Can changes in source memory-related brain activity be detected in younger adults?

A longitudinal task-based fMRI study

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Finally, I would like to dedicate this thesis to my dearest mom, who was lost to Alzheimer's last year. May the important work of research groups like LCBC continue to enhance our understanding of this devastating disease.

Abstract

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Title: Can changes in source memory-related brain activity be detected in younger adults? A longitudinal task-based fMRI study.

Supervisor: Håkon Grydeland

Contributions: The study was part of a larger project within the Research Group for Lifespan Changes in Brain and Cognition (LCBC). Data collection and preprocessing of the fMRI data had already been conducted by others, but the follow-up data had never been analyzed previously. All analyses were carried out independently by me using a combination of self-written and pre-written scripts. All writing was conducted by me in full.

Background: Declining episodic memory abilities are common in normal aging and represent one of the earliest cognitive impairments in Alzheimer's disease (AD). There are indications that more subtle deviations in the brain's processing of episodic memory exist prior to observable decline. Detecting changes early is crucial in order to be able to intervene effectively. However, the link between current biomarkers of such changes and episodic memory decline is not well understood. A more direct measure of episodic memory may enhance our capacity to predict who is at risk for memory deficits and who will maintain strong memory capabilities in older age. Nonetheless, limited knowledge exists regarding episodic memory-related brain activity changes in individuals under the age of 60. **Method:** A longitudinal task-based fMRI design on source memory was employed, as source memory is hypothesized to be the most age-sensitive feature of episodic memory. 54 cognitively healthy adults with an age range of 20 – 80 years old were scanned twice over an average interval of three years. **Aim:** The study aimed to investigate whether changes in source memory-related brain activity typically associated with later-life source memory decline could be detected in cognitively healthy adults under the age of 60. **Results:** In both older and younger adults, time-related changes in the hippocampus were observed, along with indications of subtle changes in cortical activations underlying changes in source memory performance; however, these latter observations require additional confirmation. **Conclusion:** The current study suggests that fMRI have the potential to detect changes in source memory-related brain activity also in adults under the age of 60. This highlights the potential of fMRI being a sensitive measure for identifying early, subtle changes in source memory processing.

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Introduction

Declining episodic memory abilities are common in normal aging and represent one of the earliest cognitive impairments in Alzheimer's disease (AD) (Pereira et al., 2024; Sperling, 2011). Episodic memory refers to the ability to recall specific past events and their contextual details (Tulving, 1992). A major contributing factor to this decline in both normal aging and in AD is reductions in hippocampal volume (hippocampal atrophy), which is shown to accelerate rapidly from the ages of 60 to 65 years old (Gorbach et al., 2017; Walhovd et al., 2020). Additionally, both AD and the decline in episodic memory abilities in normal aging display an increase in prevalence from this age onward (Hebert et al., 2013; Rönnlund et al., 2005).

Importantly, once such atrophy has emerged, there is currently no way in reversing it. However, there are indications that more subtle deviations in the brain's processing of episodic memory information exist prior to accelerated atrophy (Jack et al., 2018). For instance, studies have revealed how changes in AD biomarkers such as cerebrospinal fluid (CSF) levels of amyloid-beta (Aβ) can begin up to decades prior to its clinical manifestations (Jia et al., 2024). This is an important finding, as in order to be able to intervene effectively, changes need to be detected prior to becoming pronounced. Yet, despite CSF biomarkers showing associations with episodic memory deficits, the connections are relatively weak and nonspecific (Jack et al., 2018). Thus, a more direct measure of episodic memory may enhance our capacity to predict who is at risk for memory deficits and who will maintain strong memory capabilities, whether progressing to AD or not.

The arguably most direct measure of episodic memory is task-based functional magnetic resonance imaging (fMRI). Interestingly, declining episodic memory have been related to changes in brain activity as measured by longitudinal task-based fMRI (O'Brien et al., 2010; Persson et al., 2012; Pudas et al., 2018). However, these studies have primarily focused on older adults, overlooking the potential to identify changes at an earlier age. If subtle changes in how the brain is processing episodic memory information begins at a younger age, a direct measure of episodic memory such as fMRI may have the potential to detect these changes. Moreover, if patterns of changes in brain activity typically associated with later-life episodic memory deficits can be detected in younger adults, there may be opportunities to intervene before these subtle changes potentially become pronounced. Hence, the aim of this thesis is to investigate whether changes in underlying brain mechanisms responsible for episodic memory can be detected in

younger adults. I will do this by investigating longitudinal task-related fMRI on a feature of episodic memory called source memory, in a sample consisting of both older (> 60 years old) and younger (< 60 years old) cognitively healthy adults.

Early detection of episodic memory changes

Why focus on younger adults, instead of focusing on individuals actually exhibiting episodic memory deficits? The clinical diagnosis of AD is made when episodic memory deficits have become significant and additional cognitive and behavioral symptoms have begun to arise, combined meeting the diagnostic criteria for AD as a progressive disease (McKhann et al., 2011). A contributing reason for this is likely that episodic memory decline also is a common occurrence in normal aging, particularly after the age of 65 (Nyberg et al., 2012). Thus, at the time AD is clinically diagnosed, significant neuronal damage is already well underway (Sperling et al., 2011). Furthermore, there are currently no effective treatments available to cure or stop the progression of AD (Li et al., 2022), which means that once such atrophy have emerged, there is currently no way in reversing it. Hence, at the time of diagnosis, some changes are irreversible. However, research have revealed that AD biomarkers can be detected prior to when the clinical diagnosis is typically made and before significant atrophy has progressed (Villemagne et al., 2013).

Hence, an alternative approach to finding a cure is to intervene before atrophy has accelerated. In this way, the progression to clinical AD could potentially be slowed down, and perhaps, ultimately prevented. Such interventions could range from lifestyle adjustments and pharmacological strategies to cognitive exercises (e.g. Kivipelto et al., 2018). Ideally, changes need to be detected when they are at their most subtle and at the earliest possible time before any damaging changes have occurred. This requires including seemingly healthy, younger adults in the research.

The question then arises: when can subtle changes potentially be detectable? A recent comprehensive study revealed that abnormal levels of CSF biomarkers such as Aβ deposition could be identified as early as 18 years prior to the clinical diagnosis of AD (Jia et al., 2024). This is suggesting that these biomarkers could be observable as early as in the 40s for some individuals. However, although such CSF biomarkers show correlations to episodic memory decline, these correlations are weak, in addition to arguably being nonspecific to episodic

memory (Jack et al., 2018). For instance, there are individuals with high levels of Aβ who still exhibit preserved episodic memory functioning (Sturchio et al., 2021). Hence, CSF biomarkers are not optimal for actually predicting who will experience episodic memory decline or not. Therefore, a measure of episodic memory that closely correlates with performance might more accurately be able to predict who is at risk for memory deficits and who will maintain strong memory capabilities in older age.

fMRI as the most sensitive measure?

The question is then, what could seemingly be the most sensitive and direct measure of episodic memory? A significant factor contributing to the decline in episodic memory is hippocampal atrophy (Gorbach et al., 2017). Research have revealed strong associations between atrophy and episodic memory performance (Gorbach et al., 2017). Notably, although hippocampal atrophy has been found to be accelerating more rapidly from the 60s, large-scale studies have observed more subtle atrophy beginning as early as in an individuals' 20s (Walhovd et al., 2020). As such, atrophy seems to both be a direct and a sensitive measure. However, structural measures alone cannot fully capture the complete functional dynamics underlying episodic memory, including processes like the encoding and retrieval of episodic memories.

The arguably most direct measure of episodic memory functioning is functional magnetic resonance imaging (fMRI). fMRI allows for the detection of fluctuations in cerebral blood flow inferred from measuring changes in blood oxygen level dependent (BOLD) signal. This BOLD signal is considered to reflect changes in neuronal activity. When BOLD signal is measured during the performance of a specific task, fMRI is capable of identifying the brain regions active specific to this task by comparing it to the activity during either a different condition, to a control task or to a baseline condition. Hence, measuring fMRI during the encoding and/or retrieval of episodic memory tasks provides more direct insights into the functioning of the underlying brain regions supporting the actual episodic memory performance, than what structural measurements are able to.

In addition to being a highly direct measure of episodic memory, fMRI BOLD signal also appears to be a highly sensitive measure. For instance, studies have observed changes in BOLD signal corresponding to changes in episodic memory that are at least partially independent of atrophy (Filippini et al., 2009; O'Brien et al., 2010; Persson et al., 2012; Pudas et al., 2018). For

example, in the study of Persson et al., (2012) on older adults, both changes in encoding-related fMRI BOLD signal and hippocampal atrophy were associated with declining episodic memory performance, however these two measures were not correlated to each other. Such findings indicate that fMRI has the potential to identify episodic memory-related changes that cannot be fully accounted for by structural changes alone.

Moreover, some indications points to that changes in BOLD signal might also be an even more sensitive measure than structural changes. For instance, Filippini et al. (2009) investigated younger adults aged 20 to 35 and discovered that those with genetic risk for AD produced greater hippocampal activation as measured by fMRI BOLD during the encoding of an episodic memory task, relative to those without genetic risk. Notably, these findings could not be explained by other measures such as brain atrophy, suggesting that brain regions may show signs of abnormal episodic memory-activity already early in adulthood and prior to structural brain changes such as atrophy have begun. This is potentially placing fMRI toward the forefront of early detection measures. Yet, regardless of whether changes in brain activity as measured by fMRI precede or follow atrophy, fMRI appears to be a sensitive tool for informing us about the underlying mechanisms of episodic memory changes.

Nevertheless, the majority of research examining changes in episodic memory-related fMRI brain activity are cross-sectional, comparing data from a single point in time, in contrast to longitudinal, following the same individuals over time. This is an issue, due to findings showing that observations from cross-sectional and longitudinal studies can differ notably (Nyberg et al., 2010). For example, when Nyberg et al., 2010 compared cross-sectional and longitudinal analyses of the same data set, the cross-sectional analysis found decreases in brain activity measured by fMRI, whereas the longitudinal analysis in contrast found increases in the same regions. While longitudinal studies track within-person changes, cross-sectional studies infer changes by comparing different age groups, assuming similar aging trajectories. This can lead to methodological artifacts, such as differences between generations and biases in participant selection across age groups. Hence, longitudinal designs are arguable more appropriate than cross-sectional studies for accurately measuring changes over time.

Taken together, longitudinal task-based fMRI seems to be a highly direct and sensitive method for measuring subtle underlying changes in episodic memory functioning, potentially identifying early changes in this ability. Notably, whereas seven longitudinal task-based fMRI

studies on episodic memory currently exist, none of them have specifically investigated younger adults.

Previous longitudinal fMRI studies on episodic memory

The few longitudinal task-based fMRI studies on episodic memory that exist mainly involve an older cohort with a mean age of approximately 70 years old (as seen in Johansson et al., 2020; Nyberg et al., 2010, 2019; O'Brien et al., 2010; Persson et al., 2012, 2014; Pudas et al., 2018). As summarized in the evidence above, at this age changes can already be well underway, and these studies therefore misses the opportunity to detect potential changes at earlier ages. Nevertheless, these studies provide valuable insights into how changes in functional brain activity are associated with episodic memory in older ages. Notably, as episodic memory is hypothesized to be particularly vulnerable in older age, these insights can improve the understanding of patterns related specifically to episodic memory decline.

One of the studies that have looked into exactly this is Persson et al., (2012). In a sample of 26 cognitively healthy adults between the ages of 55 to 79 years old (average age 69.7 ± 8.3 years at follow-up), change in longitudinal episodic memory was correlated with change in brain activity as measured by fMRI. Here, episodic memory decline between a 10-year period was linked to a 6-year change in medial temporal lobe (MTL) activations, namely a decrease in activity in the left hippocampus and an increase in the bilateral parahippocampal gyrus during the encoding of an incidental episodic memory task. Notably, the changes in brain activity were specifically associated with the individuals who experienced a longitudinal decline in episodic memory, whereas no or little significant activity changes were observed in those whose memory remained stable or improved. Hence, this is suggesting that changes in either direction were indicative of memory deficits, whereas no changes were indicative of maintained memory capabilities.

Despite a relatively small sample size, all correlations yielded moderate effects. Notably, the changes in brain activity were not correlated to neither age, AD risk genotype nor hippocampal atrophy, suggesting that the fMRI measurements were at least partially independent of these factors. However, the group with declining memory was generally older and exhibited a more accelerated hippocampal atrophy than those with maintained memory, suggesting that the detected brain activity changes still occurred in conjunction with other processes likely affecting

the memory performance. Nevertheless, taken together, these findings indicates that episodic memory impairment in older adults can be reflected by changes in MTL activity, and that fMRI is offering direct and independent insights into these changes.

Additional longitudinal fMRI studies on episodic memory further provides support to the findings in Persson et al. 2012 of a link between episodic memory decline in older adults and changes in fMRI-based brain activity. For instance, O'Brien et al. (2010) studied 51 older adults (average age 74.8 ± 5.4 years at baseline) and observed that those individuals with early signs of clinical decline exhibited a decreased brain activity as measured by fMRI over 2 years in the right hippocampus during the encoding of an associative episodic memory task. Similar to the findings of Persson et al. (2012), no significant changes were evident in the group whose cognitive function remained stable. Moreover, the pattern of change could not be explained by AD risk genotype or hippocampal atrophy, with only a slight association with age.

Furthermore, Pudas et al. (2018) observed, in a sample of 130 cognitively healthy older adults (average age 69 years at follow-up, no reported range), an association between decreasing longitudinal episodic memory performance based on measurements over two decades and increased fMRI brain activity between a 4-year interval in the prefrontal cortex (PFC). Notably this increase was evident during both the encoding and retrieval of the episodic memory task, which consisted of making associations between faces and names. In line with Persson et al. (2012), the individuals whose longitudinal episodic memory was characterized as stable did not show any significant brain activity changes. Additionally, no differences in hippocampal atrophy rates were observed between the groups, further supporting the notion that changes in activity as measured by fMRI are detectable independently.

Taken together, the present evidence suggests that changes in episodic memory-related brain activity is evident in older adults and that these changes are detectable using longitudinal task-based fMRI on episodic memory. The consistent findings of hippocampal atrophy not fully being able to explain these observed changes, supports the notion of fMRI as a sensitive and independent tool in understanding the underlying mechanisms of episodic memory.

However, the studies also revealed several inconsistencies. The observations differed across studies in which direction the activation changed and in which regions of the brain. These inconsistencies might be explained by different sample sizes (subgroups ranging from 13 to 81), stimuli differences (novel-old words or face-name associations), differences in how the

participants were compared (median split, clinical decline, or longitudinal episodic memory trajectory) and the interval time between the fMRI scans (2, 4 or 6 years). Furthermore, neither of the studies directly assessed the performance of the in-scanner episodic memory task with the brain activity changes, and the link between the changes in behavioral performance and the changes in BOLD signal were therefore not direct. Moreover, both Persson et al. (2012) and Pudas et al. (2018) is based on the Swedish study "The Betula prospective cohort study: Memory, health, and aging" (Nilsson, 2003) and participants were subsequently originating from the same project, arguably affecting these studies generalizability.

Nevertheless, the consistent observation across the studies that declining memory was related to changes in brain activity, whereas stable cognitive function was associated with minimal changes, is suggestive of changes in episodic memory-related brain activity being a marker of episodic memory impairment in older adults. The remaining question is then; could similar episodic memory-related brain activity changes be detectable also in earlier adulthood?

Source memory as particularly age-sensitive

Taken together, if subtle changes in how the brain is processing episodic memory exist prior to the age of 60, it can be hypothesized that a direct and sensitive method such as fMRI will be able to detect these changes. For instance, if changes in episodic memory-related brain activity related to declining performance is evident in older adults, and a similar pattern is observed in younger adults, it could be an indicator that they are beginning to manifest patterns typical of later-life memory deficits. As episodic memory is expected to remain more stable in younger and middle-aged adults compared to older adults, any changes are likely to be subtle. Consequently, in order to improve the possibility to detect such subtle changes, the fMRI task needs to be as age sensitive as possible.

Within episodic memory there is a general consensus of a distinction between remembering whether something has occurred and additionally recollecting the specific context of that event (Mitchell & Johnson, 2009). Specifically, the latter, known as source memory, has been found to be particularly vulnerable to the effect of ageing (Mitchell & Johnson, 2009; Old & Naveh-Benjamin, 2008; Spencer et al., 1995). For source memory, it is not sufficient to encode an item and its context independently; the content and context must be integrated during encoding, and the information about their co-occurrence must be stored in a way that can be

accessed during retrieval. However, whether these age-related issues mainly stem from difficulties with encoding, retrieval, or a combination of both is not clear.

There is a growing consensus that binding deficits are required to explain these age-related impairments (Castel & Craik, 2003; Naveh-Benjamin et al., 2004). The medial temporal lobe (MTL), and particularly the hippocampus, has been found to be essential for such associative binding (Mitchell & Johnson, 2009). It is hypothesized to both be crucial for the forming of mnemonic representations that associate items with their context, as well as aiding in the reactivation of these memory traces during retrieval (Davachi et al., 2003; Duarte & Dulas, 2020; Eichenbaum et al., 2007). Source memory therefore seems to be particularly dependent upon underlying hippocampal activity, and, as demonstrated in the studies reviewed, longitudinal evidence suggests that changes in hippocampal activity are underlying episodic memory deficits.

The present study

The overall aim of this thesis is to investigate whether longitudinal changes in source memory-related brain activity typically associated with later-life source memory decline could be detected in cognitively healthy adults below the age of 60 years old. To do this, I will analyze data from a sample of 54 cognitively healthy adults aged 20 to 80 who have undergone fMRI scanning twice, with an average interval of approximately three years. During the scans, the participants engaged in both encoding and retrieval of an incidental source memory task. During encoding, multiple items were presented, each paired with a corresponding action. In the retrieval phase, the recall of an "old" item with its corresponding action was considered an indication of source memory. Notably, fMRI data from the baseline scan using this task have partially been reported in previous studies (e.g. Sneve et al., 2015; Vidal-Piñeiro et al., 2017, 2019, 2021) in where significant activation in regions believed to be important for source memory, such as the hippocampus, were evident.

Given that no prior longitudinal studies have specifically investigated brain activity changes related to episodic memory in younger adults, and only a few have done so in older adults, participants will be divided into two groups for analyses: an "older adults" group and a "younger adults" group. The present study will first attempt to replicate previous longitudinal observations of changes in episodic memory-related brain activation in older adults and then explore whether similar patterns also could be present in younger adults. The age cutoff between

the subgroups will be set at 60 years to facilitate for the replication. Consequently, the younger group will include adults from 20 to approximately 59 years old. Age will be controlled for in all analyses in order to detect changes that are not merely due to the effect of aging. The wide age range in the younger group is chosen to maintain as much statistical power as possible and to investigate potential changes at ages that have not previously been explored.

As the hippocampus is a region strongly hypothesized to be involved in source memory performance, and previous studies have observed changes in this region, the left and the right hippocampus will be identified as a priori regions of interest (ROIs). While analyzing a priori-defined areas allows for focused examination of specific brain areas hypothesized to be important for source memory functioning, it may also inherently limit the scope of the findings, missing potential changes in other, less-studied, or unexpected brain regions. Furthermore, due to the overall relative lack in previous longitudinal task-based fMRI studies on episodic memory, I will additionally perform the analyses across the cortical surface at a whole-brain level.

To summarize, I hypothesize that (1) changes in source memory-related brain activity related to declining source memory performance will be evident in older adults, in accordance with previous longitudinal studies. Next, I hypothesize that (2) subtle similar patterns of changes will similarly be evident in adults under the age of 60.

Methods

Participants

A total of 74 participants aged 20 - 80 years completed two BOLD fMRI scans. Out of the 74, 20 were excluded due to excessive in-scanner movement (n = 6), deviant psychometric test scores (n = 3), missing trials (n = 10) or technical errors (n = 1). The final sample included 54 participants with a mean interval between scans of approximately 3 years, grouped into an older group and a younger group for analyses (Table 1).

All of the participants were already participating in ongoing projects coordinated through the Centre for Lifespan Changes in Brain and Cognition (LCBC) at the University of Oslo. All individuals had provided written informed consent before their participation, and the study was approved by the Regional Ethical Committee (REC) of South-East Norway. For their time and effort, participants received financial compensation. Prior to inclusion, participants underwent screening through health and neuropsychological interviews, in order to ensure no history of

neurological or psychiatric disorders, chronic illness, learning disabilities, or use of medicines known to affect nervous system functioning. Furthermore, all participants were predominantly righthanded, spoke Norwegian fluently, and exhibited normal/corrected-to-normal hearing and vision. On a separate day than the fMRI study, participants completed a neuropsychological test battery, and data was discarded due to deviant psychometric test results where such data was available (IQ < 85, Beck's Depression Inventory > 16, or Mini-Mental State Examination < 25). Data was also discarded in cases where the participants were exhibiting appropriate neuropsychological test battery scores at baseline, but an increase/decrease that exceeded the threshold from baseline to follow-up.

The time interval between scans exhibited considerable variability, ranging from 0.94 to 4.74 years. It was also found to have a strong negative correlation with age ($r(52) = -.81$, $p < .001$), wherein advanced age corresponded to less time between the scans. Hence, interval between scans was controlled for in all further analyses.

Experimental design

The experimental design remained the same for both the baseline and the follow-up scan. The experimental design have previously been described in numerous prior work (e.g. Amlien et al., 2018; Roe et al., 2020; Sneve et al., 2015; Vidal-Piñeiro et al., 2017, 2019, 2021). During each scan, the participants performed an incidental encoding task followed by a surprise retrieval test after approximately 90 minutes. Both encoding and retrieval was performed inside the scanner. The scanning procedure remained the same for both timepoints, involving two encoding runs and four retrieval runs. Regardless of encoding or retrieval, each run started with a fixation cross presented for 11 seconds used as a baseline activity recording, which was also repeated during the middle and at the end of the run. The stimulus material consisted of a total of 300 black and white line drawings illustrating everyday items, for instance a house, visually presented on a screen.

Table 1

Demographics and cognitive performance

Demographics	Older adults		Younger adults	
	Baseline	Follow-up	Baseline	Follow-up
N	28		26	
Age, y (range, SD)	70.6 (60.5 – 79.9, 4.3)	73.0 (63.1 – 82.2, 4.4)	35.4 (20.7 – 55.8, 12.6)	39.0 (24.6 – 58.5, 12.2)
Gender (f/m)	14/14		17/9	
Interval, y (range, SD)	2.38 (0.94 – 3.32, 0.41)		3.58 (2.57 – 4.74, 0.64)	
MMSE (range, SD)	28.6 (25 – 30, 1.2)	28.6 (26 – 30, 1.4)	29.2 (27 – 30, 0.9)	29.1 (26 – 30, 1.1)
BDI (range, SD)	9.3 (6 – 12.5, 4.6)	5.0 (0 – 14, 3.7)	5.7 (1 - 11, 3.8)	5.4 (0 - 11, 3.4)

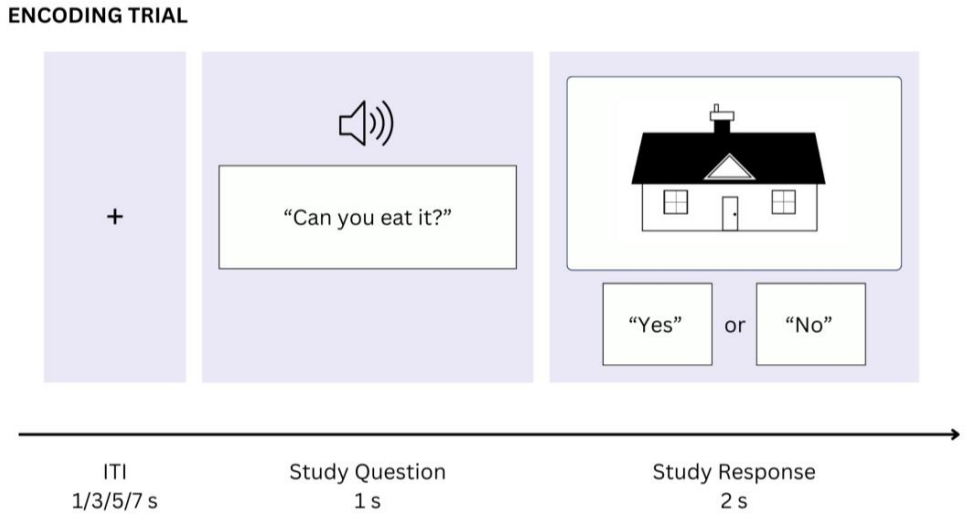
Note. Values are means (range, SD) except for gender that represent number of participants. Key: MMSE, mini-mental state examination; SD, standard deviation; BDI, beck's depression inventory.

Encoding runs

For the encoding phase, each run consisted of presenting the participants with 50 items, in which each item was preceded by a female voice asking the Norwegian equivalent of either "Can you lift it?" or "Can you eat it?" (Illustrated in Figure 1). Each question was asked for half of the items (25 times), mixed in a pseudorandom order. During the 2 seconds the item was presented on the screen, the participant had to respond "Yes" or "No" by pressing a button with their index finger on either the left or the right response grip in accordance with the instructions on the screen. The button response instructions were counterbalanced between participants. The purpose of the experimental design was to encourage the participants to picture themselves either lifting or eating each item in order to determine whether it was feasible or not, and thus create an item-action association.

The item was then replaced by a fixation cross that was present throughout the following interstimulus interval (ITI), which varied between 1 to 7 seconds with an exponential distribution over four discrete intervals (mean duration 2.98 s, SD = 2.49 s). This jittering of the onset of each stimulus was incorporated in order to facilitate for more effectively separating the fMRI data that corresponded to different encoding conditions later in the analysis. Due to subsequent memory designs being dependent on the responses of the participants, condition order and frequency varied between the participants. To account for this and to ensure that the BOLD time series remained sufficiently intricate for analysis - also for participants who predominantly responded to one type of condition - the order of the of the ITIs were optimized using the optseq2 software (http://surfer.nmr.mgh.harvard.edu/optseq/).

Figure 1



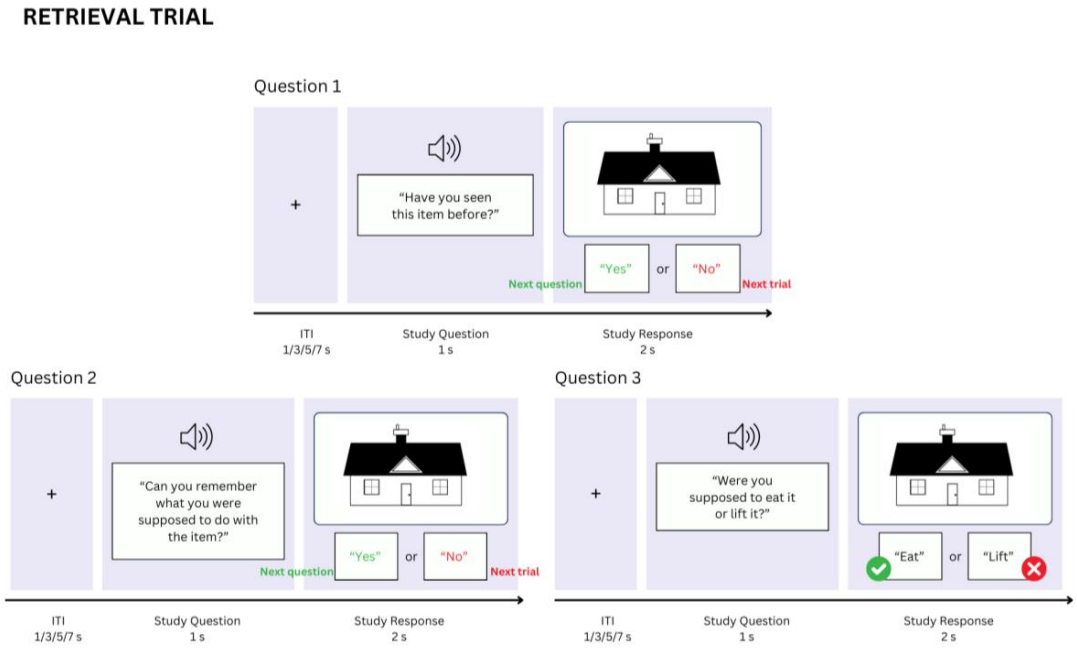
Note. Illustrated example of an encoding trial.

Retrieval runs

The participants were not informed that the experiment was related to memory until just ahead of the first retrieval run. Each retrieval run consisted of presenting the participants with a series of 50 items, where 25 were familiar from the encoding phase and 25 were new, arranged in a pseudorandom order. As there were four retrieval runs, the participants were presented with in total 200 items, in which 100 were old and 100 were new. Prior to each item, the same female voice as in the encoding phase asked the Norwegian equivalent of "Have you seen this item before?" (Question 1). The participants were then instructed to respond to the question with a "Yes" or "No" button press, in the same manner as in the encoding phase. If the participant answer "No" or failed to respond within 2 seconds, the experimental run proceeded to the next item. Conversely, if the participant responded with a "Yes", the trial continued to the next question "Can you remember what you were supposed to do with the item?" (Question 2). As before, if the participants responded with a "No" or did not respond, the run proceeded to the next item. If the participant responded "Yes", the final question was presented "Were you supposed to eat it or lift it?" (Question 3). This time, the participants were presented with a two-alternative forced choice response option, either having to respond with "Eat" or "Lift". An illustrated example of a retrieval trial is presented in Figure 2. For behavioral analyses, source

memory was defined as a correct "yes" response to Question 1 and 2 and a correct response to Question 3.

Figure 2



Note. Illustrated example of a retrieval test trial.

MRI Data Acquisition

Imaging data was collected on a Siemens Skyra 3T MRI at Rikshospitalet (Oslo) using a 24-channel Siemens head coil. The data acquisition have been previously described in numerous previous work (e.g. Amlien et al., 2018; Roe et al., 2020; Sneve et al., 2015; Vidal-Piñeiro et al., 2017, 2019, 2021). Each task run was equivalent to each other and involved the following functional imaging parameters: 43 transversally oriented slices were measured using a BOLD sensitive T2∗-weighted echo planar image (EPI) sequence (TR = 2390 ms, TE = 30 ms, flip angle = 90°; voxel size = 3 × 3 × 3 mm; field of view (FOV) = 224 x 224 mm; interleaved acquisition; generalized auto-calibrating partially parallel acquisitions acceleration factor = 2). Each encoding run consisted of 134 volumes, whereas the number of volumes in the retrieval phase varied due to the trial ending if the participants responded "no" to one of the first two questions. In order to avoid T1 saturation effects in the data, three dummy volumes were

collected at the start of each run. Anatomical T1-weighted (T1w) images were generated from 176 sagittal slices using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the parameters: TR = 2300 ms, TE = 2.98 ms, flip angle = 8°, voxel size = 1 x 1 x 1 mm, FOV = 256 x 256 mm. Additionally, for compensating the EPI distortions, a standard double-echo gradient-echo field map sequence was acquired. In the scanner, visual stimuli were presented using a 32-inch NNL LCD monitor (NordicNeuroLab) at a resolution of 1920 x1080 pixels, and auditory stimuli were presented through headphones using the scanner intercom. Participants responded using the ResponseGrip system (NordicNeuroLab).

The same scanner and parameters were used for all participants for both baseline and follow-up scans. Nevertheless, the scanner underwent standard maintenance and upgrades of hardware and software in the interval between the baseline and follow-up. Hence, the software version was differing in the interval between scans for the majority of the participants, as most participants were scanned with Syngo MR D13 software at baseline and Syngo MR E11 at follow-up.

Structural and Functional MRI Preprocessing

The fMRI data was preprocessed using FMRIPREP preprocessing pipeline (version 20.2.1) (Esteban et al., 2019). The preprocessing pipeline is similar to numerous previous work (e.g. Amlien et al., 2018; Roe et al., 2020; Sneve et al., 2015; Vidal-Piñeiro et al., 2017, 2019, 2021). The T1-weighted anatomical images underwent cortical reconstruction and volumetric segmentation using the FreeSurfer version 6.0 software suite (http://surfer.nmr.mgh.harvard.edu/fswiki) (Fischl & Dale, 2000). Firstly, due to the longitudinal nature of the data, the T1w images were combined to create an average image serving as a reference template for comparison through conforming them to RAS orientation and a common voxel size. Furthermore, additional preprocessing steps included correcting for intensity non-uniformity (INU), skull-stripping (removing non-brain tissue), brain mask refinement, spatial normalization to the standard space (ICBM 152 Nonlinear Asymmetrical template) and brain tissue segmentation of cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM). Then, the BOLD data was further preprocessed, including correction for magnetic field distortions (susceptibility distortion correction), calculating head movement parameters to account for subject movement (motion correction), aligning the BOLD reference to the T1w

reference (co-registration) using boundary-based registration and adjusting the timing of the acquired slices (slice-timing correction).

After the FMRIPREP preprocessing, additional steps were taken to minimize noise through nuisance regression, accounting for motion artifacts (translations, rotations, framewise displacement) and physiological noise through six “aCompCor” principal components derived from a WM/CSF mask. The data also underwent high-pass filtering using a discrete cosine filter with a 128-second cutoff to remove low-frequency drifts, and a prewhitening approach was applied in order to correct for temporal autocorrelations [AR(1)] in the residuals. While FMRIPREP by default does not apply spatial smoothing at the individual level, additional smoothing of the cortical surface data was applied using a 5 mm full-width at half maximum (FWHM) for each participant in order to improve the signal-to-noise ratio (SNR) by filtering out high spatial frequency noise. Surface-based smoothing is generally preferred over volume-based smoothing because it achieves greater spatial uniformity. This is due to the varying distances and angles between adjacent vertices on the cortical surface mesh. Furthermore, resampling of the volume data into the participants' cortical surface space was executed in one interpolation step. The 4D functional data was then resampled through surface-based registration into a standardized "common space" using Freesurfer's fsaverage5, combining the left and right cortical hemispheres. Furthermore, individual subjects’ functional data were realigned into MNI305 2 mm volume space using linear transformations estimated with 12 degrees of freedom. Lastly, an 8 mm FWHM smoothing was applied to each resampled surface (2D surface-based smoothing).

Because older adults typically exhibit more head motion during scanning (e.g. Pollak et al., 2023; Savalia et al., 2017), the framewise displacement (FD) threshold was further inspected. Participants who exhibited a mean FD greater than 0.5 in any run of either task were excluded. This resulted in the exclusion of 5 older adults and 1 younger adult. Setting the threshold lower would result in removing a large proportion of the older adult group and may have introduced sampling bias. As the focus of the study was to investigate change, the remaining participants all demonstrated a mean difference in FD between baseline and follow-up for each task less than 0.17. As an extra sensitivity check, when doing subgroups-analyses, between-group differences were tested on their mean difference in FD during baseline, follow-up, and their change in FD.

fMRI Data Analyses

Configuring the general linear model (GLM)

A first-level general linear model (GLM) analysis was set up and fitted to the observed BOLD signal for every run of each of the encoding and retrieval task. For the encoding task, three regressors of interest were incorporated (source memory, item memory and miss) and one regressor of no interest (no response), whereas the retrieval task incorporated five regressors of interest (source memory, item memory, miss, correct rejection, false alarm) in addition to three regressors of no interest (lack of response to either of the 3 questions). The regressors of no interests were included to control for variations in BOLD signal associated with the presentation of stimuli and were not use for subsequently analyses. The regressors were modeled as events with onset-time and stimulus durations corresponding to the item presentation period (2 seconds) and convolved with a two-gamma canonical hemodynamic response function (HRF) that included the post-stimulus undershoot.

Group analyses

The contrast between fMRI BOLD activity for items subsequently remembered with full source information versus fMRI BOLD activity for implicit baseline ("source memory versus baseline") was computed for each individual for both encoding and retrieval. This contrast was chosen over contrasting two task states (e.g. source memory versus forgotten items), as it has been suggested to improve the reliability and stability of fMRI task measures (Baranger et al., 2021). Furthermore, the contrast was brought to group level ordinary least squares GLM analysis on three different levels in order to investigate the following: (1) each timepoint separately, (2) BOLD signal change (change), and (3) BOLD signal change in relation to memory performance change (change-change). All outputs were converted to the percentage BOLD signal change between conditions. The initial analysis (1) was undertaken to enable comparisons with previous findings from a larger sample at a single timepoint (e.g. Sneve et al., 2015; Vidal-Piñeiro et al., 2017, 2019), whereas the primary focus of the thesis centers on the two latter analyses (2 and 3). All non-vertex-wise and subcortical statistical analyses were performed using RStudio (https://www.r-project.org/; v.4.2.1).

Time intervals between scans baseline age and sex were included as covariates of no interest in all analyses (except time interval for analysis of baseline and follow-up separately)

due to its known effects on brain functioning and in order to facilitate comparisons with prior studies. Age and the time interval between scans were demeaned to account for the difference in scaling with the binary variable (main intercept). While incorporating multiple covariates can increase the precision of data analysis, it may also result in overfitting: a condition where an overly complex model fits the current dataset very well but a poorly in predicting new, unseen data. This is particularly relevant when dealing with relatively small samples and can results in an overestimation of effects. To address this, covariates were sequentially introduced - initially time interval, followed by age, and subsequently sex - and manually examined to ensure no obvious confounding effects were introduced.

Cortical level. A whole-brain approach was chosen at the cortical level in order to conduct exploratory analysis and potentially producing a more complete picture of how brain function may be changing over time. Firstly, the contrast was brought to group level for baseline and follow-up separately. Furthermore, to explore longitudinal differences in cortical BOLD signal from baseline to follow-up, change in contrast values were computed for each individual. Here, contrast values for every subject at follow-up was subtracted from the contrast values at baseline in order to evaluate the change in the direction from baseline to follow-up. This approach reduces the longitudinal data to only one data point per individual and may result in some information loss, however, it was chosen in accordance with the approach conducted in Persson et. al. (2012) and in accordance with suggestion from Freesurfer developer Douglas N. Sneve (see https://www.mail-archive.com/freesurfer@nmr.mgh.harvard.edu/). Furthermore, fMRI data analyses were conducted using FsFast (FreeSurfer Functional Analysis Stream) as it facilitates for group-level statistical analyses at each vertex of the cortical surface.

The statistical estimates obtained were corrected for multiple comparisons using a a cluster-wise correction method with permutation simulations. This technique involved 1000 permutations, a cluster-forming threshold of $p < .001$ and a cluster-wise threshold of $p < .05$. Cluster correction was chosen due to it being particularly effective in detecting larger areas of activation which may be more representative of brain function as cognitive processes typically involve groups of adjacent vertices. However, in order to facilitate comparisons with the previous fMRI studies from the baseline timepoint, a vertex-wise false discovery rate (FDR) threshold of $p < .05$ was rather conducted on the analyses for each timepoint separately.

Change. The computed change-contrast was brought to group level in order to investigate BOLD signal changes between baseline and follow-up against zero. A significant positive or negative activation pattern would indicate that regardless of baseline age, sex, and time interval differences, the brain is showing an increased and/or decreased cortical engagement with time.

Change-change. Next, the computed change-contrast was brought to group level with change in source memory performance as a covariate of interest/independent variable. The primary aim was to identify changes in cortical activity which associated positively or negatively with alterations in memory performance. A significant positive or negative activation pattern would then indicate that regardless of baseline age, sex, and time interval differences, the brain would be showing an increasing or decreasing cortical engagement in relation to increasing or decreasing source memory performance between baseline and follow-up.

Hippocampal level. In addition to the surface-based cortical analyses, similar analyses were also conducted on the average BOLD signal extracted from two subcortical regions of interest (ROIs), namely the left and right hippocampus. The ROIs were identified a priori, using participant-specific, MNI152-normalized FreeSurfer subcortical segmentations (aseg).

Change. As investigating changes in hippocampal activity enables the use of more appropriate longitudinal statistical analyses, a linear mixed effects (LME) model was conducted. However, an additional change-score one sample *t*-tests were conducted as a sensitivity check for the cortical analyses in order to compare whether the models produced comparable outcomes. Similar as in the cortical analyses, the contrast values for every subject at follow-up was subtracted from the contrast values at baseline in order to evaluate the change in the direction from baseline to follow-up. The key difference between LME models and one-sample *t*-tests is that LME models can modify the best-fit line according to the trajectories of specific individuals, accounting for within-subject correlation due to repeated measurements of the same subjects, making it more sensitive to longitudinal data. Here, (demeaned) baseline age, sex, and (demeaned) time interval between scans was introduced as fixed effects in the LME model, and subjects were additionally added as random effects to control for differences in intercept.

Change-change. To investigate BOLD signal change in relation to source memory performance change, changes in percentage hippocampal BOLD signal and source memory performance were calculated by subtracting baseline scores from follow-up scores. A multiple linear regression model was conducted in where change in hippocampal BOLD signal was added as the dependent variable, whereas change in source memory performance was added the independent variable, similarly as in the cortical analyses. Also here, (demeaned) baseline age, sex, and (demeaned) time interval between scans was introduced added fixed effects of no interest. A significant positive or negative relationship would denote an increasing or decreasing hippocampal response relative to the increase or decrease in source memory performance, irrespective of age, sex, and time interval differences.

Results

Behavioral performance

All participants were presented with 100 different item-action pairings during the encoding-phase at each timepoint. The older group recalled on average 43.0 (SD = 12.1) items with source memory at baseline, and 47.5 (SD = 12.4) items at follow-up. The younger group remembered on average 55.9 (SD = 15.9) items with source memory at baseline and 54.3 (SD = 14.4) items at follow-up. Surprisingly, the older group showed a statistically significant increase in source memory performance between baseline and follow-up ($t(27) = -2.71$, $p = .012$), whereas the younger group did not show a significant change ($t(25) = 0.64$, $p = .53$).

Main fMRI analyses

In order to investigate meaningful changes in BOLD signal between baseline and follow-up, significant activations should arguably be evident during at least one of the timepoints. In the older group, the bilateral hippocampus exhibited significant BOLD activation at baseline during encoding (left: $p = .008$, right: $p = .016$), but this was not evident at follow-up (left: $p = .092$, right: $p = .065$). Moreover, the bilateral hippocampus was significantly activated at both timepoints during retrieval (baseline: left: $p < .001$, right: $p < .001$; follow-up: left: $p < .003$, right: $p < .008$). In contrast, the younger group exhibited significant hippocampal BOLD signal only in the left hippocampus during encoding at baseline ($p = .008$), but not in the right

hippocampus, nor during encoding at follow-up, or during retrieval at either timepoint (all *p*s > .05) (see Appendix A).

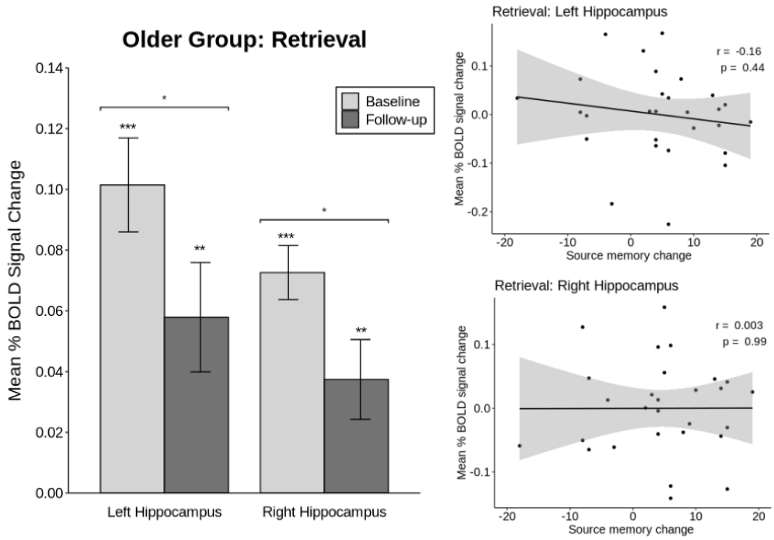
Furthermore, cortical vertex-wise BOLD signal at each timepoint for each age-subgroup activated highly similar cortical patterns at baseline and follow-up (FDR corrected, $p < .05$) (see Appendix A). Although the primary aim was to investigate changes in BOLD signal, as the in-scanner task was the same for both timepoints, the changes were arguably expected to mainly involve changes in similar regions and not abrupt distinct patterns. Moreover, the observed cortical patterns were clearly similar as findings from previous larger-scale studies conducted on the baseline data (e.g. Sneve et al., 2015; Vidal-Piñeiro et al., 2019).

Older group

Hippocampus. Were changes in successful source memory-related hippocampal BOLD signal evident in the older group? The LME model revealed a significant time-related decrease in bilateral hippocampi during retrieval (left: $p = .0196$; right: $p = .0245$) (Figure 3). This is suggesting that retrieval-related hippocampal activity decreased when compared to its own baseline (change against zero). Notably, this decrease occurred despite the older adults demonstrating an overall improvement in source memory performance across the same two timepoints. However, the multiple linear regression model revealed no statistically significant association between this change in retrieval-related hippocampal BOLD signal and the change in source memory performance in either the left or the right hippocampus (left: $p = .42$, right: $p = .99$) (partial correlations illustrated in Figure 3) Hence, this is implying that the decrease was not directly involved with the change in source memory outcomes.

This should further be evident in that less hippocampal BOLD signal during retrieval at each timepoint would not be related to greater source memory score at the same timepoint. To test for this, Pearson's correlations between BOLD signal during retrieval at each timepoint and source memory performance at the corresponding timepoint were computed. Evidently, no significant relationships were revealed (baseline; left: $r = .04$, $p = .85$, right: $r = -.10$, $p = .63$, follow-up: left: $r = .27$, $p = .17$, right: $r = .17$, $p = .39$), suggesting no clear relationship between the intensity of the retrieval-related BOLD signal and successful source memory performance at either timepoint.

Figure 3



Note. Retrieval-related changes in hippocampal BOLD signal in the older group.

During encoding, the LME model of BOLD signal change between baseline and follow-up in the hippocampi revealed no significant changes (left: $p = .23$; right: $p = .60$) (see Appendix B). Furthermore, no statistical significant association between change in encoding-related hippocampal BOLD signal and change in source memory performance in either the left or the right hippocampus were evident in the multiple linear regression model (left; p = .32, right; p = .79) (partial correlation illustrated in Appendix B). Taken together, changes in hippocampal BOLD signal did not seem to be a reliable indicator of changes in source memory performance in this older group, neither during encoding nor during retrieval.

Cortical level. Were changes in cortical successful source memory-related BOLD signal evident in the older group? No cortical clusters of vertexes survived multiple comparison correction in the analysis of cortical change in BOLD signal between the timepoints. For further exploration, regions were considered significant at a more liberal statistical threshold (uncorrected p-value < .001 with a cluster size of 20 vertexes), consistent with criteria used in prior studies (O'Brien et al., 2010; Pudas et al., 2018). However, no regions remained significant at this threshold either. Furthermore, no clusters of vertexes survived multiple comparison correction or remained

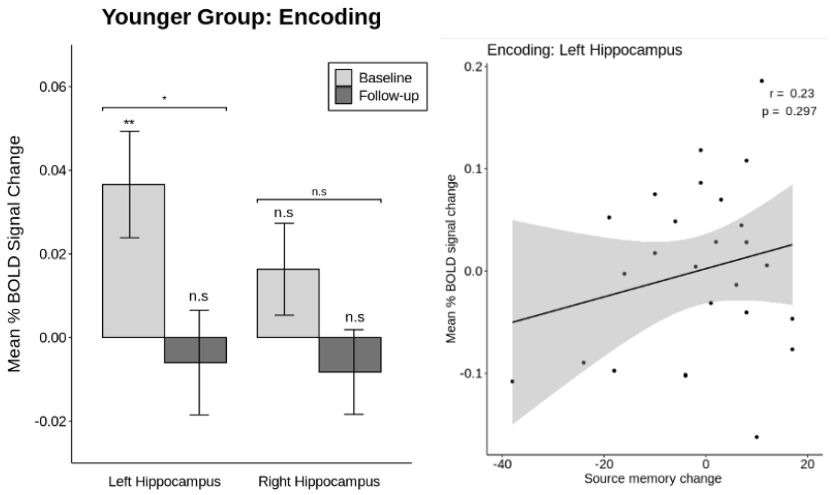
significant at the more liberal uncorrected threshold in the analysis of changes in BOLD signal in relation to changes in source memory performance.

In order to address the lack of longitudinal random effects in the cortical analysis, additional simple one-sample *t*-test were conducted on the computed hippocampal BOLD signal change values between baseline and follow-up. As shown in Appendix C, these tests revealed highly similar *p*-values to those obtained from the LME analyses. Although these results cannot disprove that different outcomes would be present in the cortical analyses addressing within-person variations, it is suggesting that differences, if present, might not be substantial.

Younger group

Hippocampus. As hippocampus was only significantly activated in the younger group during encoding in the left hippocampus at baseline, encoding-related change in the left hippocampal was the only hippocampal-related change investigated in this group. Here, the LME model revealed a significant decrease in BOLD signal during encoding in the left hippocampus (p = .027) (Figure 4). Furthermore, this decrease was seemingly not involved with changes in source memory performance, as the multiple linear regression model revealed no statistically significant association (p = .30) (partial correlation illustrated in Figure 4).

Figure 4



Note. Encoding-related changes in hippocampal BOLD signal in the younger group. Error bars denote standard error from the mean. * $p < .05$, ** $p < .01$, n.s non-significant. The scatterplot is depicting partial correlations (controlled for age, sex, and time interval).

Cortical. Similar to the older group, no cortical clusters of vertices survived multiple comparison correction in the analysis of cortical changes in BOLD signal between the timepoints in the younger group. Additionally, no regions remained significant at the more liberal threshold either. Furthermore, no clusters of vertices survived multiple comparison correction or remained significant at the more liberal uncorrected threshold in the analysis of changes in BOLD signal in relation to changes in source memory performance.

Exploratory cortical analyses

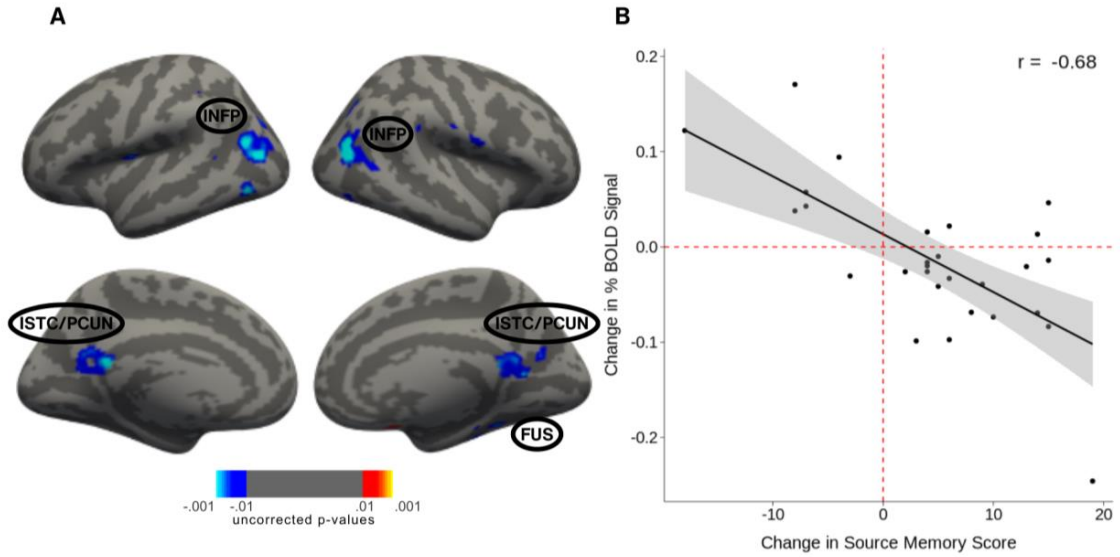
Due to the sensitive nature of measurements of changes in BOLD signal, a relatively small sample size, the extensive vertex-wise multiple comparisons correction and the whole-brain approach, it can be hypothesized that a contributing reason for the lack in statistically significant cortical results may be attributed to limited statistical power. Finding significant changes in fMRI analyses in relatively smaller samples can be especially challenging due to variability in individual trajectories of change and measurement errors introducing noise that obscures these patterns. Furthermore, using a whole-brain approach require an extensive multiple comparison correction due to the ten-thousands of vertices tested. Thus, in order to investigate whether there potentially could be any uncorrected findings that could prompt for future research, additional exploratory analyses were conducted. Here, regions were considered significant at $p < .01$ uncorrected that included cluster sizes of minimum 200 mm^2, corresponding to approximately 20 contiguous vertexes (fsaverage5).

Older adults

Here, a negative correlation between changes in BOLD signal and changes in source memory was evident during encoding (Figure 5A). No other findings were evident, either during retrieval or in the BOLD signal change against zero. As shown in Figure 5A, this association was evident bilaterally in clusters encompassing the inferior parietal cortex (peak Talaiarach coordinate; left: x = -44.9, y = -70.5, z = 13.8, right: x = 40.2, y = -66.5, z = 16.8) and the

precuneus/isthmus cingulate (peak Talaiarach coordinate; left: x = -7, y = -43, z = 13.8, right: x = 17.1, y = -54.2, z = 13.0), as well as the fusiform cortex in the right hemisphere (peak Talaiarach coordinate; x = 40.8, y = -25.6, z = -16.5).

Figure 5

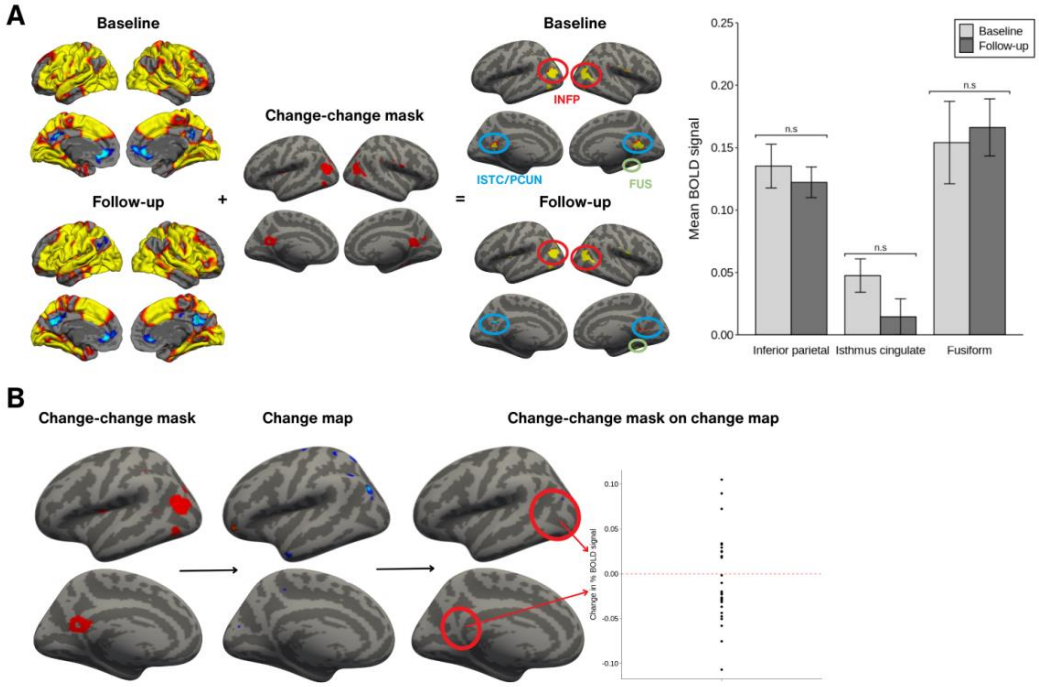


Note. A) Uncorrected significance map of correlation between changes in mean BOLD signal and changes in source memory during encoding in the older group. Black circles indicate nearby cluster locations. PCUN = precuneus; ISTC = isthmus cingulate; INFP = inferior parietal; FUS = fusiform. B) Pearson's correlation computed on the change in BOLD signal and change in source memory score across the older adults.

The significance map of these regions was used as functional binary mask on the contrast map in order to extract the mean percentage BOLD signal. To reduce the number of statistical tests, the mean BOLD signal across the left and the right hemisphere was calculated. Then, a Pearson's correlation was computed on the extracted BOLD signal values and the change in source memory scores. As seen in Figure 5B, a notable linear correlation was evident (r = -.68). The correlation had a $p < .001$ but as the BOLD signal values were extracted from an already thresholded significance map, the p-value is not of specific relevance. A strong correlation yields for further investigation, but change-associations can be challenging to interpret. The further analyses will try to illustrate the careful interpretation required. For the rest of the results-section,

"change-change" will be referring to the analysis of changes in BOLD signal related to changes in source memory performance.

Figure 6



Note. A) Illustration of extracting the values at the largest clusters in the change-change mask from baseline and follow-up contrast maps. n.s non-significant, error bars are representing standard error of the mean. B) Illustration of extracting the values from the change-change regions from the change contrast map in the left hemisphere.

As such, each large cluster (> 20 contiguous vertexes) from the change-change significance map was extracted as a label and applied to the initial significance maps for encoding during baseline and follow-up separately (Figure 6A). As evident in the bar plots in Figure 6A, no significant changes in BOLD signal were evident in either of the largest clusters from baseline to follow-up. However, if a brain region does not show a consistent change over time across all individuals in the sample - that is, if changes in the region's activity are increasing for some participants and decreasing for others - these areas may not emerge when assessing

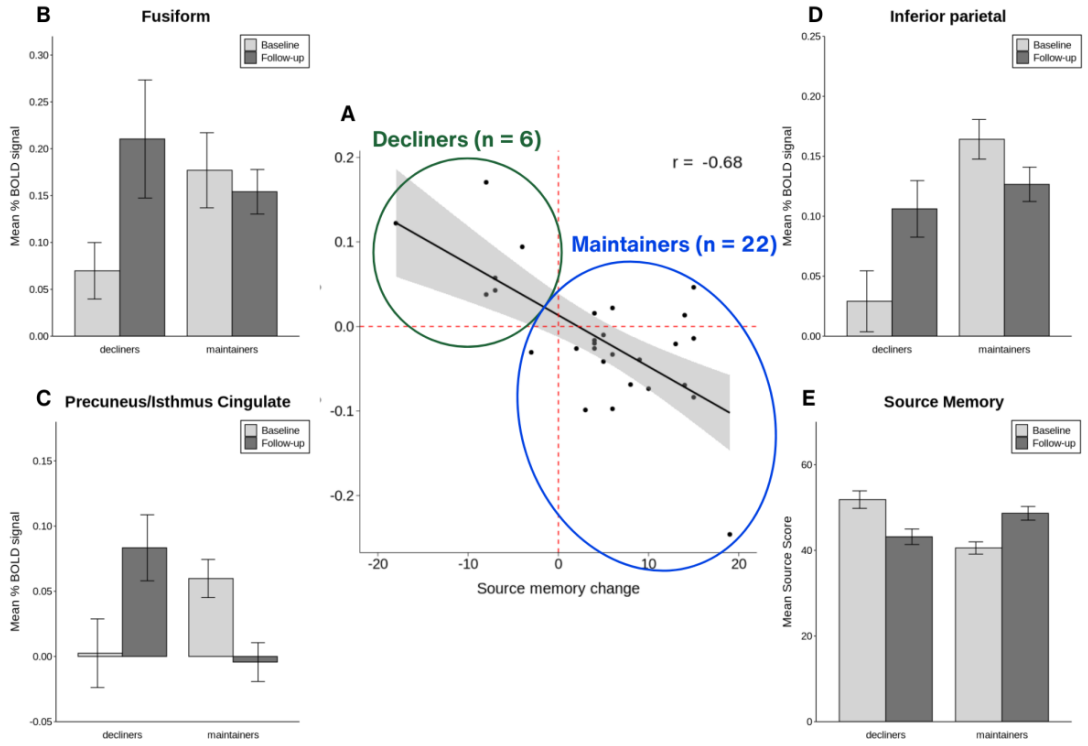
change against its own baseline while still being present in relation to changes in source memory performance. In order to illustrate this, the functional binary mask previously created from the change-change significance map was used on the corresponding change-map during encoding, and the mean BOLD signal change values from these regions were extracted and plotted. As evident in Figure 6B, it was indeed activity in both directions (positive and negative) evident in these regions, supporting the notion that these values had cancelled each other out in the change-map.

Taken together, both increases and decreases in BOLD signal were evident in the negative change-change association. Interestingly, a smaller subgroup of participants ($n = 6$) exhibited a district pattern compared to the rest of the older group, in terms of increased BOLD signal (> 0) and decreased source memory (< 0) (Figure 7A). Given the main hypothesis that declining source memory performance would be associated with deviant changes in BOLD signal, further examination was conducted on this decliner-group.

Firstly, a number of Welch two-sample t-tests was conducted in order to investigate whether these groups differed in other areas. Importantly, movement in scanner (FD) did not differ significantly, neither at baseline, follow-up nor in terms of change in movement from baseline to follow-up (all ps > .05). Furthermore, the decliners did not differ significantly from the rest of the group in terms of age, time between interval or hippocampal volume (all ps > .05). As a sensitivity check due to the large discrepancy in subgroup sizes, additional Wilcoxon signed-rank tests were also conducted, but these reveled similar results. Hence, these variables could not explain the differences in activation and in source memory score.

As evident in Figure 7B-E, the decliners BOLD signal and source memory performance revealed opposite patterns in relation to the rest of the group. Notably, in two out of three clusters (fusiform (FUSI) and inferior parietal cortex (INFP)), Welch two-sample t-tests revealed that the BOLD signal differed significantly between the subgroups at baseline (INFP: $t(9.70) = -4.48$, $p = .001$, FUSI: $t(22.0) = -2.14$, $p = .044$) but not at follow-up (INFP: $p = .48$, FUSI: $p = .43$). A similar pattern was observed for the source memory score (baseline; $t(10.0) = 2.5$, $p = .032$, follow-up: $p = .23$). Contrary, in the latter cluster (precuneus/isthmus cingulate (ISTC/PCUN)), an opposite pattern was observed (baseline: $t(8.37) = -1.90$, $p = .09$, follow-up: $t(8.80) = 2.99$, $p = .016$).

Figure 7



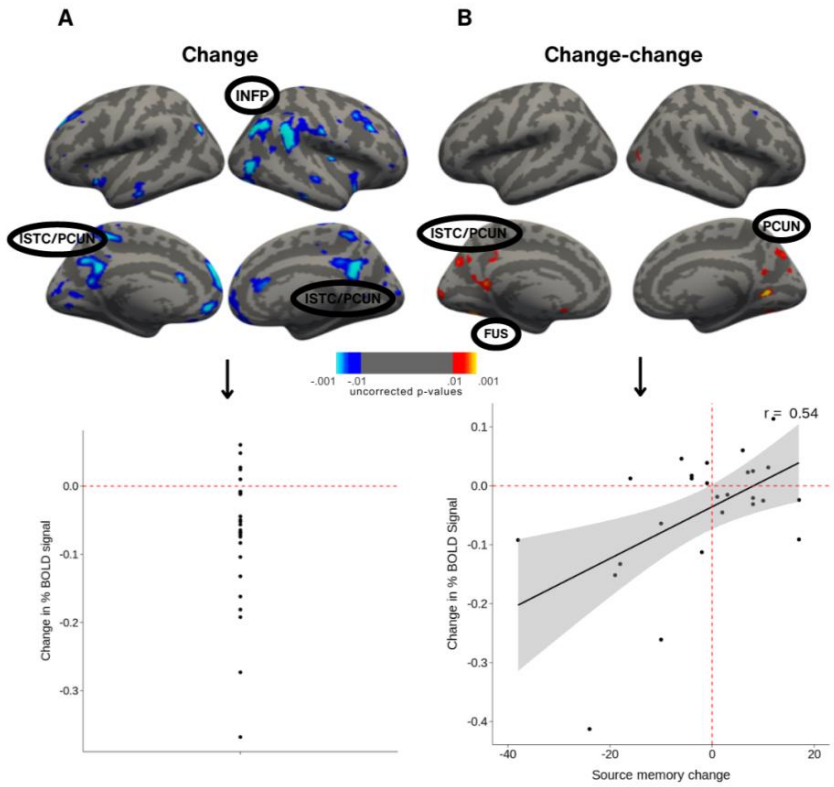
Note. A) A smaller subgroup of participants (decliners, green) showing a distinct pattern compared to the rest (maintainers, blue). B-E) Mean percentage BOLD signal level and source memory performance at baseline and follow-up for each subgroup of older adults. Error bars are representing the standard error of the mean.

Nevertheless, the two subgroups were arguably still somewhat comparable to each other at follow-up, both in terms of BOLD signal and in source memory score, but their initial baseline levels varied, wherein the decliners at baseline exhibited lower BOLD signal yet higher source memory score compared to the rest of the group. In line with this, in order to test whether lower BOLD signal level could be predicting greater source memory performance at each timepoint, a Pearson's correlation between the BOLD signal level in each cluster at each timepoint and the source memory score at the subsequent timepoint was conducted. However, although not all significant, the correlations yielded in the negative direction at baseline, whereas in a positive direction at follow-up (As seen in Appendix E). This is representing a paradoxical observation, and hence lower BOLD signal was not related to greater source memory during follow-up.

Younger adults

Further exploratory analyses were conducted on the younger adults to investigate whether similar cortical patterns could be evident during encoding in this group as well. Here, the cortical change analysis revealed an encoding-related decrease in BOLD signal from baseline to follow-up (Figure 8A). Notably, some of the primary clusters were encompassing similar regions as observed in the older group, namely bilateral precuneus (peak Talaiarach coordinate; left: x = -8.1, y=-46.4, z = 29.3 and x = -15.9, y = -41.7, z = 53.2, right: x = 11.1, y = -47.3, z = 29.2), and the inferior parietal cortex (peak Talaiarach coordinate; left: x = -39.4, y = -69.7, z = 34.2, right: x = 37.8, y = -71.4, z = 35.4). This suggests that whereas the BOLD signal in these regions differed in direction over time for the older adults, the younger adults showed a more consistent tendency of decreasing BOLD signal over time. This in isolation could suggest that the observed increase BOLD signal in the older decliners was a deviation from the "normal".

Figure 8



Note. A) Uncorrected significance map of the mean percentage change in BOLD signal during encoding in the younger group. Black circles indicate nearby cluster locations. PCUN = precuneus; ISTC = isthmus cingulate; INFP = inferior parietal; FUS = fusiform. The plot underneath is depicturing the change in the regions from the change-change map. B) Uncorrected change-change significance map. Black circles indicating nearby cluster locations. PCUN = precuneus; ISTC = isthmus cingulate; FUS = fusiform. The scatterplot is depicturing Pearson's correlation computed on the change in BOLD signal and change in source memory score across the younger adults.

Yet, when assessing changes in BOLD signal against changes in source memory performance, a different picture emerged (Figure 8B). Interestingly, again clusters in similar regions as in the older group were evident, encompassing the bilateral precuneus/isthmus cingulate (peak Talaiarach coordinate; left: x = -6.9, y = -49.6, z = 10.1 and x = -17.6, y = -71.1, z = 31.9, right: x = 17.1, y = -66.6, z = 38.7), as well as the fusiform cortex in the left hemisphere (peak Talaiarach coordinate; x = -29.0, y = -66.2, z = -1.3). The mean BOLD signal response across hemispheres were extracted and a Pearson correlation was computed on the extracted BOLD signal values and the change in source memory scores. As seen in Figure 8B, a moderate positive linear correlation was found ($r = 0.54$). As age was controlled for, and the younger group included individuals up to the ages of the older group, this positive relationship would imply an abrupt shift occurring around the age of 60. This arguably appears unlikely.

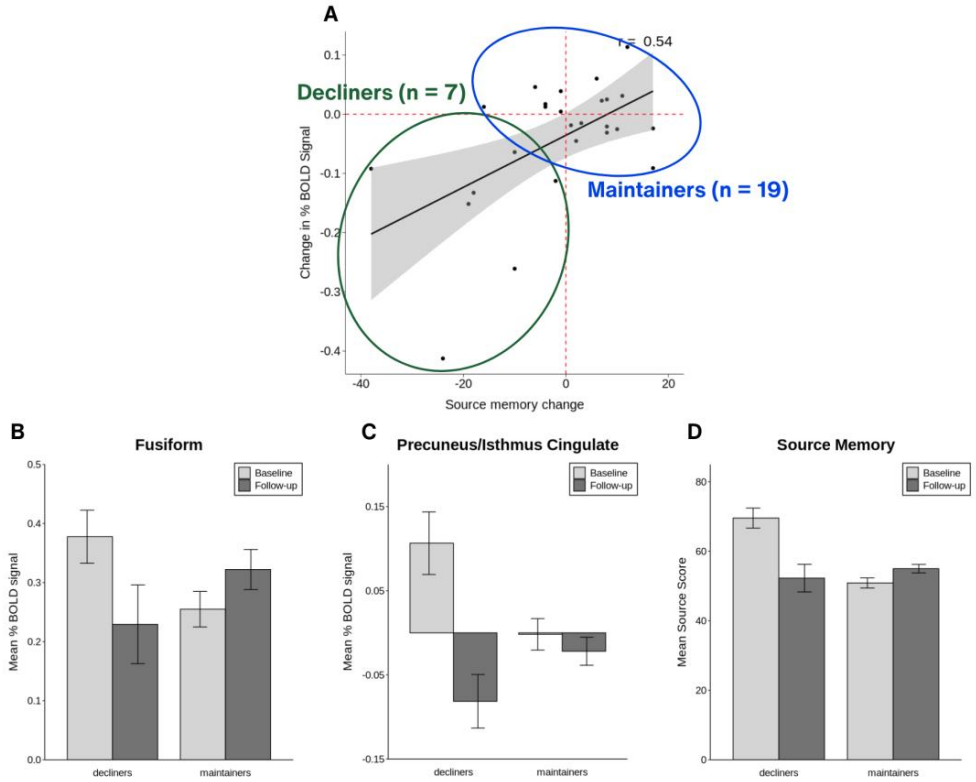
Nevertheless, the positive correlation was seemingly driven by a subgroup of decliners ($n = 7$) showing a dissimilar pattern than the rest of the younger subgroup (Figure 9A). Removing these decliners from the change-change correlation caused the correlation-coefficient to change from positive to negative (from $r = 0.54$ to $r = -0.22$), suggesting that the majority of the group did not exhibit a distinct pattern compared with the older adults.

In order to further investigate whether the decliners differed from the rest of the group in other areas possibly elucidating this finding, a number of Welch two-sample t-tests were conducted. These reveled that the decliners did not differ significantly from the rest of the group in terms of age, time between interval, hippocampal volume, or in-scanner head motion (at baseline, follow-up, nor the change in movement from baseline to follow-up) (all ps $< .05$).

Furthermore, similar to the older group, the decliners and maintainers were comparable to each other during follow-up, both in terms of source memory scores and BOLD signal levels (Figure 9B-D). This was demonstrated through Welch two-sample t-tests, which revealed

significant differences in source memory performance at baseline (t(8.95) = 2.75, p = .023), but not at follow-up (p = 0.77). Additionally, BOLD signal levels significantly differed at baseline for both the precuneus/isthmus cingulate (t(9.22) = 2.62, p = .028) and fusiform area (t(11.76) = 2.27, p = .043), but not at follow-up (ISTC/PCUN: p = .13, FUSI: p = 0.25).

Figure 9



Note. A) A smaller subgroup of participants (decliners, green) showing a distinct pattern compared to the rest (maintainers, blue). B-D) Mean percentage BOLD signal level and source memory performance at baseline and follow-up for each subgroup of younger adults. Error bars are representing the standard error of the mean.

In order to test whether a greater source memory score was associated with a greater BOLD signal in these regions at each timepoint, a Pearson's correlation between the BOLD signal level in each cluster at each timepoint and the source memory score at the subsequent

timepoint was conducted. Although only significant for the fusiform region at follow-up, all the correlations yielded in the positive direction at both baseline and follow-up (see Appendix F).

Discussion

The overall aim of the study was to investigate whether longitudinal changes in source memory-related brain activity typically associated with later-life source memory decline could be detected in cognitively healthy younger adults below the age of 60 years. Three-year changes in successful source memory-related fMRI BOLD signal and source memory performance were examined in a sample of adults initially ranging from 20 to 80 years old. The current study provided evidence for (1) changes in source memory-related brain activity being detectable both in older adults and younger adults, and (2) indications of subtle changes in source memory-related brain activity could be underlying source memory deficits in both older adults and younger adults. However, these latter indications were evident only at liberal statistical thresholds and must be further confirmed by future research. To the best of my knowledge, this is the first study to specifically use longitudinal task-based fMRI to investigate changes in episodic memory-related brain activity also in adults below the age of 60. Overall, the current study suggests that fMRI still has hope to be a sensitive and direct measurement to potentially detect subtle early changes in how the brain is processing source memory.

Was changes in source memory-related BOLD signal evident in older adults?

Firstly, the current study tried to replicate findings from previous longitudinal task-based fMRI studies on episodic memory in older adults. Accordingly, the main hypothesis was that changes in source memory-related activity signal would be underlying source memory deficits in older adults. The current study observed a decrease in activity in the bilateral hippocampus during retrieval. Yet, this decrease over time was seemingly not related to changes in source memory performance. Moreover, the current study observed no changes in activity in either the right or the left hippocampus during encoding.

However, the observed changes in the previous longitudinal studies were reportedly driven by the older individuals who were showing declining episodic memory abilities over time, whereas individuals showing maintained or improved episodic memory did not exhibit any notable changes in activity. Hence, if their samples had not consisted of a substantial proportion

of individuals exhibiting declining episodic memory abilities, these association would not have been present. Conversely, in the current study, the older adults showed a surprisingly overall improvement in source memory performance between the two timepoints. As such, the overall lack in changes in brain activity related to changes in source memory performance could indeed be in line with previous longitudinal observations.

A theoretical possibility remains that the observed time-related decrease in hippocampal activity during retrieval may still be associated with source memory performance, but that other brain regions compensated for the hippocampal decrease, assisting in improving the source memory performance. Several studies have argued that neural compensation is an essential feature of preserved memory and cognition in older age (e.g. Cabeza et al., 2002). For instance, cross-sectional studies have observed lower medial temporal lobe (MTL) activity in normal aging sometimes accompanied by greater activity in other regions of the brain, particularly the frontal cortex (e.g. Deng et al., 2021; Gutchess et al., 2005). According to these studies, this additional frontal engagement represents a compensatory response to MTL dysfunction, helping to maintain the episodic memory ability. However, longitudinal evidence have in contrast revealed increased episodic memory-related frontal activity being associated with a decline in episodic memory performance over time (Pudas et al., 2018). This is in contrast suggesting that additional increases in activations could rather represent a dysfunction or inefficiency of underlying neural activation and would not be involved with maintaining episodic memory performance.

The subsequent hypothesis was that changes in the source memory-related BOLD signal would be observable at the cortical level in older adults. Nonetheless, the primary analyses of cortical changes did not yield any significant results, providing no evidence to support either that cortical changes were underlying source memory deficits or the possibility of additional cortical activations compensating for the decreased hippocampal activity. Taken together, these findings did not support the hypothesis that changes in the BOLD signal underlie source memory deficits in older adults, as suggested by previous longitudinal research (O'Brien et al., 2010; Persson et al., 2012; Pudas et al., 2018).

Whereas it must be noted that substantial variability in episodic memory trajectories have been observed among older individuals (Duarte & Dulas, 2020; Josefsson et al., 2012; Nyberg et al., 2012; Nyberg & Pudas, 2019) an overall improvement in source memory is still not expected

in a task that has been shown to be particularly vulnerable to age-related decline. A possibility is that the overall improvement in source memory performance observed in the older adults was indicative of a practice effect. In longitudinal studies that involve repeated exposure to the same task, the participants can get better at the tasks simply through previous exposure (Salthouse, 2010). For instance, Rönnlund et al., (2005) reported evidence of practice effects on episodic memory performance persisting over intervals as long as five years. Moreover, as the source memory task was incidental, it can be hypothesized that several participants remembered the subsequent memory test at the follow-up scan.

Furthermore, another common issue in longitudinal studies is participant attrition. Attrition is referring to the observation that those who meet the strict participation criteria and attend multiple testing sessions may not necessarily be representative of the wider population (Jacobsen et al., 2021). This is particularly a common issue in longitudinal studies involving older adults (Jacobsen et al., 2021). Studies comparing older individuals who dropped out of longitudinal studies to those who continued to participate have observed that the dropouts generally performed worse on memory tests compared to the participants who came back (e.g. Jacobsen et al., 2021, Nyberg et. al. 2019). Consequently, the data from returning participants could likely overestimate the average performance level within the general population.

Separating the influence of practice effects and attrition from "true" changes in brain activity is challenging and arguably impossible in the current study. Nevertheless, regardless of the cause behind the overall improvement observed in the older group, as changes mainly were expected in participants exhibiting declining source memory performance, strong observable changes in source memory-related brain activity could perhaps not be expected in the current older sample.

Was changes in source memory-related BOLD signal evident also in younger adults?

The main hypothesis was that if subtle changes in how the brain is processing source memory exist prior to the age of 60, a direct and sensitive method such as fMRI would be able to detect these changes. In the younger adults, the present study observed a decrease in source memory-related activation during encoding in the left hippocampus. No changes in the activation were observed at the cortical level. As hippocampus is the structure most strongly hypothesized to be involved with changes in source memory, it could be argued that if any changes in source

memory-related activation would be evident in the younger adults, these would be present in the hippocampus. However, the current study did not find any indications for this hippocampal decrease being related to changes in source memory ability.

However, as changes in adults under the age of 60 is hypothesized to be very subtle, strong correlational effects with changes in source memory performance could perhaps not be expected. This is further supported by studies investigating brain-behavior changes across different age groups, which reveal marked differences between younger and older adults. Changes in the younger population tend to be less noticeable compared to those observed in older individuals (Doucet et al., 2022). Furthermore, as no hippocampal brain activity changes was associated with later-life source memory decline in the older adults, and no previous studies have investigated similar changes in a younger cohort, any further discussion on what these hippocampal activation changes in the younger group could be representing would arguably be highly speculative. Nevertheless, the finding is still valuable in illustrating how longitudinal time-related changes in source memory-related brain activity can be observable also in younger adults, which prompts for further research.

Exploratory cortical analyses

Furthermore, the hypothesis that the lack of significant cortical changes in both the older and the younger groups could be attributed to insufficient statistical power, rather than to an actual absence of changes, was further investigated. Yet, arguably, even within a small sample, any substantial changes should still have been observable. However, as discussed above, any strong observable changes in source memory-related brain activity could not necessarily be expected in the current sample, as the majority of the older adults were exhibiting an improvement in source memory over time and only subtle changes were expected in the younger adults. Hence, such exploratory analyses were considered to be of interest. Although the findings from these additional analyses are prone to false positives and must be interpreted with caution, they did reveal some intriguing patterns.

Firstly, changes in clusters of brain activation across similar cortical regions were evident during encoding for both older and younger adults. These regions included the inferior parietal cortex, precuneus, isthmus of the cingulate cortex, and/or the fusiform area. Notably, these cortical regions have previously been found to be important for source memory success, as seen

in studies by Sneve et al. (2015) and Vidal-Pineiro et al. (2019). This could further support the notion that these regions were not merely reflecting random noise in the data.

In both age groups, a smaller subset of participants displayed a distinct pattern of activity compared to the majority, associated with a decline in source memory performance. However, in the older group, this decline was related to increased activity in the observed regions, whereas in the younger group, it was related to decreased activity in similar regions. Nevertheless, the observation of a smaller subset of the individuals exhibiting signs of decline is still in line with the expected findings, as well as both increases and decreases of neural activity have been associated with neural inefficiency (McDonough et al., 2013, 2020).

Furthermore, when comparing the decliners to the rest of the participants within the respective groups, they mainly differed at baseline, whereas their follow-up levels were similar, both in source memory performance and activity levels. Baseline fMRI levels have previously been linked to later episodic memory decline in longitudinal studies. For instance, Persson et al. (2012) and O'Brien et al. (2010) identified higher baseline hippocampal activation as a predictor of subsequent memory deterioration. Additionally, Vidal-Piñeiro et al. (2019) found that older adults exhibiting longitudinal declines in source memory abilities tended to show lower BOLD signals in frontal regions at baseline compared to individuals demonstrating a longitudinal preservation of memory function. Thus, both elevated and diminished BOLD signals have been found to be predictive.

Interestingly, both decliner groups initially performed better on the source memory task than the rest of their respective groups. Nevertheless, while an increase in brain activity was associated with a decline in source memory performance in the older group, lower activity at each timepoint did not seem to predict greater source memory performance. Conversely, in the younger group, a decrease in activity was concurrent with a decline in source memory and s and there were some indications that greater activity at each timepoint was somewhat predictive of better source memory. Hence, this represents a paradoxical finding, which could be due to the non-robust nature of the results, or it may require further explanation through additional findings. Lastly, differences between the decliner subgroups and the rest of the participants could not be accounted for by age, the interval between scans, hippocampal volume, or head motion during scanning. This adds support to the interpretation that the observed differences in brain activity and memory performance are not merely artifacts of these factors.

Exploratory findings breakdown

Taken together, the notable correlations observed, the activation in relevant brain regions, and the presence of a smaller subgroup deviating from seemingly age-normative changes in both older and younger adults arguably represent an interesting observation, despite the use of a liberal threshold. This observation is further supported by the notion that no strong, observable changes in source memory-related brain activity were necessarily expected in the current sample. However, significant uncertainties still surround these findings. The older and younger adults displayed divergent patterns of decline, and the decliners in each subgroup included participants with changes close to zero, who might not exhibit truly significant variations. These findings further highlight the intricate and detailed nature of the research required to investigate changes in fMRI activity. Still, these observations arguably serve as intriguing indication of changes in source memory-related brain activity typically associated with later-life source memory decline, could be detected in cognitively healthy adults under the age of 60.

Limitations

Despite the advantages of longitudinal designs, limitations can include practice effects, anticipation effects, and subject attrition, all of which potentially was a confounding factor in this study. Yet, it can be argued that similar limitations are also relevant in the previous longitudinal studies, and hence, similar results could be expected. Furthermore, longitudinal data require somewhat more sophisticated statistical techniques because the repeated observations are usually correlated. In the present study, I chose to investigate changes in the most straightforward manner possible, by estimating changes over time as difference scores between baseline to follow-up in the mean level of BOLD signal and successful source memory performance. This approach was inspired by the method in the previous study by Persson et al. (2012) but did concurrently not account for random effects in the cortical analyses. As a sensitivity check, the hippocampal analyses were conducted both with and without random effects which yielded highly similar *p*-values, suggesting that this simplification did not necessarily produce widely deviating results.

The main limitation in the current study is arguably investigating change between only two timepoints, as this is making it susceptible to confounding variables that could influence

both the brain activity and the source memory performance. Factors such as participant motivation, attention during tasks, or other neuropsychological factors were not accounted for, which can have affected the results. Yet, these constraints should also have been present in the observed findings of the previous longitudinal task-based studies on episodic memory. Furthermore, although Persson et al. (2012) correlated BOLD signal changes with episodic memory decline over 10 years, the current study in turn involved twice as many participants.

Lastly, there are intrinsic methodological limitations with using fMRI as a tool. Despite BOLD signal being arguably the most direct measure of memory functioning, it is still an indirect measure of neuronal activity that could be reflecting other physiologic properties or noise.

Conclusion

In conclusion, the current study suggest that fMRI still has hope to be sensitive and direct tool to investigate changes in underlying brain mechanisms responsible for source memory functioning, also in younger under the age of 60. This is based on the observations that changes in source memory-related brain activity was detectable both in older adults and younger adults, as well as the subtle indications of similar patterns of source memory-related brain activity being related to source memory deficits in both older adults and younger adults. However, the study has also highlighted the considerable challenges in identifying robust findings of subtle changes, underscoring the intricate and highly complex nature of investigating changes in fMRI-related brain activity. Nevertheless, these challenges are welcome, as the potential to detect subtle within-person changes in how the brain is processing episodic memory information can provide invaluable insights into the underlying mechanisms of episodic memory change, potentially ultimately contribute to predicting future memory decline. Although fMRI might not yet be suitable to implement in the health care system for everyday scans, it can potentially be incorporated as a valuable tool in larger clinical research trials.

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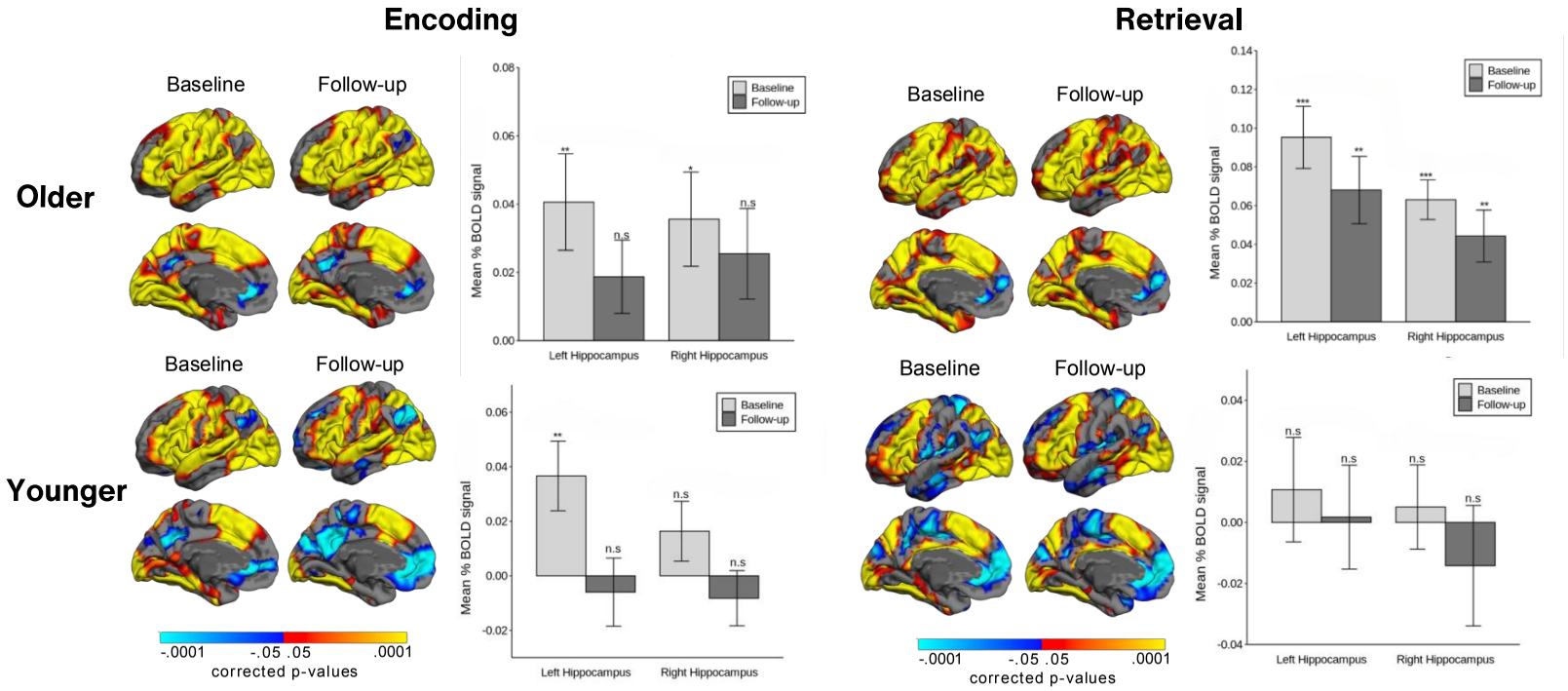
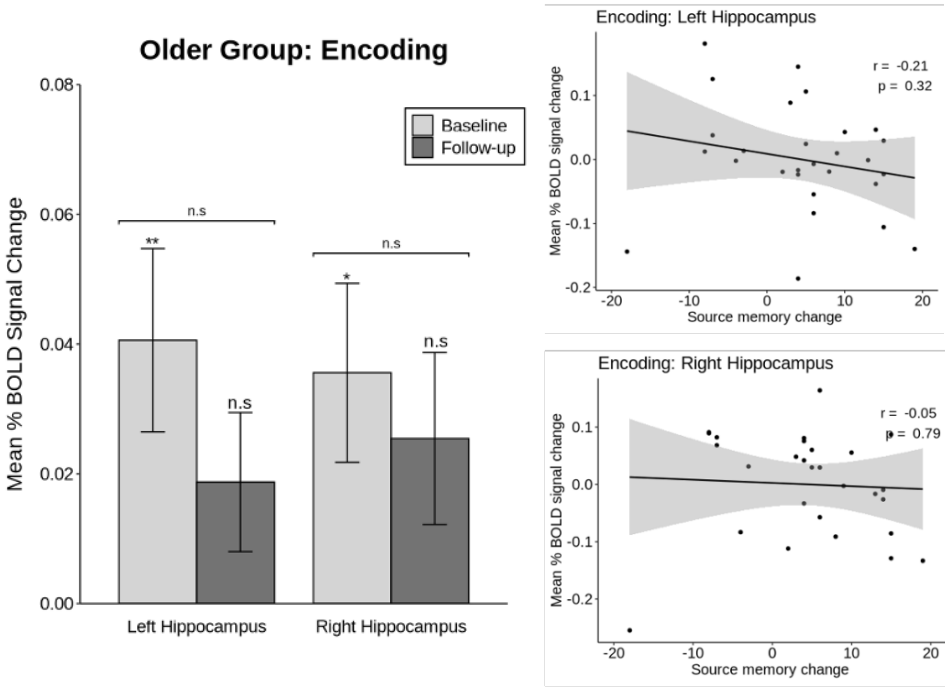
Appendices

Appendix A



Note. Cortical (FDR corrected $p < .05$) and hippocampal BOLD signal for each age-subgroup at baseline and follow-up separately.

Appendix B



Note. Encoding-related changes in hippocampal BOLD signal in the older group. Error bars denote standard error from the mean. * p < .05, ** p < .01, n.s non-significant. Scatterplots depicting partial correlations (controlled for age, sex and time interval).

Appendix C

LMER vs. One-sample t-test (older adults):

Encoding change	LME	One-sample t-test
Left hippocampus	*p* = .23	*p* = .24
Right hippocampus	*p* = .23	*p* = .24
Retrieval change	LME	One-sample t-test
Left hippocampus	*p* = .02*	*p* = .02*
Right hippocampus	*p* = .03*	*p* = .03*

Note. p-values extracted form LME models (accounting for random intercept) versus simple one-sample t-test in the older adults group. * *p* < .05

Appendix D

LMER vs One-sample t-test model (younger adults):

Encoding change	LME	One-sample t-test
Left hippocampus	$p = .03$*	$p = .03$*
Right hippocampus	$p = .11$	$p = .12$
Retrieval change	LME	One-sample t-test
Left hippocampus	$p = .93$	$p = .93$
Right hippocampus	$p = .32$	$p = .32$

Note. p-values extracted form LME models (accounting for random intercept) versus simple one-sample t-test in the younger adults group. * $p < .05$.

Appendix E

Older adults

	Fusiform	**Isthmus cingulate/precuneus**	**Inferior parietal**
Baseline	$r = -.19$, $p = .33$	$r = -.10$, $p = 0.60$	$r = -.07$, p = .72
Follow-up	$r = .10$, $p = .61$	$r = .005$, $p = 0.98$	$r = .50$, p=.0071**

Note. Pearson's correlations between BOLD signal and source memory performance at baseline and follow-up in the older adults.

Appendix F

Younger adults

	Fusiform	**Isthmus cingulate/precuneus**
Baseline	$r = .37$, $p = .06$	$r = .36$, $p = .07$
Follow-up	$r = .50$, $p = .009$**	$r = .22$, $p = .29$

Note. Pearson's correlations between BOLD signal and source memory performance at baseline and follow-up in the younger adults.