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

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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

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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

personality characteristics between those with and without subjective memory complaints. The GDS contains 2 questions that could capture variance related to cognitive complaints sans depression: (14) "Do you feel you have more problems with memory than most?" and (30) "Is your mind as clear as it used to be?" Thus, when we compared scores on this measure between those with and without subjective memory complaints we did so both with and without the inclusion of these questions. Moreover, we evaluated with χ^2 tests if participants with subjective memory complaints responded to these questions differently than those without complaints. Significance levels for all statistical tests were corrected for multiple comparisons using a Bonferroni correction unless otherwise specified.

2.3. MRI acquisition

Participants completed their scan session at the Wayne State University MR Research Facility in Detroit, MI, United States, on a 3-T Siemens Magnetom Verio scanner using a 32-channel Head Matrix coil or at the Leiden Institute for Brain and Cognition in the Netherlands on a 3-T Philips Achieva TX scanner.

In the United States, whole-brain structural images were acquired using a T1-weighted magnetization-prepared rapid gradient-echo sequence: 176 slices, repetition time (TR) = 1680 ms, echo time (TE) = 3.51 ms, flip angle (FA) = 9°, field of view (FOV) = 256 mm, and voxel size = 0.7 mm × 0.7 mm × 1.3 mm. In the Netherlands, whole-brain structural images were also acquired using a T1-weighted sequence: 140 slices, TR = 9.7 ms, TE = 4.60 ms, FA = 8°, FOV = 224 mm, and voxel size = 1.2 mm × 1.2 mm × 1.2 mm.

In the United States, functional images were acquired using a T2*-weighted gradient-echo sequence: 37 slices parallel to the AC-PC plane, TR = 2200 ms, TE = 30 ms, FA = 80°, FOV = 220 mm, voxel size = 2.8 mm × 2.8 mm × 2.8 mm, and volumes = 276. The functional scans of 2 participants without subjective memory complaints were cut short and only 242 or 161 volumes were acquired instead of 276. In the Netherlands, functional images were also acquired using a T2*-weighted sequence: 38 slices parallel to the AC-PC plane, TR = 2200 ms, TE = 30 ms, FA = 80°, FOV = 220 mm, and voxel size = 2.8 mm × 2.8 mm × 2.8 mm, volumes = 278. Functional sequences were designed concurrently across test sites to ensure equivalent parameters.

2.4. Subsequent memory task

Participants were presented with 80 scenes while lying in the MRI scanner after being instructed to remember the scenes. Scenes were randomly drawn from a larger stimuli set of 320 indoor and outdoor scenes used in previous studies (Chai et al., 2010, 2014; Ofen et al., 2007). Each scene was presented for 3.4 seconds, followed by a fixation cross with a variable intertrial interval ranging from 1 to 12 seconds. Task sequencing was optimized with optseq2 (Dale, 1999). To ensure that these scenes were properly attended to, the participants were asked to indicate if each image depicted an indoor or an outdoor scene with a 2-button response box held in the right hand. A postscan recognition test consisting of the 80 old scenes and 60 new scenes was administered approximately 30 minutes after encoding. There were fewer foils than targets to mitigate participant fatigue and to better match a roughly equal tendency to judge scenes as old or new given that participants typically judge many of the previously seen scenes as new (miss). Participants were asked to indicate if each scene presented was "old" or "new" and then if they were "sure" or "not sure" of this decision. Participants practiced the task prior to entering the scanner and were reminded of the instructions prior to the scanner task.

Scenes were presented onto an in-bore screen via an Avotec Silent Vision (SV-6011) projection system. The scenes were visible to participants through a mirror mounted on the head coil. The task was programmed and presented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA).

For 9 participants, the indoor/outdoor responses were not recorded due to technical difficulties. Imaging data from these participants was still used as they did respond to the task stimuli, their performance on the subsequent memory task was within the normal range, and the remaining participants showed high accuracy in making indoor/outdoor judgments (M = 0.99, SD = 0.02). Performance on the subsequent memory task was calculated by subtracting the false alarm rate from the hit rate for high-confidence responses similar to previous studies using this paradigm (Chai et al., 2010, 2014; Ofen et al., 2007). Consistent with previous subsequent memory studies, low-confidence responses were not included in the calculation of task performance as they show no reliable discriminability between remembered items and lures (Gutchess et al., 2005; Park et al., 2013; Wagner et al., 1998).

2.5. Imaging analysis

FSL 5.0.8 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) software tools were used for image processing and analysis. Non-brain voxels were removed from the structural and functional images using FSL's Brain Extraction Tool (BET; Smith, 2002). Additional preprocessing of the functional images consisted of removing the first 5 volumes, motion correction using MCFLIRT (Jenkinson et al., 2002), spatial smoothing with a Gaussian kernel of full width half maximum of 4.0 mm, and temporal filtering with a high pass filter of 100 seconds. FMRIB's Linear Image Registration Tool (FLIRT; Jenkinson and Smith, 2001; Jenkinson et al., 2002) was utilized to linearly register functional images to the high-resolution structural scans using boundary-based registration. The high-resolution image was then linearly registered to the standard 2-mm Montreal Neurological Institute template using 12 degrees of freedom.

Whole-brain analyses with a General Linear Model, as implemented in FSL FEAT (FMRI Expert Analysis Tool v6.00) was used for first-level and higher level analysis. FEAT used FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (Woolrich et al., 2001) for time series statistical analysis of the first-level data. Trials were back sorted based on subsequent recognition and identified as either a high-confidence hit, a low-confidence hit, or a miss. A 1-column event file specified the timing for each of these conditions. For the 2 participants with fewer encoding trials, only the scenes that were presented during encoding were treated as old scenes when calculating recognition performance. Null events were not modeled and therefore served as the baseline condition. Subsequent memory effects were calculated as the difference between activation for high-confidence hits compared to misses. Following the first-level analysis, 3 higher level analyses using FLAME (FMRIB's Local Analysis of Mixed Effects) modeling were carried out.

First, a higher level analysis was carried out to determine the main effect of the task across all participants while controlling for test site, age, and gender. Positive (hit > miss) and negative (miss > hit) subsequent memory effects were identified. Continuous clusters were defined using a Z statistic threshold of 2.3 and a corrected cluster threshold of $p = 0.001$ (Worsley, 2001).

A between-group comparison was conducted to determine differences in subsequent memory effects between those with and without subjective memory complaints. For this analysis, the presence of subjective memory complaints served as the explanatory variable of interest and test site, age, and gender were entered as covariates of no interest. Continuous clusters were defined using

Table 1
Participant characteristics and cognitive performance in those with and without subjective memory complaints (SMCs)

Measure	With SMC (n = 23)	Without SMC (n = 41)	*p*-values
Participant characteristics			
Age (range)	68.57 ± 8.18 (53–84)	67.49 ± 9.06 (50–85)	0.639
Sex (male/female)	6/17	16/25	0.222
	26.09% / 73.91%	39.02% / 60.98%	
Test site (US/NL)	13/10	26/15	0.390
	56.52% / 43.48%	63.41% / 36.59%	
Memory Functioning Questionnaire-Frequency of Forgetting (M)	3.58 ± 0.95	2.65 ± 0.81	**<0.001**
Wechsler Abbreviated Scale of Intelligence II-Full-Scale IQ	101.50 ± 12.80	104.62 ± 14.96	0.449
Mini-Mental State Examination	28.77 ± 1.11	28.93 ± 1.40	0.658
Median (range)	29 (26–30)	30 (25–30)	
Depression screenings			
Geriatric Depression Scale	5.82 ± 4.14	3.00 ± 3.84	**0.009**
Geriatric Depression Scale without Q14	5.27 (4.06)	2.98 (3.85)	0.031
Geriatric Depression Scale without Q14 and Q30	4.64 (4.04)	2.78 (3.81)	0.076
Beck Depression Inventory II	7.00 ± 5.50	4.37 ± 5.30	0.068
Personality measures			
Big Five Inventory-Neuroticism	20.32 ± 5.89	17.12 ± 5.38	0.033
Big Five Inventory-Conscientiousness	33.91 ± 5.67	36.61 ± 5.52	0.072
Cognitive functioning			
Wechsler Memory Scale IV-Auditory Memory Index	0.52 ± 0.10	0.53 ± 0.12	0.560
Wechsler Memory Scale IV-Visual Memory Index	0.56 ± 0.11	0.59 ± 0.12	0.352
Wechsler Memory Scale IV-Visual Working Memory Index	0.41 ± 0.12	0.48 ± 0.13	0.057
Wechsler Memory Scale IV-Immediate Memory Index	0.58 ± 0.08	0.60 ± 0.10	0.338
Wechsler Memory Scale IV-Delayed Memory Index	0.51 ± 0.10	0.51 ± 0.13	0.796
Rey Auditory Verbal Learning Task-Learning Rate	5.91 ± 2.58	5.17 ± 1.90	0.200
Wechsler Adult Intelligence Scale III-Digit Symbol-Coding	45.82 ± 14.25	50.43 ± 15.7	0.258
Trail Making Test (A/B) Ratio	2.60 ± 1.15	2.23 ± 0.83	0.162
Stroop Ratio	1.91 ± 0.54	1.76 ± 0.32	0.165
Verbal Fluency (number correct)	39.95 ± 7.80	41.73 ± 7.67	0.391
Subsequent memory task (percent hit—percent FA)	0.26 ± 0.20	0.30 ± 0.19	0.480

M ± SD unless otherwise noted. Significant *p*-values in bold.
Key: FA, false alarm; NL, Netherlands; US, United States.

a Z statistic threshold of 2.3 and a corrected cluster threshold of $p = 0.001$ (Worsley, 2001).

Because the majority of older adults reported some level of memory complaints, we were interested in the association between frequency of memory complaints and subsequent memory effects across all participants. To ensure that any correlation that may exist was not driven by an association between memory complaints and age or global cognitive function, we investigated the correlation of FOF scores with age and with scores on the MMSE. Owing to the non-normality of the distribution of FOF scores and of MMSE scores, this was evaluated using Spearman's correlation. MMSE scores were not correlated with FOF ($r_s = -0.180$, $p = 0.159$), indicating that any associations between FOF and subsequent memory effects are not due to a relationship between complaints and global cognitive functioning. However, we did find an association between FOF and age ($r_s = 0.259$, $p = 0.039$). Therefore, when we conducted an exploratory analysis to evaluate the influence of FOF scores on lower level subsequent memory effect maps, we included age as a covariate. This allowed us to identify brain regions in which subsequent memory effects correlated with FOF while accounting for age, gender, and test site. Continuous clusters were defined using a Z statistic threshold of 2.3 and a corrected cluster threshold of $p = 0.05$ (Worsley, 2001).

3. Results

3.1. Neurocognitive and demographic

The ratio of participants in each group did not differ between test sites, and the groups showed no significant differences in age, IQ, and other cognitive functions (see Table 1). These results remained the same after including age and gender as covariates in the models and revealed a significant age effect on Wechsler Memory Scale and digit symbol performance, such that with older age participants performed at lower levels. As anticipated, the amount of memory complaints reported by participants, as measured by the FOF subscale of the Memory Functioning Questionnaire, was significantly different between those with and without subjective memory complaints, as defined by our inclusion criteria, $t(62) = 4.139$, $p < 0.001$. Although the amount of depressive symptomology reported by those with (M = 5.82, SD = 4.15) and without subjective memory complaints (M = 3.00, SD = 3.84) differed according to the GDS, $t(61) = -2.700$, $p = 0.009$, mean scores on the GDS were not indicative of clinical depression (total score <10). Furthermore, participants with subjective memory complaints were more likely to indicate that they felt they had more problems with memory than most (GDS question 14, $\chi^2(1) = 25.63$, $p = 4.12e^{-7}$) and that their minds were not as clear as they used to be (GDS question 30, $\chi^2(1) = 13.97$, $p = 0.0002$). After removal of these questions related to the perception of cognitive performance, the group difference in GDS responding was reduced to a trend level ($t(61) = -1.80$, $p = 0.076$). The groups did not differ in depressive symptomology according to the Beck Depression Inventory II or in neuroticism and conscientiousness, as measured by the Big Five Inventory, after multiple comparison correction.

3.2. Subsequent memory task

Of the 80 studied scenes, 50.5% (SD = 19.4) were correctly identified as old with high-confidence (hit), and 40.7% (SD = 19.9) were incorrectly identified as new (miss). Of the 60 foils presented only during the postscan recognition test, 67.8% (SD = 20.8) were

Table 2
Mean proportions of recognition judgments and overall performance in those with and without subjective memory complaints (SMCs)

Measure	With SMC (n = 23)	Without SMC (n = 41)	*p*-values
High-confidence (HC) hit rate	0.54 ± 0.18	0.49 ± 0.20	0.286
Low-confidence (LC) hit rate	0.09 ± 0.10	0.08 ± 0.08	0.824
HC false alarm rate	0.28 ± 0.19	0.19 ± 0.17	0.057
LC false alarm rate	0.11 ± 0.12	0.10 ± 0.11	0.685
Miss rate	0.36 ± 0.18	0.44 ± 0.21	0.154
Correct rejection rate	0.61 ± 0.24	0.71 ± 0.19	0.068
Task performance (HC hit rate − HC false alarm rate)	0.26 ± 0.20	0.30 ± 0.19	0.480

correctly identified as new (correct rejection), and 22.1% (SD = 18.2) were incorrectly identified as old with high-confidence (false alarm) (see Table 2 for breakdown by group). Average recognition performance (percent hit—percent false alarm) for high-confidence responses was 28.4% (SD = 19.3), which is in line with previous subsequent memory studies that utilize a similar paradigm and stimuli set that found performance to range between 0.2 and 0.35 (Chai et al., 2010, 2014; Gutchess et al., 2005; Ofen et al., 2007). Importantly, recognition performance for high-confidence responses did not differ between those with (M = 0.26, SD = 0.20) and without subjective memory complaints (M = 0.30, SD = 0.19) ($t(62) = -0.711$, $p = 0.480$). Recognition performance for high-confidence responses was also not correlated with FOF ($r = -0.087$, $p = 0.495$).

3.3. Neuroimaging

3.3.1. Main subsequent memory effect

Subsequent memory effects were determined by contrasting activation during encoding of subsequent high-confidence hits with activation during encoding of subsequent misses (positive subsequent memory effect: hit > miss; negative subsequent memory effect: miss > hit). Across all participants, positive subsequent memory effects were found in bilateral lateral occipital cortex, left hippocampus, inferior temporal gyrus, and parahippocampal gyrus. Negative subsequent memory effects were found in the right angular gyrus, and posterior cingulate cortex, see Fig. 1.

3.3.2. Group difference in subsequent memory effects

The between-group analysis identified several regions in which subsequent memory effects differed between individuals with subjective memory complaints when compared to individuals without subjective memory complaints while controlling for age, gender, and test site (see Fig. 2 and Table 3). Specifically, there were 5 regions where subsequent memory effects were lower in individuals with subjective memory complaints compared to those without subjective memory complaints. These included the bilateral lateral occipital cortex, occipital pole, superior parietal lobule, and the right precentral and postcentral gyri (bottom panel of Fig. 2). We did not find regions where subsequent memory effects were higher in individuals with subjective memory complaints compared to individuals without subjective memory complaints.

Using FSLView, we created masks in standard space of the clusters identified in the between-group analysis. Individual-level maps of the contrasts were registered into standard space using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002) so these masks could be used to extract contrast of parameter estimate values in each region for each participant. These values were used to help determine if subsequent memory effects were positive or negative within each group. Within these regions, the pattern exhibited by each group seems to be different. Specifically, we observed that individuals without subjective memory complaints showed positive subsequent memory effects (greater activation for hits than misses), whereas individuals with subjective memory complaints showed either negative (greater activation for misses than hits) or no subsequent memory effects (no difference in activation for hits and misses) in the same regions (see Fig. S1). Thus, overall, our findings suggest that the direction of the subsequent memory effects was opposite between the groups in the right and left lateral occipital cortex and the superior parietal lobule, the left occipital pole, and the right precentral and postcentral gyri.

Although the scan sequences used at each site were optimized concurrently in order to match parameters as much as possible and test site was controlled for in all imaging analyses, the acquisition of data at 2 separate locations is a potential limitation of the present study. To address this, we ran the between-group analysis in each separate data set and replicated some of the group differences obtained from the combined data set, albeit with a smaller spatial extent and at a lower statistical threshold. Examination of the maps

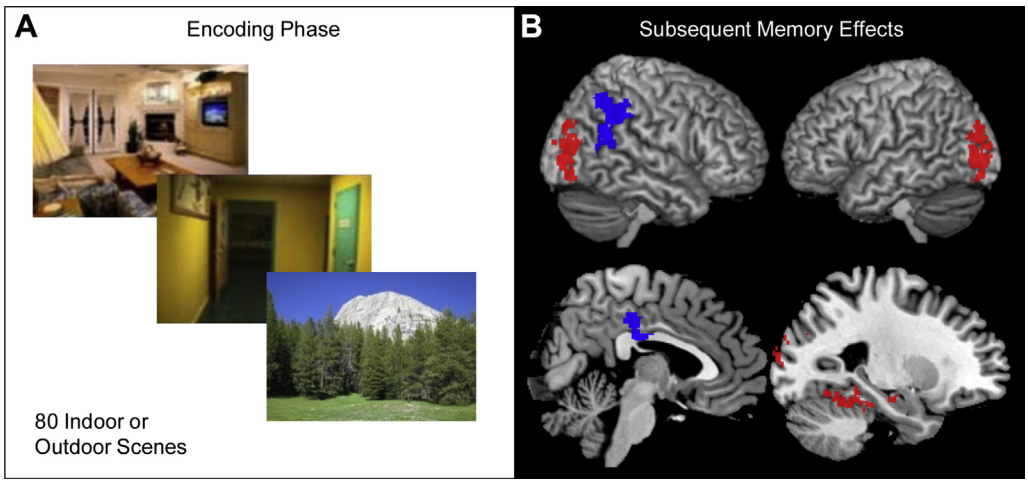

Fig. 1. Subsequent memory effects across participants. (A) Example of scenes shown in the encoding phase that was administered during fMRI scanning. A recognition test was administered following the scan to determine the subsequent memory fate of each scene. (B) Activation maps depicting the subsequent memory effects (contrast between subsequently remembered and subsequently forgotten scenes) across all participants. Red indicates positive subsequent memory effects (hit > miss) while blue indicates negative subsequent memory effects (miss > hit). Abbreviation: fMRI, functional magnetic resonance imaging. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

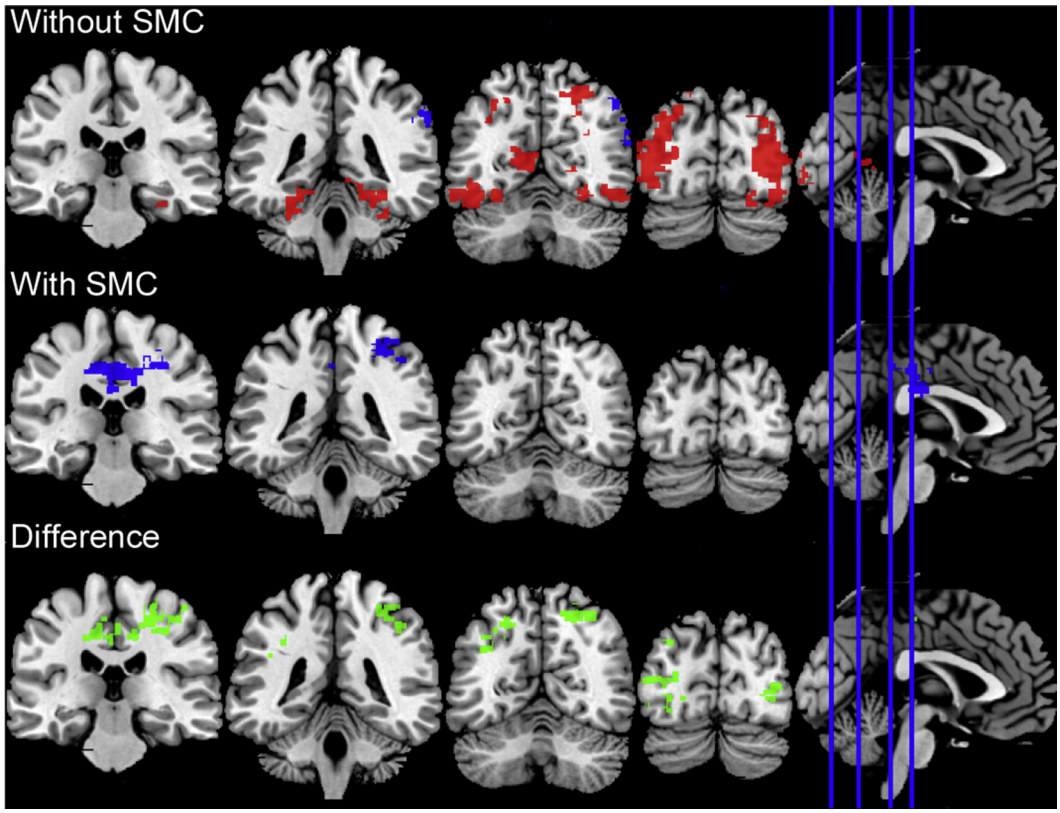

Fig. 2. Between-group comparisons of subsequent memory effects. The top panel depicts subsequent memory effects (contrast between subsequently remembered and subsequently forgotten scenes) in individuals without subjective memory complaints (SMCs) and the middle panel depicts subsequent memory effects in individuals with SMC. Differences in subsequent memory effects between the groups are depicted in green in the bottom panel. Activation maps are overlaid on coronal slices. The location of each coronal plane is noted on a midsagittal plane provided in the right. Red indicates positive subsequent memory effects (hit > miss) while blue indicates negative subsequent memory effects (miss > hit). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of the subsequent memory effect revealed a similar pattern of group differences in each data set that corresponded well with the group differences we identified in the combined data set (see Fig. S2). We therefore are confident that the observed effects are likely present in each data set but may not reach the same statistical significance due to the markedly reduced power of the smaller samples.

3.3.3. Association between subsequent memory effects and frequency of forgetting

We identified several regions, including the precuneus, posterior cingulate cortex, and ventromedial prefrontal cortex, in which subsequent memory effects were associated with FOF across all participants using a general linear model, while controlling for age, gender, and test site (Table 4). To interpret the directionality of the effects, we created masks of these regions and extracted the contrast of parameter estimate values in each region for each participant in the same manner as was done for between-group analysis described previously. The subsequent memory effects in the posterior cingulate cortex, precuneus, and ventromedial prefrontal cortex showed a negative association with FOF ($r = -0.347$, $p = 0.005$; $r = -0.353$, $p = 0.004$; and $r = -0.551$, $p < 0.001$, respectively), such that participants with more frequent memory complaints had a more negative subsequent memory effect in these regions (see Fig. 3). Correlations between subsequent memory effects and task performance were also examined but did not yield any significant results.

4. Discussion

This study utilized a subsequent memory paradigm to identify differences in memory encoding between individuals with and without subjective memory complaints. We found that individuals with, compared to without, subjective memory complaints showed lower subsequent memory effects in the occipital lobe, superior parietal lobe, and posterior cingulate cortex, despite of a lack of difference in task performance and other cognitive measures.

Table 3
Regions where subsequent memory effects differed between individuals with and without subjective memory complaints

Voxels	Z-Max	X (mm)	Y (mm)	Z (mm)	Brain regions
951	3.82	−18	−86	0	Left occipital pole
727	3.97	20	−32	54	Right precentral gyrus, right postcentral gyrus
702	4.34	6	−96	2	Right occipital pole
554	3.79	−22	−62	48	Left lateral occipital cortex, left superior parietal lobule
448	3.47	20	−58	66	Right lateral occipital cortex, left superior parietal lobule

Table 4
Regions where subsequent memory effects correlated with frequency of forgetting

Voxels	Z-Max	X (mm)	Y (mm)	Z (mm)	Brain region
326	3.51	26	−82	10	Right lateral occipital cortex
314	3.84	16	−76	48	Precuneus cortex
286	3.69	18	44	−2	Ventromedial prefrontal cortex
238	3.67	4	−44	34	Posterior cingulate gyrus
238	3.14	−30	38	4	Ventromedial prefrontal cortex

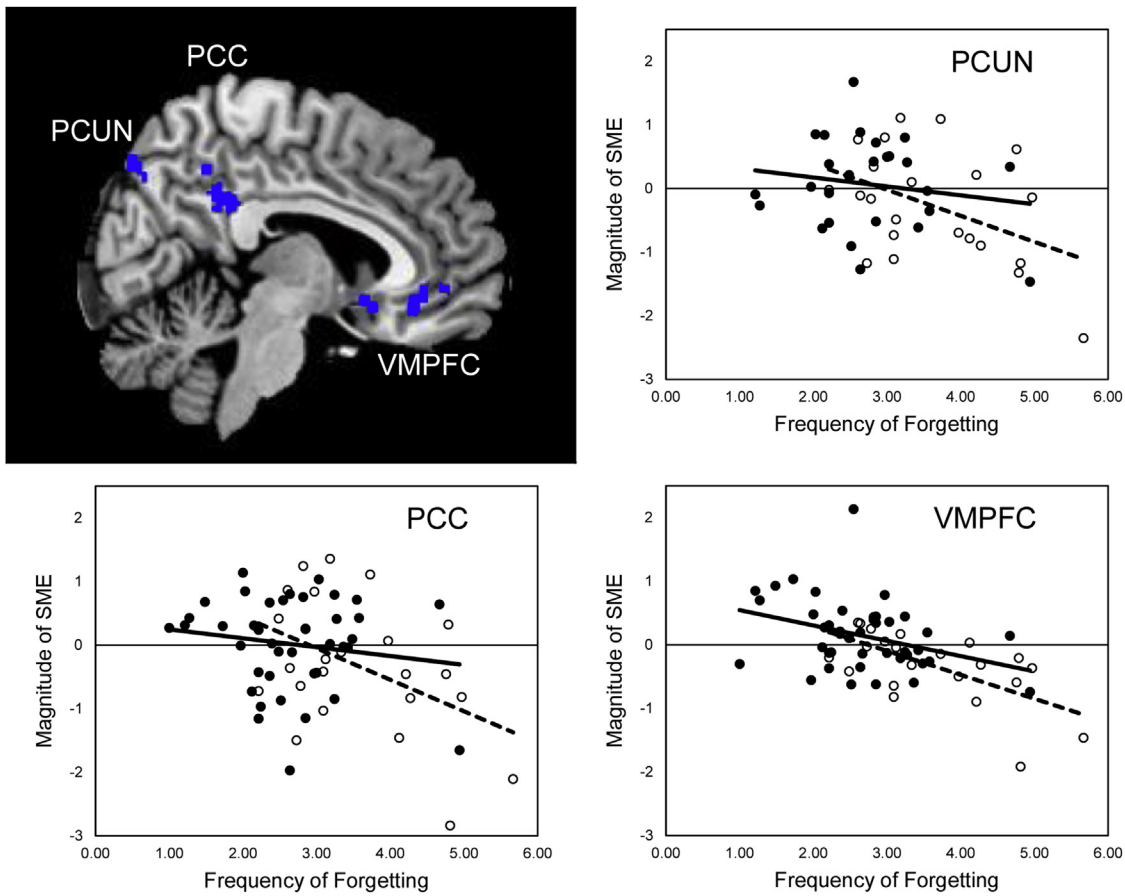

Fig. 3. Correlation of subsequent memory effect and frequency of forgetting scores. Scatterplots depicting the correlation between the magnitude of each participants' subsequent memory effect (hit > miss) in the precuneus (PCUN), posterior cingulate cortex (PCC), and ventromedial prefrontal cortex (VMPFC) and their frequency of forgetting scores. Data points for participants with and without subjective memory complaints are depicted with open and closed circles, respectively, for illustration purposes only. Trendlines for those with and without subjective memory complaints are depicted with dotted and solid lines respectively. Abbreviation: SME, subsequent memory effect.

Individuals with subjective memory complaints showed predominately negative subsequent memory effects, whereas those without subjective memory complaints showed primarily positive subsequent memory effects. This apparent shift may represent an early functional change in the brain activations supporting memory that is present prior to clinical deficits.

Previous studies have also identified encoding differences among individuals at risk for AD. In one such study, researchers found that individuals with subjective memory complaints show greater activation in the left prefrontal cortex compared to individuals without subjective memory complaints (Rodda et al., 2009). These authors, however, investigated memory encoding by utilizing a block design where memory encoding was contrasted with a baseline and a determination of trial-by-trial memory outcome is not possible. In our study, we utilized an event-related design and thus were able to contrast items remembered with items subsequently forgotten, which allowed for identification of the neural correlates of successful memory formation. Moreover, we specifically asked all participants to judge how sure they were in their old/new responses and used as hits only those correct recognition responses for which they were confident. By contrasting high confident correct recognition with forgotten items, we were able to minimize the influence of guessing and overall provide a more direct measure of the neural activations supporting memory. The difference in the specific pattern of activation between our findings and those of Rodda et al. (2009) likely reflect differences in the experimental designs described previously.

Studies of other populations at risk for development of AD have also identified differences in activation during memory encoding tasks, supporting the notion that functional changes occur before clinical deficits are detectable in those at risk for AD. For example, individuals at a genetic risk for AD have shown differential activation in the medial temporal lobe (Bookheimer et al., 2000; Borghesani et al., 2008; Filippini et al., 2009), precuneus, and cingulate gyrus (Bondi et al., 2005; Han et al., 2007) as well as reduced deactivation of the default mode network (DMN) (Persson et al., 2008; Pihlajamäki and Sperling, 2009) during encoding. It has been suggested that the functional differences observed in those with subjective memory complaints and others at risk for AD serve as a compensatory mechanism for incipient AD (Bondi et al., 2005; Bookheimer et al., 2000; Dickerson et al., 2005; Erk et al., 2011; Kircher et al., 2007; Mormino et al., 2012; Rodda et al., 2009, 2011; Trivedi et al., 2008).

While the subsequent memory paradigm has not been utilized as much as general encoding tasks in the study of individuals at risk for cognitive impairment, it has been used to investigate age-related differences in subsequent memory effects. In a meta-analysis of 18 previously published functional MRI studies, Maillet and Rajah (2014) show that older compared to younger adults exhibit lower subsequent memory effects in the occipital cortex and superior parietal lobule. Consistent with this finding, we found that these are 2 of the regions in which individuals with subjective memory complaints showed lower subsequent memory effects compared to individuals without subjective memory complaints.

The occipital cortex may not be considered a primary memory region; nevertheless, the consistent observation of its involvement in the subsequent memory effect across studies suggests that higher level visual processing may be related to differences in memory processes. Taken together, our findings suggest that individuals with subjective memory complaints compared to those without show similar differences in subsequent memory effect as previously observed with older age, which could reflect advanced aging, though future studies that include longitudinal assessment are required to test this notion.

In addition, we found that as individuals reported more memory complaints on the Memory Functioning Questionnaire (Gilewski et al., 1990), the subsequent memory effects in the precuneus, posterior cingulate, and ventromedial prefrontal cortex were more negative. While characterizing memory complaints in a binary manner is useful for clinical applications, the frequency of memory complaints is continuous in nature and as such, the FOF subscale may serve as a more sensitive measure to capture individual differences in a preclinical state. Indeed, the amount of reported memory complaints as measured by the Memory Functioning Questionnaire showed large variance within both groups. This analysis helps illuminate the potential influence of memory complaints on successful memory formation, regardless of whether participants categorize themselves as having memory concerns or not. Given the frequency of memory complaints in older adults, the underlying neural mechanisms associated with such complaints are relevant to understanding normal as well as abnormal aging.

Interestingly, the areas in which we found an association between the number of reported memory complaints and the magnitude of the subsequent memory effect belong to major cortical hubs in the DMN. The DMN is most active when individuals are at rest or engaged in self-referential mental explorations (Buckner et al., 2008). Previous research has shown that the precuneus and poster cingulate cortex typically “deactivate” during external tasks, including memory formation (Daselaar et al., 2004). Differences in the connectivity of the DMN as assessed with resting-state fMRI have been shown in normal aging (Damoiseaux, 2017), in individuals with AD (Damoiseaux et al., 2012) and subjective memory complaints (Hafkemeijer et al., 2013), and have been linked to differences in cognitive performance (Damoiseaux, 2017). Reduced deactivation of the DMN during cognitive tasks has been observed in normal aging (Miller et al., 2008), those at a genetic risk for AD (Persson et al., 2008; Pihlajamäki and Sperling, 2009), and those with MCI and AD (Pihlajamäki and Sperling, 2009). Individuals in the preclinical stage of AD, determined by levels of amyloid-β in cerebrospinal fluid, show greater activation of the precuneus and posterior cingulate during memory encoding (Rami et al., 2012). The association we observed between subsequent memory effects in DMN regions and memory complaints is consistent with the differences observed in the DMN among older adults (Park et al., 2013) and those with or at risk for cognitive impairment (Pihlajamäki and Sperling, 2009). Overall, more negative subsequent memory effect in DMN regions may reflect decreased task-directed attention among individuals with subjective memory complaints, which could explain the disparity between levels of subjective and objective memory functioning.

Recently some limitations of parametric analyses using cluster thresholding have been identified (Eklund et al., 2016). When applying a p threshold of 0.001, as in our between-group analysis, these limitations appear negligible. However, when applying a threshold of $p < 0.05$, as in our association between subsequent memory effects and FOF, the amount of false-positives may be greater than expected. These results should therefore be interpreted with caution. Nevertheless, our findings are consistent with previous studies showing functional changes in DMN regions among individuals at risk for development of AD. Thus, although exploratory, we believe these findings are nonetheless worth reporting.

The observed differences between those with and without subjective memory complaints are of particular clinical interest because individuals with such complaints have a higher risk for development of cognitive impairments or dementia in the future (Jessen et al., 2014b; Mitchell et al., 2014). Differences in subsequent memory effects between healthy older adults with and without memory complaints may serve as a potential early marker for future decline. However, this interpretation is limited due to the cross-sectional nature of this study. The true predictive value of subjective memory complaints as a marker for AD can be better determined through longitudinal studies that avoid potential confounds from other variables that also change over time. In addition to the need for longitudinal follow-up, future studies should strive to better characterize the role of potential confounding factors. Given the trend-level differences we observed in depressive symptomology and personality between those with and without subjective memory complaints, this warrants further investigation.

5. Conclusions

Our findings demonstrate that the patterns of activations within the brain regions supporting successful memory formation differ between healthy older adults with and without subjective memory complaints. It is possible that this may reflect decreased task-directed attention among those with subjective memory complaints. Given the higher risk for AD among those with subjective memory complaints, future work of a longitudinal design is warranted to further investigate if such functional differences may be an early sign of incipient cognitive impairment.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2017.08.015.

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