and Wolfson, 1985) A and B, the digit symbol-coding subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997), and the Stroop test (Stroop, 1935). We also administered a semantic verbal fluency task in which participants were asked to generate as many animals as they could think of in 60 seconds and then as many occupations as they could think of in 60 seconds. None of the cognitive scores were age normed. For the Wechsler Memory Scale, proportional index scores were calculated based on the raw scores that retained age-related variance. For all cognitive tasks, independent samples t tests evaluated differences in performance between those with and without subjective memory complaints.

Participants also completed self-report questionnaires to assess personality (Big Five Inventory; John et al., 1991), handedness (Edinburgh Handedness Inventory; Oldfield, 1971), degree of memory complaints (Memory Functioning Questionnaire; Gilewski et al., 1990), and depressive symptomology (Beck Depression Inventory II; Beck et al., 1996; and Geriatric Depression Scale [GDS]; Yesavage et al., 1983). The frequency of forgetting (FOF) subscale of the Memory Functioning Questionnaire was used to quantify the amount of memory complaints reported by each participant, as it has previously been shown to be a good marker for memory self-efficacy (Hertzog et al., 1989). As responses of 7 on the Likert scale for the Memory Functioning Questionnaire indicate no complaints or worry, scores were reflected so that larger scores indicate more complaints, and the mean response to items from the FOF subscale was calculated for more intuitive interpretation.

Since depression (Montejo et al., 2011; Schmand et al., 1997) and high neuroticism (Comijs et al., 2002; Ponds and Jolles, 1996) have previously been shown to co-occur with subjective memory complaints, we tested for differences in depressive symptomology and