

The effect of ageing on the neural substrates of incidental encoding leading to recollection or familiarity

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ABSTRACT

It is well-known that the ageing process disrupts episodic memory. The aim of this study was to use an fMRI visual recognition task to characterize age-related changes in cerebral regions activated, during encoding, for images that would subsequently lead to a recollection-based or to a familiarity-based recognition. Results show that, for subsequent recollection, young adults activated regions related to semantic processing more extensively than older ones. On the other hand, despite putatively producing less semantic elaboration, older adults activated contralateral regions supplementary to those found in young adults (which might represent attempted compensation), as well as regions of the default-mode network. These results suggest older adults could achieve subsequent recollection through different processes, for instance an appraisal of the self-relevance of the stimuli. For subsequent familiarity, the comparisons only revealed greater activations in young adults, in the dorsal frontoparietal attention system as well as in the hippocampus, again suggesting that, even if older adults are able to produce recollection- and familiarity-based recognition, the semantic processing might still be weaker in old adults, who might nonetheless use qualitatively different strategies in order to produce such responses. Further studies are necessary in order to characterize those strategies.

KEYWORDS: aging, episodic memory encoding, recollection, familiarity, fMRI

Introduction

Ageing, even in the absence of any pathology, is associated with a decline in episodic memory (Grady, 2012; Harada, Natelson Love, & Triebel, 2013; Reuter-Lorenz, 2013). Notably, healthy older adults have a decreased capacity to recollect the specific details and context associated with an event. In contrast, they usually can rely as efficiently as young adults on feelings of familiarity to judge that an item has been previously encountered. Most, although not all studies, show altered recollection and preserved familiarity in older participants using the Remember-Know paradigm (e.g. Angel et al., 2013; Bastin & Van der Linden, 2003; Bugajska et al., 2007; Davidson & Glicks, 2002; Koen & Yonelinas, 2014). Studies in cognitive psychology have suggested that age-related differences in episodic memory (and specifically recollection) can at least partly stem from inefficient encoding (Friedman & Johnson, 2014), for two main reasons: older adults have reduced binding capacities and they are less able than young adults to self-initiate appropriate encoding strategies (Craik & Rose, 2012).

Functional MRI (fMRI) studies have provided some insights into the neural bases of the age effects on episodic memory, and more specifically on encoding processes, using the subsequent memory effect procedure. The subsequent memory effect (SME) refers to the greater signal (for instance, fMRI or ERP: event-related potentials) found at encoding for items that are successfully retrieved later on compared to items that are forgotten (Park, Shannon, Biggan, & Spann, 2012; Rypma & D'Esposito, 2003), thus giving an indication of successful encoding-related neuronal activity. Typically, SME is found across a network comprising the left inferior frontal cortex, the fusiform cortex, the medial temporal lobe (MTL, hippocampus and parahippocampal gyrus), the premotor cortex and the bilateral posterior parietal cortex (for a meta-analysis in young participants, see Kim, 2011). In the older population, there has been evidence towards a preserved pattern of encoding-related activations (Ankudowich, Pasvanis, & Rajah, 2016). More specifically, such a preserved pattern was found in frontal regions (Maillet & Rajah, 2014; Morcom, Good, Frackowiak, & Rugg, 2003) and in the MTL (Ankudowich et al., 2016; de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016; Maillet & Rajah, 2014, 2016; Miller et al., 2008; Morcom et al., 2003; Vidal-Piñeiro et al., 2017). However, there was also evidence of reduced activations (Vidal-Piñeiro et al., 2017) or less distinctive pattern of activation (Saverino et al., 2016) at encoding in older adults. However, there was also evidence of reduced activations at encoding in older adults. In a meta-analysis, Spreng, Wojtowicz and Grady (2010) found reduced MTL activations. Reduced hippocampal activity is usually interpreted as associated with altered binding abilities (for a review see Sperling, 2007). Indeed, it appears that the cortical input to the hippocampus is compromised with age (Leal & Yassa, 2015; Shing et al., 2011; Yassa, Muftuler, & Stark, 2010) and that older adults experience difficulties forming new memories because encoding in the hippocampus is hindered by prior memories (Fandakova, Lindenberger, & Shing, 2013; Yassa & Stark, 2011). Consequently, older adults are more susceptible to episodic memory interference (Dodson, Bawa, & Krueger, 2007; Dodson, Bawa, & Slotnick, 2007; Wilson, Gallagher, Eichenbaum, & Tanila, 2006). Furthermore, there has also been evidence of older adults recruiting additional frontal regions that are not observed in young adults (Andukowich

et al., 2017; de Chastelaine et al., 2016; Duverne, Motamedinia, & Rugg, 2009; Gutchess et al., 2005; Kensinger & Schacter, 2008; Maillet & Rajah, 2014; Morcom et al., 2003). Reasons for these mixed results are not clear but may depend on methodological differences between studies.

Actually, recruitment of additional cerebral areas is often found in older adults and has been discussed in several models of cognitive ageing (Reuter-Lorenz, 2002; Reuter-Lorenz, 2013). However, the interpretation of the meaning of these supplementary activations is not always straightforward as this process has been found to be either beneficial or deleterious in different instances. Indeed, despite the impediments sustained by the brain during the ageing process, older individuals sometimes appear to be able to partly compensate (with various degrees of efficiency) for their deficits. Different models tried to explain this compensation phenomenon (see Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014). Notably, the STAC (Scaffolding Theory of Aging and Cognition) (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) and CRUNCH (Compensation-Related Utilization of Neural Circuits Hypothesis) (Reuter-Lorenz & Cappell, 2008) models posit that the older adults' brain strives to counter its declining efficiency and to accommodate to cognitive difficulties using compensatory strategies via supplementary cerebral areas. The HAROLD (Hemispheric Asymmetry Reduction in Older Adults) model (Cabeza, 2002) also assumes that the supplementary activation often found in older adults in the contralateral hemisphere when they are compared to younger adults performing the same task can be explained by a compensation mechanism. However, it posits that those supplemental activations can also stem from a dedifferentiation phenomenon observed in ageing, that is, a less specialized use of neuronal networks. According to the dedifferentiation theory (e.g. Voss et al., 2008), decreased neuronal processing specificity is an inherent characteristic of cognitive ageing and is accompanied by a change in the spatial pattern of brain activation (see also Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007). Findings from several studies demonstrated significantly less neural specialization for different kinds of stimuli in older compared to young adults (Park et al., 2004; see Li, Brehmer, Shing, Werkle-Bergner, & Lindenberger, 2006, for a review). Age-related neuronal dedifferentiation has been evidenced in the prefrontal cortex and in hippocampal regions (Daselaar et al., 2013; Voss et al., 2008). This age-related dedifferentiation is thought to be associated with impaired neurotransmission, particularly in systems having a modulatory role such as the dopaminergic system (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Li, Lindenberger, & Sikström, 2001).

Despite the fact that the ageing process affects predominantly recollection, only a few fMRI studies focused on age-related changes in encoding-related brain activity during associative memory paradigms, thought to rely primarily on recollection and to depend minimally on familiarity (Cansino et al., 2015); de Chastelaine, Wang, Minton, Muftuler, & Rugg, 2011; de Chastelaine et al., 2016; Miller et al., 2008). Those studies found age-invariant SME in the left inferior frontal (de Chastelaine et al., 2011, 2016), parietal and fusiform cortex (de Chastelaine et al., 2011) as well as in the hippocampus bilaterally (de Chastelaine et al., 2011, 2016; Miller et al., 2008). In addition, both de Chastelaine et al., 2011 and Miller et al.,

2008 described less (or nonsignificant) deactivations in regions of the default mode network, in particular parietal regions, in older adults compared to young adults, suggesting an age-related difficulty to deactivate these areas during encoding. Furthermore, Cansino et al. (2015) also found lower activations in older adults in frontal regions. Another similar study compared activation at encoding between young and middle-aged adults (Kwon et al., 2016). There was no difference in middle-aged adults, relative to young adults. Both groups demonstrated SME in bilateral frontal regions as well as in the right parahippocampal cortex. Furthermore, studies focusing on the negative SME using an associative memory task have found it to be attenuated in default-mode network (DMN) regions in older adults (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2015; Mattson, Wang, de Chastelaine, & Rugg, 2014). At retrieval, it has been shown that older adults demonstrate a reduced hippocampal activity during recollection, but enhanced rhinal activity during familiarity judgements (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006). Accordingly, in a previous study (Angel et al., 2013) that focused on activation at retrieval using the same task as here, decreased activations in frontal and parahippocampal regions were found, in old adults, for recollection judgements.

Given the specific decline of recollection processes in ageing, it appeared of interest to look into how age could influence the encoding process leading to such responses. The two previous studies on the SME mentioned above only indirectly assessed recollection via context or relational memory. So, no study has specifically investigated the effect of age on cerebral activity during encoding using the Remember/Know procedure. This paradigm has the advantage of allowing to capture all types of recollection, including non-criterial recollection, using an introspective approach. In addition, the neural correlates of familiarity processes can also be examined with this procedure (Migo, Mayes, & Montaldi, 2012). Here we explored encoding-related activations for pictures that were later judged as remembered (recollected) or known (familiar). Our hypotheses are that the processing of items subsequently leading to recollection, compared to subsequent familiarity, should activate more frontal regions. Indeed, they are often found to be involved in deep semantic processing, as well as in relational encoding (Leshikar, Gutchess, Hebrank, Sutton, & Park, 2010), which are thought to increase the likelihood of subsequent recollection. We also expect recollection and familiarity to recruit different regions of the medial temporal lobe. While subsequent recollection should activate the hippocampus as well as parahippocampal regions, subsequent familiarity would rely more on activations in perirhinal/entorhinal regions (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004; Uncapher & Rugg, 2005). Finally, on the basis of the studies that have focused on age-related differences on SMEs related to recollection (Cansino et al., 2015; de Chastelaine et al., 2011), we should observe common activations for younger and older adults in several regions, including the left inferior frontal, parietal and fusiform cortex as well as the hippocampus bilaterally. We could also expect reduced deactivations for older, compared to younger adults, in default mode network regions which may reflect the engagement of processes that partially compensate for functional decline (de Chastelaine et al., 2011). Given that older adults have difficulties implementing efficient encoding strategies based on semantic elaboration, these brain differences during the encoding of subsequently recognized items,

should be especially notable for subsequent recollection-related retrieval (for similar results during retrieval, see (Angel et al., 2013)).

Methods

Participants

Twenty young adults (eight males) aged 19-29 and 19 older adults (seven males) aged 60-78 participated in this experiment. Participants' characteristics for each age group are shown in Table 1. Older adults were recruited from senior clubs in Liège and most of the young participants were students at the University of Liège. All were right-handed, as assessed by the Edinburgh laterality test (Oldfield, 1971). None reported any history of psychiatric or neurological disease or were taking medication likely to affect the central nervous system. All had normal or corrected-to-normal vision and none suffered from hearing problems. The two groups did not differ in cultural level as assessed by the Mill Hill vocabulary test (Deltour, 1993), and had similar scores on the Beck Depression Inventory (BDI, Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). However, young adults had significantly more years of education than older adults (see Table 1). All the older adults performed well (range: 137-144) on the Mattis dementia rating scale (Mattis, 1976), reducing the risk of including anyone suffering from a neurodegenerative disease. The experimental procedures were approved by the Ethics committee of the University of Liege and were performed in accordance with the ethical standards laid down in the Declaration of Helsinki of 1964. All participants gave their signed informed consent prior to the experiment and were paid 20 euros for their participation.

[Please insert table 1 around here]

Materials

The set of stimuli was composed of 300 black-and-white line drawings selected from Cycowicz, Friedman, Rothstein, and Snodgrass (1997)'s database and standardized for French speakers (Alario & Ferrand, 1999). The images were randomly divided into three lists of 100 pictures, according to two possible versions. The lists were matched for name agreement, image agreement, complexity, familiarity, variability and age of acquisition (for a detailed description of each characteristic, see Alario & Ferrand, 1999). Each subject was allocated one version of the stimulus lists. In each version (for each list, $n = 100$ items), the three lists were used for: (1) study items presented once (Hard condition), (2) study items presented twice (Easy condition), and (3) new items presented only during the test phase. The Hard/Easy manipulation had initially been designed to match recognition performance between young and older adults, so that their retrieval-related cerebral activity could be compared. We will not look further into the effects of this manipulation here (see Angel et al., 2013) and only analyse items presented only one (Hard condition) during encoding, as for items presented twice (Easy condition) we could not disentangle the respective contribution of each presentation of the item to the response made during the recognition phase. Fifteen additional items were selected to form practice lists for the study and test phases. We also included 30 scrambled pictures to serve as null events. Study

lists were created by pseudo-arranging critical items and null events, with the constraint that two presentations of the same stimulus should be separated by at least ten stimuli. Two additional pictures were used at the beginning of the study phase to reduce the risk of primacy effects. Test lists consisted of items from the study lists, mixed with new items and null events, so that no more than three items of the same condition (studied, new or null events) should occur consecutively. Two filler items were added at the beginning of the block.

Procedure

The experiment included a study phase and a test phase, both performed in the fMRI scanner. Before entering the scanner, participants carried out a practice session for the study phase. Then, they were positioned in the scanner and the study phase began. The study phase consisted of 332 trials corresponding to the 100 items presented once (Hard condition), 100 items presented twice (Easy condition), 30 null events, and the two filler items. All stimuli appeared on a black screen that participants could see in an overhead mirror. For each trial, a fixation cross was displayed for 500 msec in white and for 500 msec in red. Then, the item appeared for 3000 msec, with a jitter set randomly from 0 to 750 msec. Participants were not informed of the subsequent memory task. However, to encourage deep incidental encoding of the item and to reduce between-group variability in encoding strategies, a semantic task was introduced in which participants had to decide whether the depicted object would fit into a shoebox (yes-no answer). They answered using a response box held in their right hand. There was a short break (30 sec) after every 110 items. After the study phase, participants left the scanner, received instructions regarding the test phase and the Remember/Know procedure (5 min) and then performed a practice session for the test phase. Justifications for some of their responses to the practice session were asked, in order to verify that the instructions were correctly understood. When they recalled the object was presented, participants were instructed to give a Remember response when they could remember precise details about the context of its presentation and to give a Know response when they could not recall any contextual information about the item presentation. The test phase included 332 trials, with the 100 items studied in the Easy condition, the 100 items studied in the Hard condition, 100 unstudied items, 30 null events and two filler items. Each test trial began with a white fixation cross for 500 msec that then became red for 500 msec. The item was displayed until the subject responded, with a maximum of 4000 msec. Depending on response speed, a black screen sometimes appeared after the item to ensure inter-trial intervals of 3000 msec minimum, with a jitter from 0 to 750 msec. For each item, participants were instructed to choose between three possible answers: Remember (studied item associated with the recollection of some contextual detail), Know (studied item recognized as old but without any contextual information), New (unstudied item). The answer was given by pressing one of the buttons of the response box. There was a short break (30 sec) after every 110 items. After the test phase, participants were debriefed about the experiment, outside the scanner. In particular, correct use of the Remember/Know categories was checked by asking them to explain the basis of their Remember responses for 10 randomly selected items.

fMRI acquisition

Functional MRI time series was acquired on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil. Multislice T2*-weighted functional images were acquired with a gradient echo-planar imaging sequence using axial slice orientation and covering the whole brain (34 slices, FoV = 192 x 192mm², voxel size 3 x 3 x 3 mm³, 25% interslice gap, matrix size 64 x 64 x 34, TR = 2040 msec, TE = 30 msec, FA = 90°). The three initial volumes were discarded to avoid T1 saturation effects. Gradient-recalled sequences were applied directly after the study and test phases to acquire two complex images with different echo times (TE = 4.92 and 7.38 msec respectively) and to generate fieldmaps for distortion correction of the echo-planar images (EPI). The other acquisition parameters were TR = 367 msec, FoV = 230 x 230mm², 64 x 64 matrix, 34 transverse slices (3 mm thickness, 25% inter-slice gap), flip angle = 90°, bandwidth = 260 Hz/pixel. For anatomical reference, a high-resolution T1-weighted image was acquired for each subject [T1-weighted three-dimensional (3D) magnetization-prepared rapid gradient echo (MPRAGE) sequence, TR = 1960 msec, TE = 4.43 msec, inversion time (TI) = 1100 msec, FoV = 230 x 173 mm², matrix size = 256 x 192 x 176, voxel size = .9 x .9 x .9mm³].

Data analysis

Only fMRI data from the encoding phase were analysed and discussed here (data from the recognition phase were presented in Angel et al., 2013, 2016) Furthermore, we have not analysed here items from the Easy condition as we cannot ascertain that recognition performance was associated to the first and/or second presentation of easy items. These items were nevertheless included in the fMRI matrix design. fMRI data were preprocessed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, <http://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB (Mathworks Inc., Sherborn, MA, USA). For each subject, EPI time series were corrected for motion and distortion using Realign and Unwarp (Andersson, Hutton, Ashburner, Turner, & Friston, 2001) together with the FieldMap toolbox (Hutton et al., 2002) in SPM. Next, functional scans were realigned using rigid body transformations, iteratively optimized to minimize the residual sum of squares between the first and each subsequent image separately, and a mean realigned image was created. The structural T1-image was coregistered to this mean functional image using a rigid body transformation optimized to maximize the normalized mutual information between the two images. The mapping from subject to MNI space was estimated from the structural image with the “unified segmentation” approach (Ashburner & Friston, 2005). The warping parameters were then separately applied to the functional and structural images to produce normalized images of resolution 2 x 2 x 2 mm³ and 1 x 1 x 1 mm³ respectively. Finally, the warped functional images were spatially smoothed with a Gaussian kernel of 8 mm full-width at half maximum (FWHM).

For each participant, neural activity was modelled at each voxel with a general linear model, using event types as regressors. These events were sorted by item status during encoding (Hard, Easy) and participants' response in the test phase (Remember, Know, New, No response). Consequently, the design matrix included thirteen events related to item presentation: (1) Hits-Remember in the Hard condition, (2) Hits-Know in the Hard condition,

(3) Misses in the Hard condition, (4) Hits-Remember in the Easy condition for the first presentation, (5) Hits-Know in the Easy condition for the first presentation, (6) Misses in the Easy condition for the first presentation, (7) Hits-Remember in the Easy condition for the second presentation, (8) Hits-Know in the Easy condition for the second presentation, (9) Misses in the Easy condition for the second presentation, (10) Null events, (11) No responses, (12) Breaks, (13) Buffer. The onset vector of each event type was convolved with a canonical hemodynamic response function. The design matrix also included the realignment parameters to account for any residual movement-related effect. A high-pass filter was implemented using a cut-off period of 128 sec in order to remove low-frequency drifts from the time series. Serial autocorrelations were estimated with a restricted maximum likelihood algorithm with an autoregressive model of order one (plus white noise).

To explore the neural correlates of subsequent recollection and familiarity processes, a series of linear contrasts were performed at the individual subject level. First, the brain areas associated with subsequent recollection were isolated by comparing, for the encoding phase, items (from the Hard condition only) leading, at recognition, to a Hit Remember response and those leading to a Hit Know response. Second, a contrast was also ran in order to determine the neural underpinnings of subsequent familiarity by comparing brain activity at encoding for items (from the Hard condition only) later producing a Hit Know versus a Miss response. Individual contrast images were further smoothed (8 mm) in order to reduce remaining noise due to between-subject differences in anatomical variability in the individual contrast images (leading to a total equivalent applied smoothing of 11.3 mm). They were submitted to a second-level analysis corresponding to a random effects model in which subjects are considered as random variables. These individual contrast images were used to analyse: (1) neural activity common to both age groups, and (2) between-group differences. First, to identify the effects common to the two age groups for subsequent recollection and familiarity, the effects observed in the young group were inclusively masked with the effects observed in the older group at an uncorrected threshold of $p < .001$. These statistical maps were thresholded at $p < .001$ uncorrected for multiple comparisons. Secondly, we focused on age-related differences in the neural correlates of subsequent recollection and familiarity. We performed t-test comparisons between young and older participants, thresholded at $p < .001$ uncorrected for multiple comparisons. In order to implement a correction for multiple comparisons at a $p < .05$ threshold, a Monte Carlo simulation was used, with 10 000 iterations (Slotnick, 2003. See also Carlisi et al., 2018; Madore et al., 2017; St Jacques et al., 2017; for a more recent use of this method), which yielded a threshold of 18 voxels.

Results

Behavioural results

The behavioural performance at retrieval (accuracy and reaction times) of the young and older groups is summarized in Table 2 (see Angel et al., 2013, for complete data for both Hard and Easy conditions). More Correct Rejections were made by the young than by the older group [$t(37) = 2.84, p < .01$]. Older adults produced more Remember responses to unstudied items

(false alarms) than young adults [$t(37) = -2.78, p < .01$] and they also made more Know responses to unstudied items [$t(37) = -2.57, p < .05$]. To examine this potential bias, memory accuracy was estimated using the discrimination index (Pr), computed as the difference between the probability of hits and the probability of false alarms, for both Remember and Know responses (Snodgrass & Corwin, 1988). According to independence models of recollection and familiarity (Yonelinas & Jacoby, 1995), probabilities for correct Know judgments and false alarms with Know responses were estimated respectively using the following formulae: $pc(\text{Hits-Know}) = p(\text{Hits-Know}) / (1 - p(\text{Hits-Remember}))$ and $pc(\text{False alarms-Know}) = p(\text{False alarms-Know}) / (1 - p(\text{False alarms-Remember}))$ (Stanislaw & Todorov, 1999). All groups showed Pr values that differed reliably from 0, as assessed by one-sample t-tests. t-tests were ran on each discrimination index (Pr(R) and Pr(K)) separately, given that R and K judgments are assumed to depend on independent processes (Yonelinas & Jacoby, 1995). The discrimination index for Remember responses was found to be higher for young adults compared to older adults [$t(37) = 3.45 ; p < .01$]. A similar analysis of the discrimination index for Know responses did not show any significant age group difference [$t(37) = 1.82 ; p = .08$].

Additionally, in order to determine whether the higher false alarm rates for Remember responses in the older group could be due to differences in decision criteria, we also performed analyses on response bias estimates (Br) for Remember and Know responses. They were computed respectively by using the following formulae: $Br(\text{Remember}) = p(\text{False alarms-Remember}) / (1 - (p(\text{Hits-Remember}) - p(\text{False alarms-Remember})))$ and $Br(\text{Know}) = p(\text{False alarms-Know}) / (1 - (p(\text{Hits-Know}) - p(\text{False alarms-Know})))$. A t-test comparing the Br for Remember judgments between age groups indicated that older adults showed a more liberal decision criterion to produce Remember responses than young adults [$t(37) = -2.61 ; p < .05$]. This finding suggests that the higher false alarm rate in the older group may be due to their more liberal response bias. By contrast, for the response bias for Know responses, no age group difference was found [$t(37) = -1.46 ; p = .15$]. Finally, we analysed whether reaction times differed as a function of age. Reaction times for Correct Rejections did not differ reliably between the two age groups [$t(37) = -0.52 ; p = .60$]. When comparing reaction times for correct Remember responses between age groups, no differences were found [$t(37) = -0.62 ; p = .54$]. The same comparison for Know responses indicated no age differences either [$t(37) = 0.42 ; p = .68$].

[Please insert table 2 around here]

fMRI results

As described above, we examined: (1) subsequent recollection-related and subsequent familiarity-related memory effects common to young and older groups; and (2) age-related differences in the subsequent recollection-related and subsequent familiarity-related memory effects.

Effects common to both groups

Recollection

Analyses revealed few regions exhibiting greater activity at encoding for subsequent Hits-Remember than subsequent Hits-Know for both younger and older adults. These areas included the right inferior frontal gyrus and the presupplementary motor area (pre-SMA) (see Table 3).

[Please insert table 3 around here]

[Please insert figure 1 around here]

Familiarity

When looking at regions exhibiting greater activity for subsequent Hits-Know than subsequent Miss, no significant activation was found.

Age-related differences

Recollection

The comparison of subsequent recollection memory effects between age groups revealed differences in several regions (see Table 4). Bilateral inferior frontal regions showed greater activity for subsequent Hits-Remember than Hits-Know in the young group compared to the older group. We also found greater activity in the young group in the left middle temporal gyrus (see Figure 2). On the contrary, other regions in right frontal (middle frontal gyrus and superior frontal gyrus) and right temporal (superior temporal gyrus at the temporoparietal junction, TPJ) areas and in the right middle cingulate gyrus as well as in the left and right precuneus exhibited greater activity for subsequent recollection-related memory effects in older adults compared to young adults (see Figure 3). Given that activation in the precuneus (MNI coordinate: 10, -58, 30) was the only one that survived the FWE correction and to explore the significance of these differences in recollection-related encoding activations in favour of the older group, we computed the correlations between the activity in the different significant regions of the precuneus (MNI coordinates: 10, -58, 30; 4, -66, 32 and -6, -76, 36. See Table 4) and the Pr(Remember) in this condition. To account for multiple comparisons, a Bonferroni correction was applied to the alpha value, which was calculated at $.05/6=.0083$. It appears that one area in the right precuneus (MNI coordinate: 4, -66, 32) was negatively correlated with the accuracy of Remember responses in the young group ($r=-0.58$, $p<.0083$) while it showed no significant correlation with memory performance in older adults ($r=-0.11$ $p=.66$). However, a comparison of the two correlations failed to show any significant difference between the two ($p=.061$).

[Please insert figure 2 around here]

[Please insert figure 3 around here]

[Please insert table 4 around here]

Familiarity

The comparison of subsequent familiarity memory effects between age groups revealed some differences, with greater activations for subsequent Hits-Know than subsequent Miss in the young group compared to the older group (see Table 5). Those were found in the left superior frontal gyrus, in the right posterior hippocampus and in the right intraparietal sulcus (IPS, see Figure 4). There was no greater activation in the older group in comparison to the young group.

[Please insert figure 4 around here]

[Please insert table 5 around here]

Discussion

The aim of this study was to look into the neuronal underpinning of episodic memory following incidental encoding of items subsequently leading to recollection or to familiarity during recognition and to examine age-related differences in brain activity associated with recollection and familiarity processes as measured using the Remember-Know paradigm.

The behavioural results indicate that the accuracy of older adults is impaired for recollection processes compared to young adults, but not for familiarity processes. Such results are consistent with a rich literature showing that ageing impairs recollection processes more than familiarity processes (e.g. Bastin & Van der Linden, 2003; Bugajska et al., 2007; Davidson & Glisky, 2002). It has been suggested that decreased recollection abilities in ageing may partly stem from impoverished encoding operations (e.g., Perfect & Dasgupta, 1997), such as less efficient binding and less self-initiated strategic processes. Interestingly, older adults produced more errors in their Remember judgments than young adults. This finding resonates well with the observation of elevated illusory recollections in old age (e.g., Dodson, Bawa, & Krueger, 2007; Dodson, Bawa, & Slotnick, 2007; Fandakova et al., 2013; Shing et al., 2011; Shing, Werkle-Bergner, Li, & Lindenberger, 2009; Wilson et al., 2006). Older adults' tendency to produce this kind of false memories may have resulted from a reduced distinctiveness of memory traces (Li, Brehmer, Shing, Werkle-Bergner, & Lindenberger, 2006; Shing et al., 2011), in combination with less efficient strategic support at retrieval (Fandakova et al., 2013). The examination of the effect of age on the brain regions involved during the encoding of items that are subsequently recollected or judged familiar should inform about the putative encoding mechanisms that are most affected.

With regard to the fMRI results, the main findings were the following. First, activation common to both age groups for subsequent recollection involved areas, such as the inferior frontal cortex and the pre-SMA, which are often found in the literature (see Kim, 2011, for a review). For subsequent familiarity, no common activation was found. Second, in ageing, we observed decreased subsequent recollection-related effect at encoding in inferior frontal regions bilaterally and in left temporal regions as well as increased activity in the right middle and superior frontal gyri, the right superior temporal gyrus, the right middle cingulate gyrus and the precuneus bilaterally in comparison with young adults. While one of these areas in the right precuneus was negatively correlated to performance in young adults, it did not correlate with

performance in older adults (note however that there appears to be no significant difference between the two correlations). Finally, for subsequent familiarity-related activations, increased activations were found in the left superior frontal gyrus, in the right posterior hippocampus and in the right inferior parietal cortex in young, but not older, adults.

Common fMRI effects

Amongst the regions showing activations associated with subsequent recollection was the right inferior frontal gyrus, which is consistent with the literature focusing on the SME. Indeed, inferior frontal activations in young adults are mostly left-lateralized (Duverne et al., 2009). But even though right-lateralized inferior frontal activations are more frequent in older adults (Duverne et al., 2009; Kwon et al., 2016; Morcom et al., 2003), they are not unheard of in young individuals, especially when pictorial materials are used (Kim, 2011). The inferior frontal cortex is thought to be involved in modulating other brain regions' activations during the processing of stimuli (Kirchhoff, Wagner, Maril, & Stern, 2000) as well as in controlled semantic retrieval and elaboration (Kim, 2011; Wagner et al., 1998). Indeed, the inferior frontal cortex seems to be more active during deep, semantic encoding than during shallow encoding (Kim, 2011), suggesting that a deep processing is required in order to subsequently make a recollection-based recognition. We also found pre-SMA activations common to both age groups for items leading to subsequent recollection. Although pre-SMA activations have been reported in the SME literature (see for instance Kim, 2011), the role of this area in memory encoding was hardly ever discussed thoroughly and remains unclear. Nevertheless, Liu and colleagues (2014) suggested it might be involved when more resources are necessary to perform a particular task. Based on this interpretation, we can speculate that the pre-SMA activations in this study could arise from a more effortful -although not intentionally so, given the incidental nature of our memory encoding task- form of encoding.

With regard to encoding activity leading to familiarity, we did not find activation common to both age groups.

Age differences in fMRI subsequent recollection memory effects

First, many regions showed a greater subsequent recollection-related activity in younger adults. In frontal regions, such activations were found in the bilateral (although mainly left-lateralized) inferior frontal gyrus. As specifically stated earlier, those activations are thought to underlie semantic processing (Kim, 2011). Furthermore, right inferior frontal gyrus activations have been reliably found in encoding tasks using pictorial items, in addition to activations in the left inferior frontal gyrus (Kim, 2011; Kwon et al., 2016). As already mentioned in the introduction, Morcom et al. (2003) had also found right inferior frontal gyrus activations but those were restricted to their older participants. Also, their task used verbal rather than pictorial materials. In temporal regions, young participants showed greater activity in the left anterior middle temporal gyrus. The anterior temporal lobes are thought to store semantic representations from all modalities, and its activity appears to be sensitive to the number of meanings retrieved (Jefferies, 2013). Therefore, this more distributed pattern of activity in frontal and temporal regions suggests that for young adults, at encoding, subsequent

recollection ability relies on a deeper processing of, as well as on a greater number of information processed for the subsequently recollected items. It is consistent with findings showing that even if recollection is subjectively intact in older adults, it is impoverished compared to young adults when using more objective measures at retrieval (Duarte, Henson, & Graham, 2008; Johnson, Nessler, & Friedman, 2013). This could at least partially stem from the fact that the items leading to recollection are simply less deeply processed at encoding in old adults (even though this processing is sufficient to yield a subsequent recollection-based response). Indeed, evidence consistent with our results suggest that older adults spontaneously perform less elaborative encoding than young adults (Coane, 2013; Craik & Rose, 2012).

Interestingly, some regions demonstrated greater subsequent recollection-related activations in older adults, in line with studies showing greater activations in older adults (e.g. Reuter-Lorenz, 2002; Reuter-Lorenz, 2013). Those areas included the right middle and superior frontal gyri, the right middle cingulate gyrus, the right superior temporal gyrus as well as the precuneus bilaterally.

Concerning activations in the precuneus and in the superior temporal gyrus around the TPJ, those regions are often associated with the DMN (i.e. Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). Although the DMN is often seen as a task-negative network and was linked to subsequent forgetting in young adults (Kim, 2011), neuronal networks are thought to be less specialised in the older population (Turner & Spreng, 2015). An attenuated deactivation of the DMN is often seen in older adults when performing a task, especially when the cognitive load is high (Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). More precisely, this attenuated deactivation of the DMN was also found during memory encoding tasks (Mattson et al., 2014, de Chastelaine et al., 2015). Turner and Spreng (2015) even hypothesised the existence of a frontoparietal and default mode networks coupling in older adults, whereas it is better segregated in young participants. Thus, the DMN activations found here could be indicative of the reduced efficiency of the frontoparietal network in the old group. Our results show that one area in the right precuneus (MNI coordinate: 4, -66, 32) was negatively correlated with performance in younger adults while it showed no significant correlation with performance in older adults. Nevertheless, no significant difference was observed between the two correlations, these results can be tentatively interpreted in the light of works showing age-related changes in the default-mode network (Spreng, 2012; Spreng & Schacter, 2012). For instance, Turner & Spreng (2015) found a reduced suppression of the precuneus, a core DMN region, during a task requiring prefrontal engagement, in older adults. However, due to methodological issues, they were not able to determine whether or not this activation was deleterious to performance. Our analyses suggest that a decreased suppression of the precuneus impaired performance in young adults, while it did not significantly influence performance in older adults (or at least not as much as for young adults). An explanation could be that successful encoding leading to subsequent recollection does not depend on the same strategies in young and older adults, hence the differences in activations. Some studies have found that the recruitment of the DMN could support the task at hand under particular circumstances (Spreng et al., 2014), which could be the case here. Indeed, older adults' recollective experience is often shown to be less rich when compared to that of young adults. Additionally, they have been found to report more emotional

reactions than contextual information when exhibiting recollection of a scene (Comblain, D'Argembeau, Van der Linden, & Aldenhoff, 2004). The precuneus activation found in this study could reflect the fact that older adults rely more on self-referential appraisal of stimuli at encoding in order to later perform recollection, in contrast to young adults who engage more into semantic and relational elaboration, and for whom performance might be negatively correlated with precuneus activation because it is associated with more mind-wandering and thus less focusing on the task, leading to a poorer memory performance. Therefore, in addition to favouring different neuronal networks and strategies, both age group might also benefit differently from them and what appears deleterious for one could well be better suited for the other. However, this observation could be specific to the design used here, as Dulas & Duarte (2014) found self-referencing processes to be deleterious for subsequent memory performance in older adults using a source memory paradigm. Indeed, while more internal cues for recollection are valid in a RK paradigm, it is not the case for a source memory paradigm. As the experimental design was not build up to answer the question of age-specific encoding strategies, the data at hand do not allow us to do much more than to emit hypotheses that need confirmation in future studies specifically built-up to respond these questions. More precisely, future studies should assess the nature of information that is processed and generated at encoding by young versus older adults, for instance via a think-aloud paradigm (Lampinen, Meier, Arnal, & Leding, 2005) in order to test the hypothesis that older participants encode qualitatively different information compared to young adults.

Finally, the contrast between old and young adults concerning recollection-related activation also revealed increased activity in the right middle and superior frontal gyri in the older group. Those activations mirror those found in the contralateral hemisphere in younger adults. Such a pattern of supplementary activations appearing in the contralateral hemisphere in older adults when compared to young adults is frequent in neuroimaging studies of ageing - in the SME literature for example, supplementary right frontal activations are often found in older adults (Duverne et al., 2009; Morcom et al., 2003) in addition to the left frontal activations found in young adults- and was formalised in the HAROLD (Hemispheric Asymmetry Reduction in Older Adults) model (Cabeza, 2002). According to this model, this kind of activation in older adults can be the result of a compensation mechanism. However, in this study, activations in contralateral areas did not correlate with performance in the older group. These activations could still be interpreted as attempted compensation, meaning neuronal compensation that is not able to lead to a non-deficient behavioural performance (Cabeza & Dennis, 2012). An alternative explanation is that they could be attributed to a dedifferentiation mechanism, through which the ageing brain undergoes a decrease in the specificity of its neuronal responses (e.g. Bäckman et al., 2006; Cabeza, 2002; Grady, 2012; Li et al., 2001, 2006; Park et al., 2004; Reuter-Lorenz & Park, 2010). However, the data at hand do not allow us to favour one hypothesis over the other.

Age differences in subsequent familiarity effects

A few regions demonstrated a subsequent familiarity-related effect greater for young adults. Indeed, increased activity (in comparison with older participants) was found in the left superior frontal gyrus at the frontal eye field (FEF), as well as in the right IPS. Those regions are part of the dorsal frontoparietal attention system (Corbetta, Patel, & Shulman, 2008; Petersen & Posner, 2012), which acts as a top-down control mechanism of attention. This network is thought to regulate attention during encoding (Kim, 2011). We also found greater activations in the right posterior hippocampus in young participants compared to older ones. In the literature, subsequent recollection-related activation at encoding is often associated with anterior hippocampal activations (de Vanssay-Maigne et al., 2011; Uncapher & Rugg, 2005), while subsequent familiarity-related activation at encoding is more frequently linked with right extrahippocampal regions (de Vanssay-Maigne et al., 2011; Uncapher & Rugg, 2005). Some work however suggested that both recollection and familiarity can activate the hippocampus if one considers the two functions as different levels of memory strength (Wais, Mickes, & Wixted, 2008; Song, Jeneson, & Squire, 2011). According to this view, the current result may indicate that young adults engaged into encoding processes that made the memory trace stronger (and thus induced greater hippocampal activation) than the one formed by older adults.

Limitations

A limitation of this study lies in the smaller number of Remember judgments in older compared to young adults. As raised by several authors (Angel et al., 2013; Morcom et al., 2003), between-group differences in the pattern of brain activation could be attributed to age but also to differential memory performance. The smaller number of Remember responses contributing to the average brain activations could lead to a more variable brain activation and thus a poorer chance of showing a reliable activation in older adults. Therefore, the difference of activation towards young adults could have been overestimated. Then, findings of reduced brain activity should be interpreted with caution. However, we should note that we ran a complementary analysis controlling for performance, using Pr(R) as a covariate. The results remain mostly unchanged, with modifications in cluster sizes and Z scores, as well as the loss of a left anterior temporal region in young adults. This region is currently interpreted as adding to the semantic processing already supported by inferior frontal regions.

Furthermore, when looking at the results altogether, it seems that young adults engaged regions that allow a deeper processing of the stimuli at encoding than older adults did. Interestingly, this was the case for both items that were later recollected and for items that were subsequently judged as familiar. In other words, when older adults reported that they recollected or found familiar some item, it may be the case that the actual memory trace leading to such judgement was qualitatively different from that built by young adults. This raises the question of what criterion one uses to decide that retrieved information qualifies for a Remember or a Know judgments, and how this criterion changes with age. This illustrates a limitation of using a subjective measure of recollection and familiarity. Indeed, when not using, for instance, oral reports for each response (see Comblain et al., 2004), it is impossible to determine whether each age group base their response on a similar decision criterion. However, one can easily grasp the

difficulty and inadequacy of implementing such reports when the recognition phase is done in an MRI environment.

This leads to another limitation of our study, which is the use of a dichotomous measure of recollection and familiarity. Indeed, studies (e.g. Brown & Bodner, 2011) suggest that Remember and Know judgements are not necessarily mutually exclusive, so that some level of overlap can be found between the two. One recommendation (Brown & Bodner, 2011) to avoid this pitfall is to use independent ratings for both measures instead of asking for a binary response, which could be done in a study used to specifically assess the neuronal correlates of encoding.

Conclusion

To conclude, this study suggests that, despite some age invariances, subsequent recollection-related and familiarity-related activations found at encoding using the Remember/Know procedure differ both according to age group. More specifically, it seems that regions involved in semantic processing are recruited to a greater extent in young adults, suggesting that the qualitatively impoverished recollection sometimes found in older adults might depend on a failure to implement efficient elaboration processes at encoding. Furthermore, greater DMN activations were found at encoding in older adults for recollection-related items and did not seem deleterious for their later memory performance. This may reflect the fact that qualitatively different encoding strategies can allow subsequent recollection, and various age-groups differ in the extent to which they privilege one or another. While young adults more often engage in semantic and relational elaboration, older adults might rely more on self-referential and/or emotional encoding. Even though the strategies mostly employed by older adults appear less efficient, as evidenced by the age-related poorer recollective experience, they are still good enough to allow them to make some correct recollection judgements. However, it might also be the case that young and older adults base their recollection and familiarity judgments on different criteria, therefore explaining, at least partly, how different neuronal activations and, supposedly, strategies at encoding can result on a seemingly similar memory judgment in the end.

Finally, we would like to underline the fact that these interpretations should remain cautious as our experimental design does not allow us to draw definitive conclusions. However, this study provides results that could be used to elaborate testable hypotheses for later, more controlled studies as more data would be needed in order to buttress the suggestions raised by this study.

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Tables

Table 1: Participants' characteristics. Mean (standard deviation) age, education, vocabulary (Mill Hill), Beck Depression Inventory (BDI) and Mattis Dementia Rating Scale (for older group only).

	Young (N=20)	Older (N=19)	t(37)
Age	25.4 (3.0)	67.8 (5.3)	
Education	16.3 (2.4)	14.3 (2.3)	2.66*
Mill Hill	27.1 (2.9)	29.1 (4.1)	-1.59
BDI	5.35 (3.77)	7.74 (6.04)	-1.49
Mattis	-	141.1 (2.2)	-

*p<0.05

Table 2: Behavioral performance. Response rates for studied and unstudied items according to response type (Remember, Know, New, standard deviations in parentheses), discrimination index and response bias for Remember and Know responses (standard deviations in parentheses) and mean reaction times for studied and unstudied items according to response type (Remember, Know, New, standard deviations in parentheses).

	Young	Older	t-test results
Response Rates			
Studied items			
Remember (Hits)	.40 (.15)	.28 (.12)	p < .01
Know (Hits)	.40 (.15)	.47 (.14)	NS
New (Omissions)	.20 (.08)	.25 (.08)	NS
Unstudied items			
Remember (False alarms)	.01 (.01)	.04 (.05)	p < .01
Know (False alarms)	.07 (.04)	.13 (.10)	p < .05
New (Correct Rejections)	.92 (.05)	.82 (.15)	p < .01
Performance Indices			
Discrimination Index			
Pr (Remember)	.39 (.15)	.24 (.13)	p < .01
Pr (Know)	.59 (.12)	.50 (.18)	NS
Response Bias			
Br (Remember)	.02 (.02)	.07 (.09)	p < .05
Br (Know)	.15 (.13)	.73 (1.78)	NS
Reaction Times			
Studied items			
Remember (Hits)	1510.75 (248.74)	1578.00 (414.70)	NS
Know (Hits)	1710.75 (248.74)	1666.53 (383.54)	NS
New (Omissions)	1603.30 (309.59)	1595.37 (396.93)	NS
Unstudied items			
Remember (False alarms)	1396.50 (337.80)	1687.14 (751.98)	NS
Know (False alarms)	1829.40 (444.38)	1835.80 (543.27)	NS
New (Correct Rejections)	1342.65 (239.00)	1386.16 (297.06)	NS
Note: standard deviations in parentheses. $Pr(\text{Remember}) = p(\text{Hits-Remember}) - p(\text{false-alarms-Remember})$ $Pr(\text{Know}) = pc(\text{Hits-Know}) - pc(\text{false-alarms-Know})$ $Br(\text{Remember}) = p(\text{false-alarms-Remember}) / (1 - (p(\text{Hits-Remember}) - p(\text{false-alarms-Remember})))$ $Br(\text{Know}) = p(\text{false-alarms-know}) / (1 - (p(\text{Hits-Know}) - p(\text{false-alarms-know})))$			

L/R	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
Conjunction analysis between young and older adults, with inclusive mask at $p < 0.001$							
R	Inferior frontal gyrus, opercular part	52	12	32	30	4.81	<.03*
R	Inferior frontal gyrus, triangular part	46	30	18	18	4.39	<.001
L	Presupplementary motor area	-2	24	46	11	4.81	<.03*
		-2	24	40	79	4.25	<.001

Table 3: Regions showing subsequent recollection memory effects common to both age groups at a voxel p-value of <.001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 2; * $p < 0.05$ FWE-corrected

Table 4: Regions showing age-related differences in subsequent recollection effects at a voxel p value < .001 uncorrected.

L/R	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
Young>older participants							
L	Inferior frontal gyrus, orbital and triangular part	-52	28	22	19	3.61	<.001
		-50	32	10	26	3.52	<.001
		-36	34	-16	23	3.4	<.001
R	Inferior frontal gyrus, opercular part	38	-2	20	38	3.65	<.001
		40	8	28		3.5	<.001
L	Middle temporal gyrus	-38	0	-24	19	3.62	<.001
Older>young participants							
R	Middle frontal gyrus	38	22	44	38	3.97	<.001
		26	50	2	31	3.76	<.001
L	Superior frontal gyrus, dorsolateral	-26	26	36	25	3.77	<.001
R	Superior frontal gyrus, dorsolateral	18	28	40	33	3.71	<.001
R	Middle cingulate and paracingulate gyri	14	-26	44	40	3.61	<.001
R	Superior temporal gyrus	52	-44	22	132	3.83	<.001
L&R	Precuneus	10	-58	30	1784	4.7	<.044*
		4	-66	32		4.45	<.001
		-6	-76	36		4.38	<.001

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 1; * $p < 0.05$ FWE-corrected

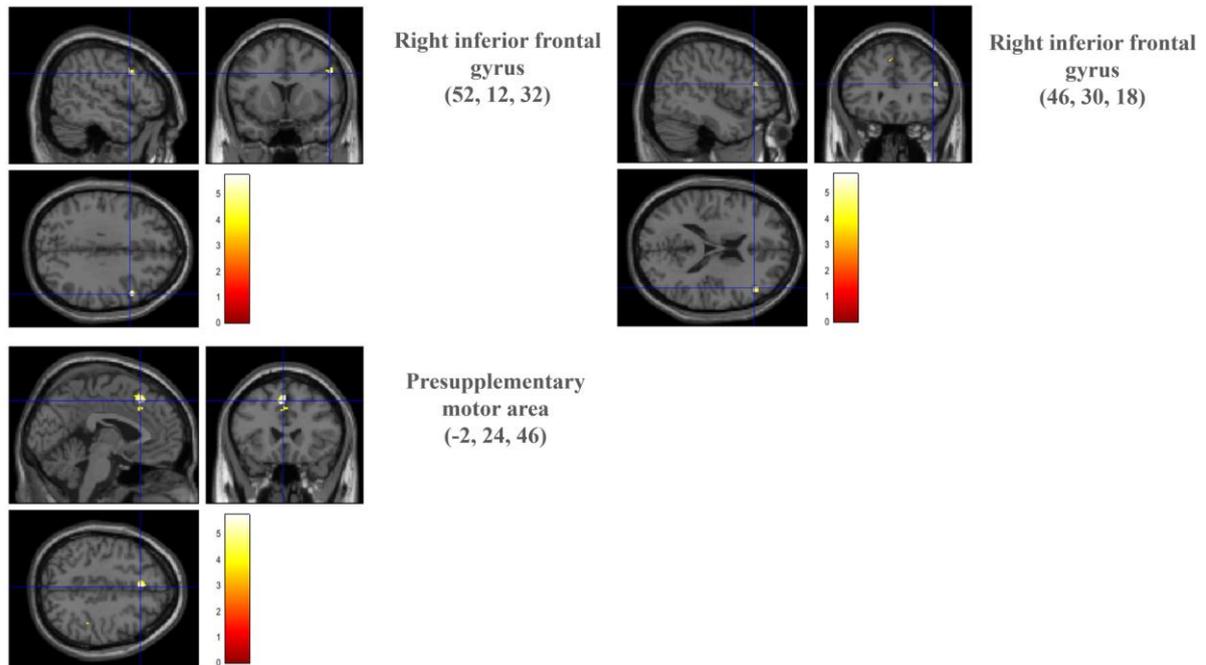
Table 5: Regions showing age-related differences in subsequent familiarity effects at a voxel p value < .001 uncorrected.

L/R	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
Young>older participants							
L	Superior frontal gyrus, dorsolateral and medial	-10	4	60	28	3.53	<.001
		-6	12	62		3.14	<.001
R	Hippocampus	32	-32	4	21	3.81	<.001
R	Inferior parietal cortex	26	-50	50	23	3.66	<.001
Older>young participants							
None							

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). Cluster size min = 1

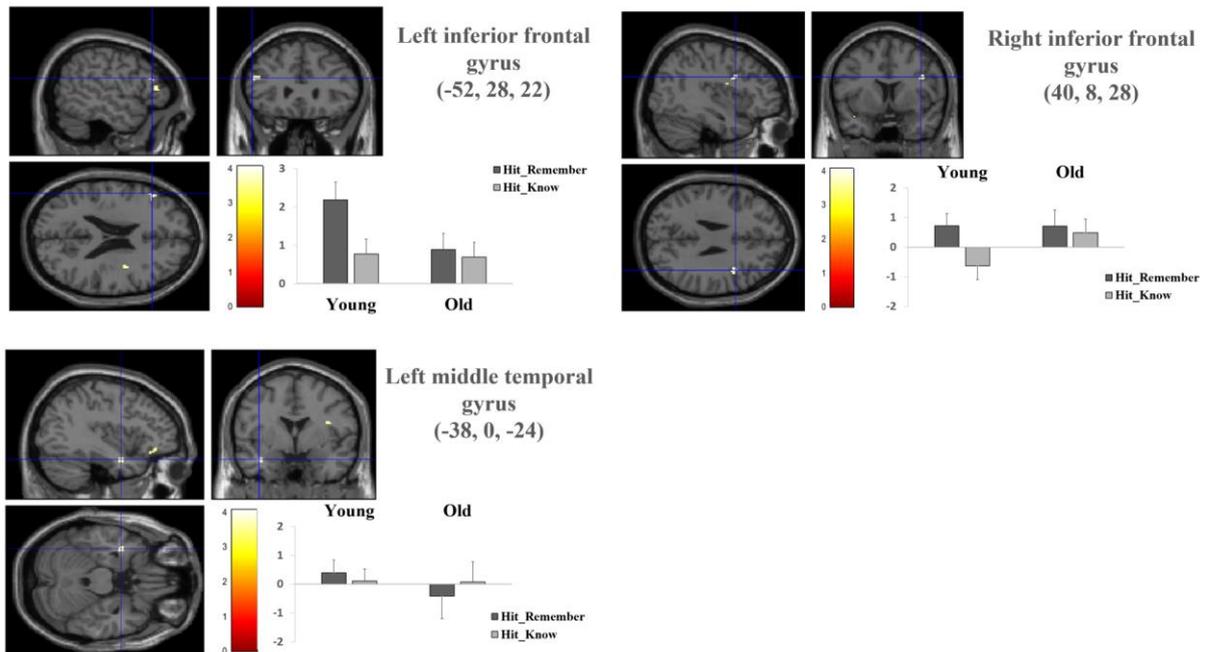
Figures

Figure 1: Regions showing a recollection effect (Hits-R > Hits-K) common to both age groups.



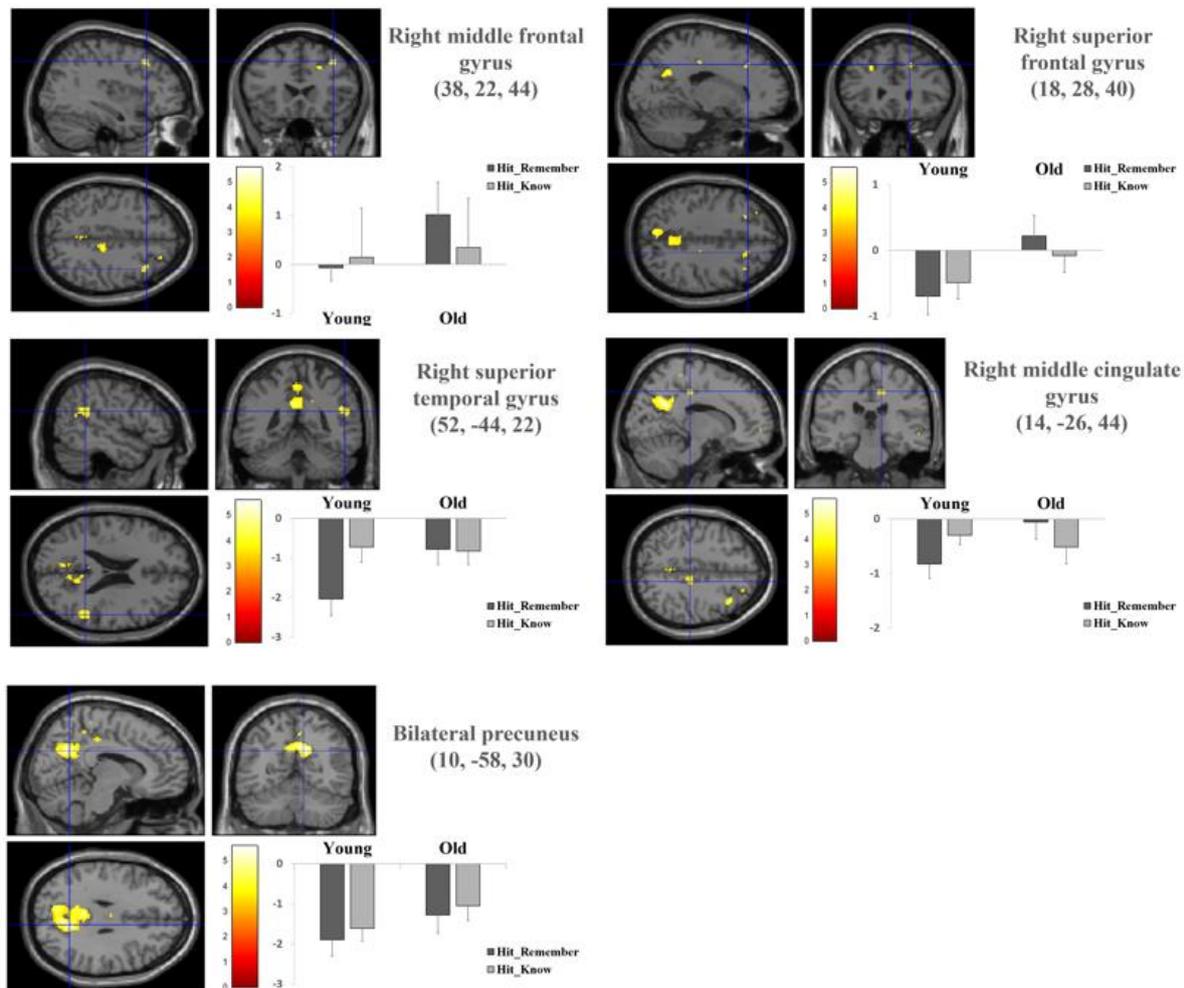
The regions are displayed on the MNI template. See Table 3 for coordinates.

Figure 2: Regions showing a difference in recollection effect (Hits-R > Hits-K) in favour of the young group. Bars represent standard errors.



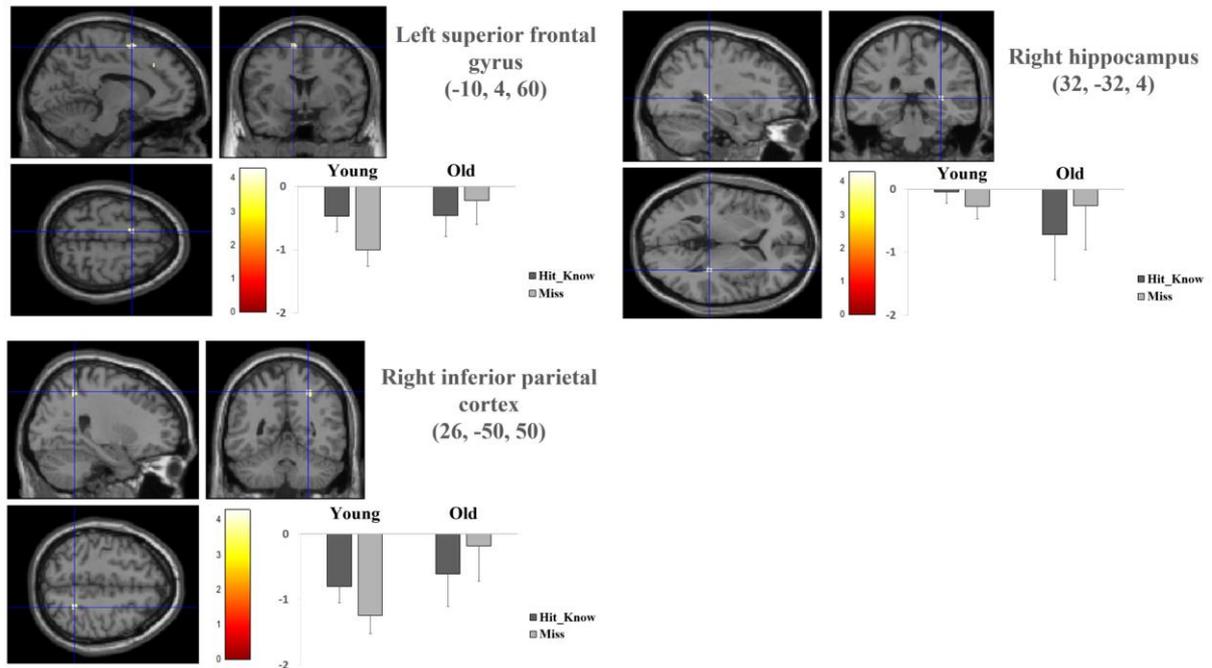
The regions are displayed on the MNI template. See Table 4 for coordinates. Young: beta estimates in young adults; Old: beta estimates in older adults; Hit_Remember: beta estimates at encoding for items (from the Hard condition only) leading, at recognition, to a Hit Remember response; Hit_Know: beta estimates at encoding for items (from the Hard condition only) leading, at recognition, to a Hit Know response.

Figure 3: Regions showing a difference in recollection effect (Hits-R > Hits-K) in favour of the old group.
Bars represent standard errors



The regions are displayed on the MNI template. See Table 4 for coordinates. Young: beta estimates in young adults; Old: beta estimates in older adults; Hit_Remember: beta estimates at encoding for items (from the Hard condition only) leading, at recognition, to a Hit Remember response; Hit_Know: beta estimates at encoding for items (from the Hard condition only) leading, at recognition, to a Hit Know response.

Figure 4: Regions showing a difference in familiarity effect (Hits-K > Hits-N) in favour of the young group. Bars represent standard errors



The regions are displayed on the MNI template. See Table 5 for coordinates. Young: beta estimates in young adults; Old: beta estimates in older adults; Hit_Know: beta estimates at encoding for items (from the Hard condition only) leading, at recognition, to a Hit Know response; Miss: beta estimates at encoding for items (from the Hard condition only) leading, at recognition, to a Miss response.