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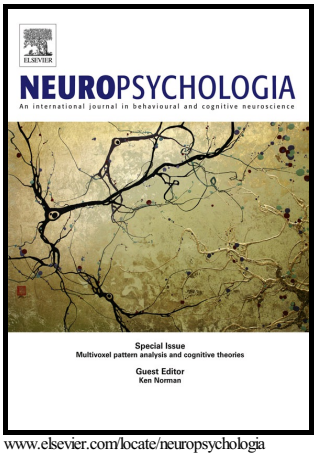

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Age-related changes in the relationship between visual exploration and hippocampal activity

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Abstract

Deciphering the mechanisms underlying age-related memory declines remains an important goal in cognitive neuroscience. Recently, we observed that visual sampling behavior predicted activity within the hippocampus, a region critical for memory. In younger adults, increases in the number of gaze fixations were associated with increases in hippocampal activity (Liu, Shen, Olsen, Ryan, 2017. Visual Sampling Predicts Hippocampal Activity. J. Neurosci. 37, 599–609). This finding suggests a close coupling between the oculomotor and memory system. However, the extent to which this coupling is altered with aging has not been investigated. In this study, we gave older adults the same face processing task used in Liu et al. (2017) and compared their visual exploration behavior and neural activation in the hippocampus and the fusiform face area (FFA) to those of younger adults. Compared to younger adults, older adults showed an increase in visual exploration as indexed by the number of gaze fixations. However, the relationship between visual exploration and neural responses in the hippocampus and FFA was weaker than that of younger adults. Older adults also showed weaker responses to novel faces and a smaller repetition suppression effect in the hippocampus and FFA compared to younger adults. All together, this study provides novel evidence that the capacity to bind visually sampled information, in real-time, into coherent representations along the ventral visual stream and the medial temporal lobe declines with aging.

Keywords: fMRI, visual exploration, eyetracking, memory, face processing, hippocampus, neuroimaging

1. Introduction

Eye movements are important for the development of memory representations (Castelhano et al., 2009; Castelhano and Henderson, 2005; Foulsham and Kingstone, 2013), and visual exploration is related to functional activity in the hippocampus (Liu et al., 2017; Voss et al., 2017; Wirth et al., 2017). Previous studies have shown that the number of gaze fixations made to a visual stimulus predicts subsequent memory for that stimulus (Chan et al., 2011; Loftus, 1972; Olsen et al., 2016), and the restriction of gaze fixations through experimental instructions during either encoding or retrieval impairs memory, when compared to free viewing conditions (Henderson et al., 2005; R. Johansson et al., 2012; Johansson and Johansson, 2014). At a neural level, the hippocampus (HPC) is critical for the formation of memories that include information regarding the relations among distinct items (Davachi, 2006; Eichenbaum and Cohen, 2014; Olsen et al., 2012), and patterns of visual exploration are influenced by HPC-dependent memory representations (Hannula et al., 2010; Olsen et al., 2015; Ryan et al., 2007a). We have recently shown that, in younger adults, the number of gaze fixations made during viewing of novel stimuli was associated with activation in the HPC (Liu et al., 2017). Moreover, an increased number of gaze fixations made during viewing of novel stimuli was associated with larger decreases in neural responses in HPC upon subsequent presentations of the same stimuli (i.e., *repetition suppression*). Greater HPC activation is often observed for novel compared to repeated stimuli, and this repetition suppression effect has been frequently used as an indicator of the development of a lasting representation (Kremers et al., 2014; Kumaran and Maguire, 2009, 2007; Suzuki et al., 2011a, 2011b; Vannini et al., 2013). All together, these results suggested that visual exploration and HPC binding processes are inherently linked during the formation of memory representations (Liu et al., 2017; Voss et al., 2017). Specifically, as visual information is

acquired during sequences of gaze fixations, the hippocampus may be needed to bind visual features and their spatial and temporal relations in real time. The resulting coherent memory representation can then be used to influence ongoing visual exploration of the external world (Liu et al., 2017; Voss et al., 2017; Hannula et al., 2010; Ryan & Cohen, 2004).

Aging disproportionately affects HPC-dependent relational memory (also termed *associative memory* in the aging literature; see Grady & Ryan, 2017, for review; Old and Naveh-Benjamin, 2008a, 2008b). Compared to younger adults, older adults often demonstrate impaired performance on tasks such as free recall, cued recall, and recognition (Craik and Rose, 2012; Drag and Bieliauskas, 2010; Old and Naveh-Benjamin, 2008a; Park and Reuter-Lorenz, 2009; Schaie and Willis, 2015; Shing, 2010; Uttl, 2011). Aging is associated with structural changes and/or functional declines in the HPC and broader medial temporal lobe (MTL; Olsen et al., 2017; Park and Reuter-Lorenz, 2009; Grady, 2012; Lustig and Lin, 2016; Grady and Ryan, 2017; Bettio et al., 2017), including over-recruitment or under-recruitment of the HPC compared to younger adults, depending on the task or nature of performance (see Grady & Ryan, 2017 for review). Older adults have also shown alterations in patterns of visual exploration that are indicative of a relational memory deficit, similar to what has been observed in amnesic cases who have HPC/MTL compromise (Ryan et al., 2007b). Additionally, older adults typically execute more gaze fixations, relative to younger adults, during viewing of visual stimuli (Boutet et al., 2015; Firestone et al., 2007; Heisz and Ryan, 2011). Despite the extensive literature describing how aging is typically associated with declines in memory as well as a separate body of work showing changes in visual exploration behaviour with age, the link between visual exploration and HPC function has only been examined in younger adults. The extent to which this relationship is affected by aging is currently unknown, however, current evidence points to

changes in HPC structure and function with aging that may be linked to, or reflected in, changes in visual exploration behavior.

In the current study, we examined the influence of aging on the relationship between visual exploration and HPC activity using combined eyetracking-fMRI recordings and the same visual processing task as in (Liu et al., 2017). We compared the findings from a group of older adults with those from their younger counterparts, as previously reported in (Liu et al., 2017). Participants were shown novel and repeated face stimuli and were asked to perform an age judgement task while viewing the faces. As in our previous work, neural responses were interrogated in the HPC, and in the fusiform face area (FFA) given that faces were used as stimuli (Kanwisher et al., 1997). Additionally, since aging is often associated with atrophy in the HPC (Jack et al., 2000, 1998, 1997; Petersen et al., 2000; Scahill et al., 2003; Šimić et al., 1997), we explored whether age-related changes in gaze fixations and associated neural responses were associated with age-related changes in the overall HPC volume.

Based on prior work, we expected that older adults would make more gaze fixations than younger adults (Boutet et al., 2015; Firestone et al., 2007; Heisz and Ryan, 2011; Olsen et al., 2015) and have smaller HPC volumes (Jack et al., 2000, 1998, 1997; Petersen et al., 2000; Scahill et al., 2003; Šimić et al., 1997). We further predicted that older adults would show weaker responses in the HPC and the FFA relative to younger adults during viewing of novel faces, based on prior research showing age-related declines in HPC responses to face stimuli (Fischer et al., 2010; Iidaka et al., 2002), and age-related declines in selectivity (or category specificity) for face stimuli in the FFA (Burianová et al., 2013; Grady et al., 1998).

The inclusion of repeated stimuli in the present design allowed us to examine any age-related changes in repetition suppression. The literature has robustly shown that repetition

suppression effects in the hippocampus are tightly coupled with subsequent memory, and therefore, can serve as a proxy measure of encoding success (Kremers et al., 2014; Kumaran and Maguire, 2009, 2009; Miller et al., 1991; Suzuki et al., 2011a, 2011b; Vannini et al., 2013). Using explicit memory encoding tasks, several studies have found that older adults with Alzheimer's disease or mild cognitive impairment show reduced repetition suppression in the MTL and/or visual perceptual regions, compared to healthy older adults (S. C. Johnson et al., 2008; Jurick et al., 2017; Pihlajamaki et al., 2008; Pihlajamäki et al., 2011; Yu et al., 2016). However, it is unclear whether similar declines are observed in healthy aging (MacDonald et al., 2015; Mitchell et al., 2010; Rand-Giovannetti et al., 2006; Schmitz et al., 2014).

Ultimately, the critical question here was whether, despite any observed changes in visual exploration, HPC volumes, and/or neural responses during viewing of novel or repeated stimuli, older adults express a similar relationship between visual exploration and neural activity as younger adults. We expected the relations between visual exploration and neural activity, including the relationship between gaze fixations during novel viewing and subsequent repetition suppression, to be significantly weaker in older adults. This would be suggestive of an age-related reduction in the online binding of visual information across gaze fixations, which may contribute to age-related deficits in visual memory that have been pervasively documented in the literature (Craik and Rose, 2012; Drag and Bieliauskas, 2010; Old and Naveh-Benjamin, 2008a; Park and Reuter-Lorenz, 2009; Schaie and Willis, 2015; Shing, 2010; Uttl, 2011). The extent to which the relationship between visual exploration and neural activity can be accounted for by changes in HPC volumes would further add to our comprehensive understanding of the underlying mechanisms that contribute to age-related changes in memory.

2. Methods

2.1. Participants

Twenty-one healthy older adults (12 females; age: *Mean* = 71.43 years, *SD* = 4.04 years; range = 64-79 years; education: *Mean* = 17.67 years, *SD* =3.54)) and 20 younger adults (8 females; age: *Mean* = 22.95 years, *SD* = 2.68 years; range = 19-28 years; education: *Mean* = 16.65 years, *SD* =2.43) with normal or corrected-to-normal vision participated in this study. The relationship between visual exploration and HPC/FFA responses for the younger adults was reported previously (Liu et al., 2017). Here, we compared findings from our previous sample of younger adults to a group of education-matched older adults. All participants were recruited from the Toronto community and reported having no neurological or psychological conditions. We also administered the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) to older adult participants (with one missing data). Consistent with participants' self-report, MMSE scores showed that older adult participants' cognitive function was in the normal range, *mean MMSE* = 29.1, *SD* = 1.17, range from 26 – 30 with only one participant having MMSE score of 26 (Crum et al., 1993; O'Bryant et al., 2008). All participants provided written informed consent and were compensated $50 for their participation. The study was approved by the Research Ethics Board at the Rotman Research Institute at Baycrest.

2.2. Procedure overview

The experimental design, procedures, and fMRI data preprocessing were identical to those reported in (Liu et al., 2017). For clarity, these details are repeated here.

2.2.1. Stimuli. One hundred and twenty color images of nonfamous faces (480 x 480 pixels) were used in this study (Figure 1). Half of the images were of female faces and half were of male faces. Face images were taken from a larger stimulus database that has been used in our

prior work (Heisz and Ryan, 2011; Ryan et al., 2007a). A single scrambled image of a face stimulus was used for the control condition (i.e., null trials; Figure 1). Stimuli were presented using a computer with a screen resolution of 1280×1024 pixels and refresh rate of 60 Hz (Dell, Round Rock, TX).

2.2.2. Task. Each trial began with a 2-second presentation of a fixation cross "+" against a gray background (Figure 1). Following the fixation cross, a face (image size: 5.75^{o} by 5.75^{o}) was presented for 4 seconds. Participants were asked to judge whether each face was younger or older than 35 years of age by pressing 1 (< 35 years old) or 2 (> 35 years) on a MRI-compatible response box. If the image was of a scrambled face (null event trial as a baseline control condition), participants were instructed to press 3. Participants were instructed to respond as quickly and accurately as possible.

Six blocks were presented, each containing 70 trials. Of the 70 trials, 20 trials were of novel faces (i.e., *novel* condition) and 14 trials were of scrambled images (*scrambled* condition). The remaining 36 trials contained repetitions of the 20 faces presented in the novel condition (*repetition* condition). Specifically, among the 20 faces, 4 were repeated once, 4 were repeated twice, and 8 were repeated three times. The remaining 4 novel faces were not repeated. The repetition of the 16 face images produced 36 trials (4 x 1 + 4 x 2 + 8 x 3 = 36) in the *repetition* condition. We then ordered these 36 trials such that in 16 trials (4 + 4 + 8 = 16) participants viewed faces that had been previously viewed once in the same block (*repetition1* condition), 12 trials (4 + 8 = 12) presented a face that had been previously viewed twice (*repetition2*), and 8 trials presented a face that had been previously viewed three times (*repetition3*) in the same block. For each block (i.e., fMRI run), the faces that were repeated and the number of repetitions per face were counterbalanced across the participants. Faces were counterbalanced by assigning

the 20 novel faces to ten "sets" of two faces (one female, one male), which were then assigned to different groups of images for the abovementioned repetition scheme (i.e., 4 x 1, 4 x 2, and 8 x 3) across participants. Therefore, different face images were repeated for different participants. This was done to ensure that any observed repetition effects were not due to face-specific features. Within each block, the 20 novel and 36 repeated face trials were also organized into seven "mini-blocks" (each containing 8 faces) such that novel faces were introduced throughout each block instead of clustered at the beginning of the blocks (see Johnson et al., 2008 for more details). The first three mini-blocks were used to establish multi-item presentations and allowed for the control of the lag between items. The final four mini-blocks contained equal numbers of 1st 2nd 3rd and 4th presentations. The mean lag between the 1st and 2nd, 2nd and 3rd, and 3rd and 4th presentation was 8.1, 7.9, and 8.0 face stimuli, respectively. Male and female faces were balanced within each face condition. Each scanning block lasted 7 minutes and 28.8s. The sequence of the face versus scrambled trials was optimized using Optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq/) to obtain adequate design efficiency (Dale, 1999). Due to apparatus malfunction, three participants in each age group completed only 5 out of the 6 scanning blocks.

2.2.3. Structural and functional MRI. A 3T Siemens MRI scanner with a standard 32-channel head coil was used to acquire MRI images. Head movements were minimized by inserting soft cushions into the head coil. For the structural MRI scan, T1-weighted high-resolution MRI volumes were obtained using a standard 3-dimensional MPRAGE (magnetization-prepared rapid-acquisition gradient echo) pulse sequence (160 slices; field of view (FOV) = 256 x 256 mm; 192 x 256 matrix; 1 mm isotropic resolution, TE/TR=2.63/2000 ms, flip angle = 9 degrees, and scan time = 386 s). For the functional MRI scan, blood

oxygenation level-development (BOLD) signal was assessed using T2*-weighted echo-planar imaging (EPI) acquisition procedure with 204 time points, TE = 27 ms, TR = 2200 ms, 3.5 mm slices (with 0.5 mm gap and a bottom-up interleaved order), and flip angle = 62° (FOV = 225 x 225 mm; 64 x 64 matrix, 2.3 x 2.3 mm in-plane resolution). The images were acquired in an oblique axial orientation parallel to the longitudinal axis of the hippocampus. T1-weighted image acquisition used the same slice orientation.

Stimuli were presented with Experiment Builder (SR Research), back-projected to a screen (projector resolution: 1280×1024), and viewed with a mirror mounted on the head coil. Responses were collected with an MRI-compatible response box.

2.2.4. Eyetracking. A MRI-compatible eyetracker (Eyelink 1000; SR Research Ltd., Mississauga, Ontario, Canada) with a sampling rate of 1000 Hz was used to monitor participants' eye movements in the MRI scanner. Calibration was done using the built-in Eyelink 9-point calibration procedure at the beginning of the experiment. Drift correction was performed between trials when necessary to ensure tracking accuracy. Fixations and saccades were categorized using Eyelink's default eye movement event parser. Specifically, a velocity threshold of 30 degrees/second and acceleration threshold of 8000 degrees/second were used to classify saccades. Blinks were defined when pupil signal was missing or severely distorted by eyelid occlusion. Events not defined as saccades or blinks were classified as fixations.

2.2.5. Eye movement measures. Eye movement data from the Eyelink eyetracker (i.e., in EDF file format) was read into Matlab (MathWorks, Natick, MA) using freely available toolboxes (edfimport toolbox: http://kobi.nat.uni-magdeburg.de/edfImport and iTrack toolbox: https://github.com/jashubbard/iTrack) and custom Matlab scripts. For each trial, the number of

gaze fixations was counted during the time window in which the face stimuli were on the screen (i.e., 4 s).

2.2.6. fMRI data preprocessing. SPM8 (Statistical Parametric Mapping, Welcome Trust Center for Neuroimaging, University College London, UK; www.fil.ion.ucl.ac.uk/spm/, version 4661) in the MATLAB environment was used to preprocess the EPI functional images. The first five EPI volumes from each run were discarded to allow the magnetization to stabilize to a steady state. Volumes for the last 4 TRs (with only the fixation cross on the screen) were also truncated, resulting in 195 volumes preprocessed in each run. Prior to preprocessing, for each participant, anatomical images, as well as several raw functional images randomly selected from each run, were checked for quality control and no artifacts were found. Then, slice timing was corrected using sinc-interpolation with the midpoint slice as the reference. All functional images were then aligned to the first image of the first run using a 6-parameter linear transformation. Next, for each participant, EPI image movement parameters obtained from the previous step, as well as EPI image global signal intensity, were manually checked using the freely available toolbox ART (http://www.nitrc.org/projects/artifact_detect/) to detect volumes with excessive movement and abrupt signal changes. Volumes indicated as outliers by ART default criteria, e.g., with large movement, were excluded from following statistical analyses using additional nuisance regressors. Anatomical images were co-registered to the aligned functional images, and segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) using SPM8 default tissue probability maps. These segmented images were then used to calculate the transformation parameters mapping from the individuals' native space to the MNI template space. The resulting transformation parameters were used to transform all functional images to the MNI template. For each participant, co-registration and normalization quality was checked

by inspecting 12 randomly selected functional images. The functional images were finally re-sampled at 2 x 2 x 2 mm resolution and smoothed using a Gaussian kernel with the FWHM (full-width at half maximum) of 6 mm.

2.3. fMRI analysis

We used SPM8 to conduct the first (i.e., individual) level whole brain voxel-wise parametric modulation analysis to examine brain activation and fixation modulation effects during novel and repeated face processing. Because we had specific *a priori* brain regions of interest, i.e., the hippocampus (HPC) and fusiform face area (FFA), at the second (i.e., group) level we used a region of interest (ROI) analysis approach to obtain the mean beta estimates within each ROI and tested ROI effects using one-sample *t*-tests.

2.3.1. Parametric modulation analysis. First, at the individual-level general linear model (GLM) analysis, we entered trial onset times and durations for all trials of the four face conditions (i.e., *novel, repetition1, repetition2, and repetition3*) and one null event condition (i.e., *scrambled*), as main effect regressors to obtain estimates of brain activation in these conditions. Then, for each condition in each run, a parametric modulator was added by entering the trial-by-trial number of fixation scores, resulting in 4 parametric modulator regressors in each run. When creating these fixation parametric modulators, we excluded trials in which the number of fixations was larger or smaller than 2.5 standard deviations of the mean number of fixations across trials within each condition and run for each participant. We note that, on average, there were only 2.4 (SD = 3.9) and 1.1 (SD = .93) trials were excluded in each run for the younger and older age groups, respectively (i.e., fewer than 1 trial for each condition). There was no group difference on the number of excluded trials (t = 1.56, p = .13).

We previously found that reaction time, face sex, and face size did not affect the fixation modulation effect (Liu et al., 2017). As these variables shared very little (less than 3%) variance with the number of gaze fixations in both age groups, we did not include these regressors in the current analyses. Moreover, only a linear modulation effect was considered given that there were no significant quadratic modulation effects in our previous investigation (Liu et al., 2017). These regressors were convolved with the SPM8 canonical hemodynamic response function (HRF) to form the final design matrix. We also included the six raw motion parameters obtained from image alignment preprocessing and one additional composite movement parameter by aggregating movement trajectory measures at 6 brain edge plane locations to further covary out movement-related artifacts. Functional images detected as outliers were also excluded using additional regressors. The default high pass filter with a cut-off of 128 seconds was applied. A first-order autoregressive model AR(1) was used to account for the serial correlation in fMRI time series in the restricted-maximum-likelihood estimation of the GLM.

To examine age-group differences in neural responses that are elicited during face processing in general, we first contrasted the *novel* condition with the *scrambled* condition. To examine age-group differences in neural responses that are elicited during repeated face processing (without regard for the number of repetitions), we averaged the three repeated conditions and then contrasted this averaged *repeated* condition with the *scrambled* condition, as well as with the *novel* condition.

We constructed parametric modulation contrasts to examine the effect of the number of gaze fixations during viewing of novel and repeated faces. For the fixation modulation effect in the novel face processing condition, we contrasted the fixation linear modulation effect in the *novel* condition with that in the *scrambled* condition. We also averaged the fixation modulation

effect for the three *repeated* conditions and contrasted it with the fixation modulation effect in the *scrambled* condition to create a single contrast for the fixation modulation effect during repeated face processing.

Similar to our previous work (Liu et al., 2017)[1], we investigated whether a greater number of fixations during viewing of novel faces predicted larger reductions in neural responses (i.e. repetition suppression) during the subsequent presentation (i.e., *repetition1*) of the same faces. To this end, we modified the design matrix of our main analyses by replacing the fixation scores during the second presentation of the face (*repetition1*) with those of the *novel* condition. This way, the *novel* and *repetition1* conditions had the same *number of fixations* modulator. The extra four trials in the novel condition that were not subsequently repeated were excluded from this analysis. Then, we constructed a *t*-contrast to examine the beta value differences for the two parametric modulation effects (i.e., *novel* modulation minus *repetition1* modulation) to reflect the effect of the number of fixations during novel face viewing on neural repetition suppression effects. The detailed logic of this analysis using a GLM formula can be found in our previous report (Liu et al., 2017).

For all above-mentioned contrasts, we first calculated mean beta estimate values within each ROI from the first, i.e., individual, level voxel-wise analyses and tested at the second, i.e., group, level using two-tailed one sample *t*-tests to obtain these neural effects for each age group. Then, we used independent sample *t*-tests to obtain age differences on these neural effects. Voxel-wise contrast estimate images obtained from the first level analyses were also carried into

[1] The younger adults' results reported here were overall similar, although not identical, to those reported in our previous report (Liu et al., 2017). This is because in the current study (1) all fixation modulation effects in face conditions were contrasted with the *scrambled* condition, (2) the HPC masks here were generated using the latest version of Freesurfer (v.6.0), (3) only linear parametric regressor was used in the design matrix, and (4) we excluded functional images detected as outlier trials. However, there was no change in the overall pattern of results as reported in (Liu et al., 2017).

the second level SPM8 within (one sample *t*-tests) and between group analysis with participants as a random factor. This step produced whole-brain voxel-wise images so that activation within and outside the current ROIs may be visualized and reported in supplementary tables.

2.3.2. ROI definition. The bilateral anatomical hippocampal ROIs in individuals' native space were first obtained using FreeSurfer recon –all function, version 6.0 (http://surfer.nmr.mgh.harvard.edu.myaccess.library.utoronto.ca) (Fischl, 2012). These ROI masks were checked for each participant by two of the authors (ZL and RO). Then, the same normalization parameters obtained from SPM normalization procedure were used to transform these hippocampal masks into MNI normalized space.

To obtain functional FFA ROIs, we contrasted neural responses for all faces conditions with the scrambled condition at individual level analyses using SPM. Then at each age group level, we localized the local maximum activation in the bilateral fusiform gyrus at the threshold of $p = .05$ (with family-wise error multiple comparison correction and 10-voxel extension). To make the final functional ROI masks for each age group, a spherical volume with 8 mm radius was obtained around the maximum activation voxel (For younger adults, left FFA: [-38 -50 -20], right FFA: [40 -47 -20]; For older adults, left FFA: [-42 -50 -20], right FFA: [38 -50 -20]).

2.4. Hippocampal volumes

HPC volumes for each participant were obtained using FreeSurfer (methods described above). The volume of the HPC masks in each individual's native space segmented by FreeSurfer was calculated separately for the left and right HPC. These volume measures were then divided by the individual's intracranial volume to control for individual differences in overall brain size.

2.5. Statistical thresholding

The threshold for statistical significance was set at $p < .05$ for the ROI analyses that were used to test our main hypotheses (i.e., the one and independent sample *t*-tests). Results for aging effects from whole brain voxel-wise analyses were thresholded at $p = .005$ (uncorrected) with 10 voxel extension to facilitate future meta-analysis (Lieberman and Cunningham, 2009). The automated anatomical labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) was used to identify the anatomical labels for regions that showed aging effects in each analysis and are reported in Supplementary Tables. We note that each participant's eye movement and fMRI/MRI data that were included in the analyses were within 2.5 standard deviations of each age group's mean.

3. Results

3.1. Gaze Fixations

We calculated the mean number of gaze fixations for each condition in each run. This fixation measure was then averaged across runs and participants in each age group. Gaze fixation data in the three repeated face conditions were also averaged. A 2 x 2 (*age* by *repetition*) ANOVA revealed that older adults made more fixations than younger adults ($F(1, 39) = 6.73$, $p = .016$, effect size partial eta square: $\eta^2 = .140$), the number of gaze fixations decreased across repetitions ($F(1, 39) = 31.99$, $p < .0001$, $\eta^2 = .451$), and repetition-related decreases in gaze fixations were larger for younger than older adults ($F(1, 39) = 6.90$, $p = .012$, $\eta^2 = .150$; Figure 1B).

The distribution of the gaze fixations, aggregated from all novel face trials and all participants in each age group, is presented in Figure 1C. Each face stimulus was divided into 5 regions: eyes, nose, mouth, face (excluding the eyes, nose, mouth regions), and hair. As shown in Figure 1D, the eyes attracted the largest number of fixations, consistent with previous reports (Bindemann et al., 2009; Bortolon et al., 2016; Heisz and Ryan, 2011; Riggs et al., 2014). The proportion of fixations directed to each face region did not significantly differ between age groups ($p > .05$). A similar pattern of fixation distribution was found for the *repeated* conditions (not shown). Therefore, although older adults engaged in increased visual sampling behaviour, the nature of the sampling behaviour (i.e., distribution of gaze fixations) was similar to that of younger adults.

3.2. Response Times

Response times (RT) were also examined for each group and condition using a 2 x 2 (*age* by *repetition*) ANOVA. Older adults responded significantly slower (*novel:* 1720.8ms; *repeated*:

1499.1ms) than younger adults (*novel:* 1528.3ms; *repeated*: 1230.0ms; $F(1, 39) = 5.66$, $p = .022$, $\eta^2 = .127$). RT significantly decreased with repetition, ($F(1, 39) = 106.77$, $p < .0001$, $\eta^2 = .732$), but did not interact with *age* ($F(1, 39) = 2.31$, $p = .136$, $\eta^2 = .056$).

3.3. fMRI Results

Age-related changes in HPC and FFA responses were examined for *novel* and *repeated* conditions separately, each with respect to the scrambled condition, as well as age-related changes in neural repetition suppression. Additionally, age-related changes in the relationship between gaze fixations and neural responses for the HPC and FFA were investigated. To ensure that the findings reported below were not due to a potential confound of age-related differences in the shape of hemodynamic response, we confirmed that the shape of the hemodynamic response, *aggregated across all conditions*, was similar between the two age groups (Supplementary Figure 2).

3.3.1 Age-related Changes in HPC and FFA Activity. Older adults demonstrated significantly greater neural responses for novel faces compared to scrambled pictures in the right HPC; however, there were no significant differences in neural responses for repeated faces versus scrambled pictures (for detailed statistics, see Figure 2). By contrast, younger adults showed significantly stronger activation bilaterally in the HPC for the novel and repeated condition (versus the scrambled condition). Younger adults showed stronger HPC activation than older adults bilaterally during viewing of novel ($t = 4.25$ and 4.72, $p < .0005$, *Cohen's d* = 1.33 and 1.47, for the left and right HPC, respectively) and repeated faces ($t = 2.89$ and 3.07, $p < .006$ and .004, *Cohen's d* = 0.90 and .96, for the left and right HPC, respectively).

In the FFA, both younger and older adults showed stronger activation during the novel and repeated condition, each compared to the scrambled condition (for detailed statistics, see

Figure 2). A marginal effect of age group was observed only in the novel condition: younger adults showed greater activation than older adults in the left FFA (t = 1.92, p = .062, *Cohen's d* = 0.60). No age difference was found in the right FFA (t = 1.23, p = .226, *Cohen's d* = 0.38) during viewing of novel faces, nor in either the left or right FFA (t = -.03 and -.81, p = .98 and .43, *Cohen's d* = 0.01 and .25, respectively) during viewing of repeated faces. Voxel-wise whole brain results for age differences for the novel and repeated face condition are presented in Supplementary Table 1 and 2.

For *repetition suppression* effects, younger and older adults showed significant repetition suppression*:* activation decreased in HPC and FFA with stimulus repetition (p < .0001; For detailed statistics, see Figure 2). Directly comparing the two age groups yielded a marginally significant age difference (younger > older) in the left HPC (t = 1.99, p = .054, *Cohen's d* = 0.62), and significant age differences in the right HPC (t = 2.09, p = .044, *Cohen's d* = 0.65) and FFA bilaterally (t = 4.82 and 3.92, p < .0001 and .0005, *Cohen's d* =1.51 and 1.22, for the left and right ROI respectively). Voxel-wise whole brain results for age differences are presented in Supplementary Table 3.

Thus, during viewing of novel and repeated faces, older adults showed weaker responses in the HPC compared to the younger adults, but predominantly similar responses in the FFA. Although older adults exhibited repetition suppression effects in the HPC and FFA, these effects were smaller than those exhibited by younger adults.

3.3.2. Age Differences in Fixation Modulation Effects. For each age group, parametric modulation analyses were used to examine the extent to which the number of gaze fixations predicted HPC and FFA activation in the *novel* and *repeated* conditions, controlling for the fixation modulation effect in the *scrambled* condition. During viewing of novel faces, no

significant fixation modulation effect was observed for older adults in either the HPC or FFA (*ps* > .36; for detailed statistics, see Figure 3); likewise no significant modulation effect was observed in either the HPC or FFA during viewing of repeated faces (p = .23 ~ .96; Figure 3). For the younger adults, as detailed previously (Liu et al., 2017), the trial-wise number of fixations in the *novel* condition positively predicted, significantly or at a trend level, bilateral HPC and right FFA activation (p = .097 ~ .0003; Figure 3), and the trial-wise number of fixations in the *repeated* condition positively predicted bilateral FFA activation and left HPC activation (p = .021 ~ .009). Directly comparing the two age groups revealed that the modulation effect of the number gaze fixations on left HPC activity during novel viewing was significantly larger for younger than older adults (t = 2.31, p = .026, *Cohen's d* = 0.72). No significant age differences were found for the other ROIs (t = 1.16, 1.42, and 1.31, p = .26, .17 and .20, *Cohen's d* = .36, 44, and .41 for the right HPC, and left and right FFA, respectively), and no significant age differences were observed for the *repeated* condition (t = 1.15 and -.11, p = .26, and .91, *Cohen's d* = .35, and .03 for the left and right HPC; t = .45 and .65, p = .65 and .52, *Cohen's d* = .14, and .20 for the left and right FFA, respectively; Figure 3). Voxel-wise whole brain results for age differences in fixation modulation effect in the *novel* and *repeated* conditions are presented in Supplementary Table 4 and 5, respectively. All together, these results indicate that the association between visual exploration and neural activity was generally weaker in older adults, particularly in the HPC for viewing of novel faces.

3.3.3. Age Differences in the Prediction of Gaze Fixations on Subsequent HPC

Repetition Suppression. Previous studies have shown that repetition suppression, i.e., less activation due to encoding of repeated stimuli, in the HPC is associated with successful memory formation (Kremers et al., 2014; Kumaran and Maguire, 2009; Miller et al., 1991; Suzuki et al.,

2011a, 2011b; Vannini et al., 2013). Consistent with this idea, we previously reported that, for younger adults, the number of gaze fixations made during viewing of the novel faces positively predicted repetition suppression in the HPC, but not in FFA (Liu et al., 2017). We repeated the analyses again here: the number of fixations made during viewing of the novel faces positively predicted the magnitude of repetition suppression bilaterally in HPC ($p < .011$), but not in FFA ($p > .57$, for detailed statistical values, see Figure 4). For older adults, the number of fixations made during viewing of the novel faces marginally predicted repetition suppression in the left HPC ($p = .067$). There was no significant effect in the right HPC and the FFA (for detailed statistical values, Figure 4). Directly comparing the two groups did not produce any significant age differences ($t = .39 \sim .11$, $p > .27$, *Cohen's d* = .12 ~ .03). However, voxel-wise whole brain results did reveal a cluster of voxels in the left HPC (MNI coordinates: [-22 -28 -10] with peak $p = .00007$ without correction and $p = .032$ after family-wise error correct within the left HPC mask) that showed a stronger effect in younger adults compared to older adults. This voxel cluster is illustrated in Supplementary Figure 1 using a lenient statistical threshold ($p < .05$ with 10-voxel extension and no corrections, only for illustration purposes). Voxel-wise whole brain results for age differences in this fixation modulation effect are presented in Supplementary Table 6. These results indicate that aging is associated with declines in the relationship between visual sampling behaviour and subsequent repetition suppression, an indirect index of memory, in the HPC, FFA, and broader neocortex.

3.3.4. Hippocampal Volumes Do Not Predict Fixation Modulation Effects.

Hippocampal volumes were significantly larger on the right, and marginally larger on the left, for younger compared to older adults ($t = 6.57$, $p < .0001$, *Cohen's d* = 2.05; $t = 1.75$, $p = .088$, *Cohen's d* = .55, respectively; Figure 5). However, HPC volumes were not correlated with the

number of gaze fixations during either *novel* or *repeated* viewing for either age group or for the whole sample (i.e., when the two age groups were aggregated), r = -.30 ~ .11, p = .19 ~ .78 (Supplementary Figure 3A).

HPC volumes were marginally correlated with HPC activity during *novel* viewing, when younger and older adults were aggregated into a single group (r = .27 and .30, p = .09 and .056, for the left and right HPC, respectively). However, within each age group, there was no significant correlation between HPC volume and HPC activation (r = -.34 ~ .22, p = .14 ~ .80), suggesting that the correlations in the whole sample were driven by age group differences in the two variables (Supplementary Figure 3B). Finally, HPC volumes were not significantly correlated with fixation modulation effects in HPC during viewing of novel faces, either within each age group or across the whole sample, r = .04 ~ .20, p = .20 ~ .86 (Supplementary Figure 3C), or with fixation modulation effects on subsequent repetition suppression in the HPC, r = -.22 ~ .25, p > .26. Thus, the age-related changes in the fixation modulation effects do not appear to be due to age-related changes in HPC gross anatomical structure.

4. Discussion

In this study, we observed an age-related decline in the relationship between visual exploration and neural activity in the HPC, a structure critical for the formation of lasting memory representations (Davachi, 2006; Olsen et al., 2012; Eichenbaum and Cohen, 2014), as well as in the FFA, a region important for the perceptual processing of faces (Kanwisher et al., 1997). Older and younger adults were given a face processing task (i.e., age judgment) in which novel and repeated faces were presented while eye movements and neural responses were simultaneously recorded. Aging was associated with an increase in visual exploration: older

adults made more gaze fixations than younger adults, although the distribution of fixations across the different features of the face stimuli was similar between the two age groups. In contrast, aging was associated with declines in neural responses: older adults showed significantly weaker activation in HPC and marginally weaker activation in FFA during viewing of novel faces compared to younger adults. Weaker activation in the HPC of older versus younger adults was further observed during viewing of repeated faces. Moreover, older adults showed weaker repetition-related suppression in the HPC and FFA compared to younger adults, and only showed a marginal relationship between the number of gaze fixations during viewing of novel faces and subsequent repetition suppression in the left HPC. Importantly, these age-related increases in visual exploration, accompanied by age-related decreases in neural activity, including neural repetition suppression, resulted in a nonsignificant relationship between neural responses and visual exploration in the HPC and the FFA for older adults. This is in contrast to the findings from younger adults in which the number of gaze fixations positively predicted activation in the HPC during viewing of novel, but not repeated faces, and predicted subsequent repetition suppression in the HPC. Taken together, these results suggest that visual exploration is related to the development of a lasting memory representation. The only difference between the novel and repeated faces is in the viewers' prior experience; the change in the relationship between gaze fixations and HPC activity is therefore due to a change in memory status (no existing memory representation vs. a representation that has been maintained in memory). Likewise, repetition suppression has been taken as an index of memory (Brown and Aggleton, 2001; Grill-Spector et al., 2006; Kremers et al., 2014; Kumaran and Maguire, 2009; Miller et al., 1991; Suzuki et al., 2011a), and the relationship between gaze fixations directed to novel faces and subsequent repetition suppression points to visual exploration as a means by which visual memories are

formed. However, despite an increase in visual exploration, aging is associated with declines in the accumulation of visual information as sampled through gaze fixations, and declines in neural responses, each of which may underlie age-related deficits in the development of lasting memory representations.

Although there were no significant relationships found between gaze fixations and neural activity in either the HPC or FFA at the ROI level for older adults, using SPM small volume correction methods we did find activity in a set of clusters in the left HPC that showed a significant relationship with gaze fixations during *novel* viewing, when the *scrambled* condition was not used as a baseline (for details, see Supplementary Figure 4). Therefore, it seems that older adults do exhibit a similar, albeit weaker, pattern of association between gaze fixations and neural activity to that observed in younger adults. Similarly, increases in the number of gaze fixations during the viewing of novel faces marginally predicted stronger repetition suppression in the left HPC in older adults, although this effect was still weaker than what was observed in younger adults (Supplementary Figure 1). These data indicate that the association between visual exploration, measured by the number of gaze fixations, and neural activity in HPC and FFA indicative of mnemonic and perceptual processing, was not completely absent in older adults, but was nonetheless significantly reduced.

The findings reported here build on our recent work demonstrating that the oculomotor and medial temporal lobe memory systems are structurally (Shen et al., 2016) and functionally (Liu et al., 2017; Ryan et al., 2018) well integrated. Here, we show that aging changes the functional interactions between the two systems. The finding that visual exploration is associated with functional activation in HPC and FFA in humans is consistent with previous neurophysiological studies in monkeys and humans that found that gaze fixations and saccades

directly modulate neuronal activity in the HPC as well as other temporal and occipital regions (Andrillon et al., 2015; Hoffman et al., 2013; Jutras et al., 2013; Lee and Malpeli, 1998; Rajkai et al., 2008; Ringo et al., 1994; Sobotka et al., 1997; Sobotka and Ringo, 1997; Wirth et al., 2017). We and others have proposed that the HPC binds information sampled from individual, successive, fixations to build coherent memory representations, and consequently uses such representations to facilitate active vision (Liu et al., 2017; Voss et al., 2017). This online binding process may facilitate not only the encoding of visual features acquired through successive gaze fixations, but also the registration of the spatiotemporal relationships among these visual features. When increasing numbers of fixations are deployed during visual exploration of novel visual information, stronger involvement of the ventral visual stream and the hippocampal system would be expected to process and encode the fixation-related information. Our findings with older adults suggest that this visual binding behavior is altered along the ventral visual processing stream, including the HPC, and may be an underlying mechanism that contributes to age-related deficits in visual memory.

Older adults made more gaze fixations than their younger counterparts during viewing, consistent with previous research (Firestone et al., 2007; Heisz and Ryan, 2011). This age-related difference in visual exploration has been observed for novel (Firestone et al., 2007) and repeated faces, and in the context of a free viewing task (Heisz and Ryan, 2011), in addition to the age judgment task presented here. Repetition-related decreases were larger for younger adults compared to older adults, again consistent with previous findings with older adults (Heisz and Ryan, 2011), which is also more generally consistent with previous eye movement research demonstrating that prior experience influences visual sampling behavior (Chan et al., 2011; Henderson et al., 2005; R. Johansson et al., 2012; Roger Johansson et al., 2012; Johansson and

Johansson, 2014; Loftus, 1972; Olsen et al., 2016; Ryan et al., 2007a). Moreover, it has been shown that an amnesic case with a compromised HPC system and impaired recognition memory, similarly made more fixations during a face encoding task compared to healthy controls (Olsen et al., 2016). Together, these results suggest that the ability to bind information across successive fixations into a lasting representation may decline with aging, and that increased visual exploration during *novel* viewing may reflect HPC binding deficits. That is, older adults may increase visual exploration behavior in an effort to up-regulate HPC binding efforts. However, such an interpretation is speculation at this point, and further investigation is warranted.

Reflecting potential deficits in binding, older adults exhibited weaker HPC activation than younger adults during viewing of novel, as well as repeated, faces, consistent with previous research showing weaker activation in the HPC for older versus younger adults in perception and memory tasks that use faces as stimuli (Dennis et al., 2008; Fischer et al., 2010, 2005; Iidaka et al., 2002). Moreover, HPC repetition suppression effects, which have traditionally been considered to reflect successful memory formation (Brown and Aggleton, 2001; Grill-Spector et al., 2006; Kremers et al., 2014; Kumaran and Maguire, 2009; Miller et al., 1991; Suzuki et al., 2011a), were diminished with aging. This work provides novel evidence that HPC repetition suppression is reduced in even healthy aging, adding to findings of reduced repetition suppression effects in Alzheimer's disease and mild cognitive impairment (S. C. Johnson et al., 2008; Jurick et al., 2017; Pihlajamaki et al., 2008; Pihlajamäki et al., 2011; Yu et al., 2016). Although we did not directly test the participants' explicit memory on these faces, age-related changes in repetition suppression suggest that encoding was impaired in these older adults, which is consistent with the broader literature on aging-related memory declines.

Only marginal age-related changes in activity were observed for the face processing region FFA during viewing of novel faces, and no significant age differences were observed during viewing of repeated faces. However, the repetition suppression effect in the FFA was significantly larger for younger than older adults. These results are also consistent with previous studies that have shown that aging is associated reduced FFA sensitivity in differentiating within-category (i.e., different types faces) and between-category (e.g., faces vs. objects/scenes) stimuli (Burianová et al., 2013; Goh et al., 2010; Grady et al., 1998; Lee et al., 2011; Park et al., 2012; Schmitz et al., 2010), and are consistent with a recent meta-analysis of 114 aging studies which found disengagement, i.e., hypo-activation, in the visual stream in older adults under a variety of task conditions and with a range of stimuli (Li et al., 2015). Thus, in addition to the age-related changes observed in visual exploration, and HPC responses, age-related changes were observed in the ventral visual stream, as well as in the broader neocortex (see Supplementary Tables for the whole brain results).

It should be noted that we cannot exclude the possibility that the age-related differences observed in the current study are due to age-related changes in vision/lower-level perceptual processing. Although our older participants had normal or corrected-to-normal vision, they may have reduced contrast sensitivity and/or reductions in the stability of fixations (Owsley, 2011; Port et al., 2016) which were not tested here. Indeed, previous studies have found that face processing can be affected by age-related deterioration in contrast sensitivity (Barnes et al., 2011; Owsley et al., 1981; Owsley and Sloane, 1987). However, there is also evidence that age-related changes in cognitive function can be observed independently from age-related sensory changes; perceptual changes may then not fully explain aging effects in higher-order cognitive functions (Hofer et al., 2003; Houston et al., 2016; La Fleur and Salthouse, 2014). Moreover, in

the current study, we used viewing of the scrambled pictures as a baseline condition to control for any age-related changes in lower level sensory/perceptual process differences. Examining the neural changes from processing scrambled pictures to viewing of face images should then account for a significant component of age-related perceptual changes/changes in neural responses in early regions of the visual processing hierarchy that would be common across both conditions. In this manner, we focused on higher-level perceptual and memory processing supported by the FFA and the HPC. Compared to younger adults, older adults robustly showed weaker activation in the bilateral HPC in the novel face condition whereas only a trend level age difference was observed for responses the left FFA. This is consistent with the current literature in age-related deficits in HPC function. Therefore, we suggest that the observed age-related changes in the relationship between visual exploration and neural activity are due to an age-related decline in the binding or integration of visual input.

One possible concern is that the weaker relationship between gaze fixations and HPC responses that was observed in the older adult group may be due to the use of a canonical, rather than an optimized, HRF for each age group, and the reduced HPC response observed in older adults did not permit a relationship to be observed with gaze fixations. However, the FFA showed robust activation during the novel face condition in the older adult group (Figure 2), and yet there was still no significant fixation-FFA relationship in this age group (Figure 3). Therefore, whether there was a significant behavior-brain relationship was not entirely determined by the mean activation of a specific brain region. Moreover, weaker mean HPC activation in older adults (Figure 2) in a specific condition does not necessarily reflect a smaller trial-wise variability of HPC activation. It would still be possible that with a zero mean activation, trial-wise HPC activation could be predicted by other variables such as the number of

fixations. Therefore, we suggest that the weaker relationship between the number of fixations and HPC activation in older adults likely reflects a reduced sensitivity of HPC in the online binding of information acquired through sequences of fixations.

Although older adults had smaller HPC volumes (in the right hemisphere) compared to younger adults (Jack et al., 2000, 1998, 1997; Petersen et al., 2000; Scahill et al., 2003; Šimić et al., 1997), HPC volumes were not related to the fixation modulation effect on neural activity. Across the whole sample (age-aggregated), there was a marginally significant positive correlation between HPC volume and HPC activation. This effect may have largely been driven by age *group* differences in HPC volume and activation, rather than a direct association between the overall HPC volume and the neural activity. Although it remains to be investigated whether anatomical properties in HPC subfields and/or other medial temporal lobe regions are related to age-related changes in visual exploration and visual exploration-HPC activation coupling, the present findings suggest that this functional relationship may be orthogonal to HPC gross anatomical structure.

In conclusion, aging is associated with a reduction in the functional relationship between visual exploration and neural activity. This suggests that the visual memory deficits often observed in aging may be due to declining binding processes along the visual processing hierarchy, as well as the hippocampus, that would ordinarily serve to accumulate and integrate visual information across space and time to form a coherent and lasting memory representation.

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Figure Captions

Figure 1. A. fMRI-eyetracking task schematics. There were 70 trials per block; each block contained 20 novel face trials, 36 repeated face trials (up to 3 repetitions) and 14 null even trials (with a scrambled image). **B.** Number of fixations per trial for younger and older adults in the *novel* and *repeated* conditions. * $p < .05$, ** $p < .01$, *** $p < .0001$; $\otimes$: ANOVA age by repetition interaction. **C.** Distribution of the number of fixations (aggregated from all images and participants) for each age group in the *novel* condition. **D.** Illustration of two example face stimuli with different face regions (i.e., eyes, nose, face, mouth, and hair) highlighted. Fixations from all participants from each age group in the *novel* condition are presented, with the size of the circle proportional to the duration length of fixations. Heatmaps for these fixations are also added on the stimuli. The pie graphs show similar distribution of the proportion of fixations for each face region in the two age groups.

Figure 2. Activation in the hippocampus (HPC; left bar graphs) and fusiform face area (FFA; right bar graphs) in older and younger adults during viewing of novel and repeated faces, compared to scrambled pictures. Activation decreases from viewing of novel to repeated faces (i.e., repetition suppression) are also presented. Statistics (i.e., t and p value) for these ROI neural

effects in each age group are indicated under each bar graph. For each effect, voxel-wise age difference brain images thresholded at p = .005, with 10-voxel extension (no correction) are presented for illustration purposes (for detailed results, see Supplementary Table 1, 2 and 3).

Figure 3. Modulation effects of the number of fixations on activation in the hippocampus (HPC; left bar graphs) and fusiform face area (FFA; right bar graphs) in older and younger adults during viewing of novel and repeated faces, compared to viewing of scrambled pictures. Statistics (i.e., t and p value) for these ROI neural effects in each age group are indicated under each bar graph. For the *novel* condition, brain images for the fixation modulation effect, thresholded at p = .005, with 10-voxel extension (no correction), are presented separately for the older and younger adults for illustration purposes. For detailed voxel-wise results, see Supplementary Table 4 and 5.

Figure 4. Higher number of fixations predicted stronger repetition suppression in the hippocampus (HPC; left bar graphs) and fusiform face area (FFA; right bar graphs) in older and younger adults. For detailed voxel-wise results, see Supplementary Table 6.

Figure 5. Age group differences in HPC volumes. Boxplots, individual data points, group means (long black horizontal line) and standard deviations (short black horizontal line above and below the mean), and statistics for age differences are presented.

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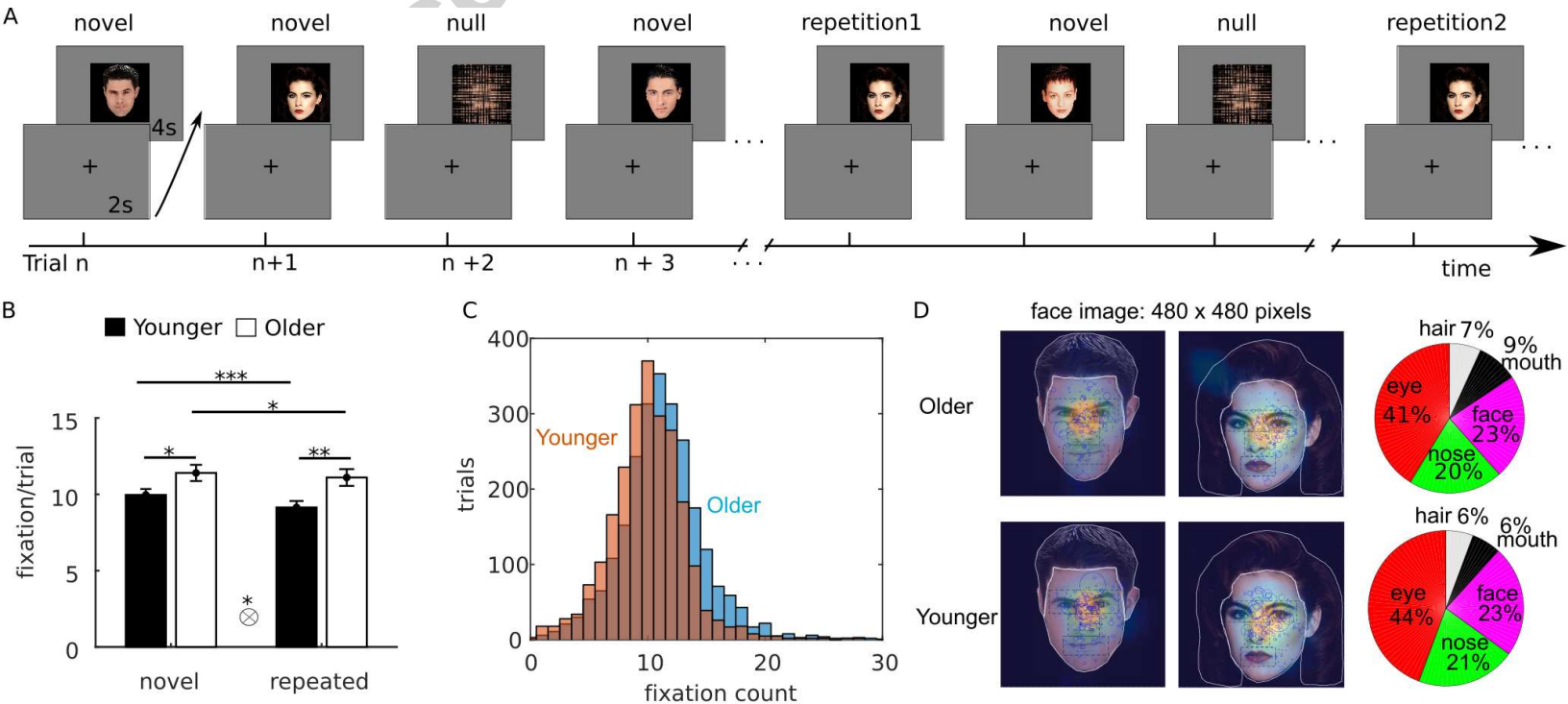
Highlights

The visual exploration-hippocampal activity relationship is weakened with aging

Hippocampal responses to novel and repeated faces are reduced in older adults

Older adults show increased visual sampling behavior



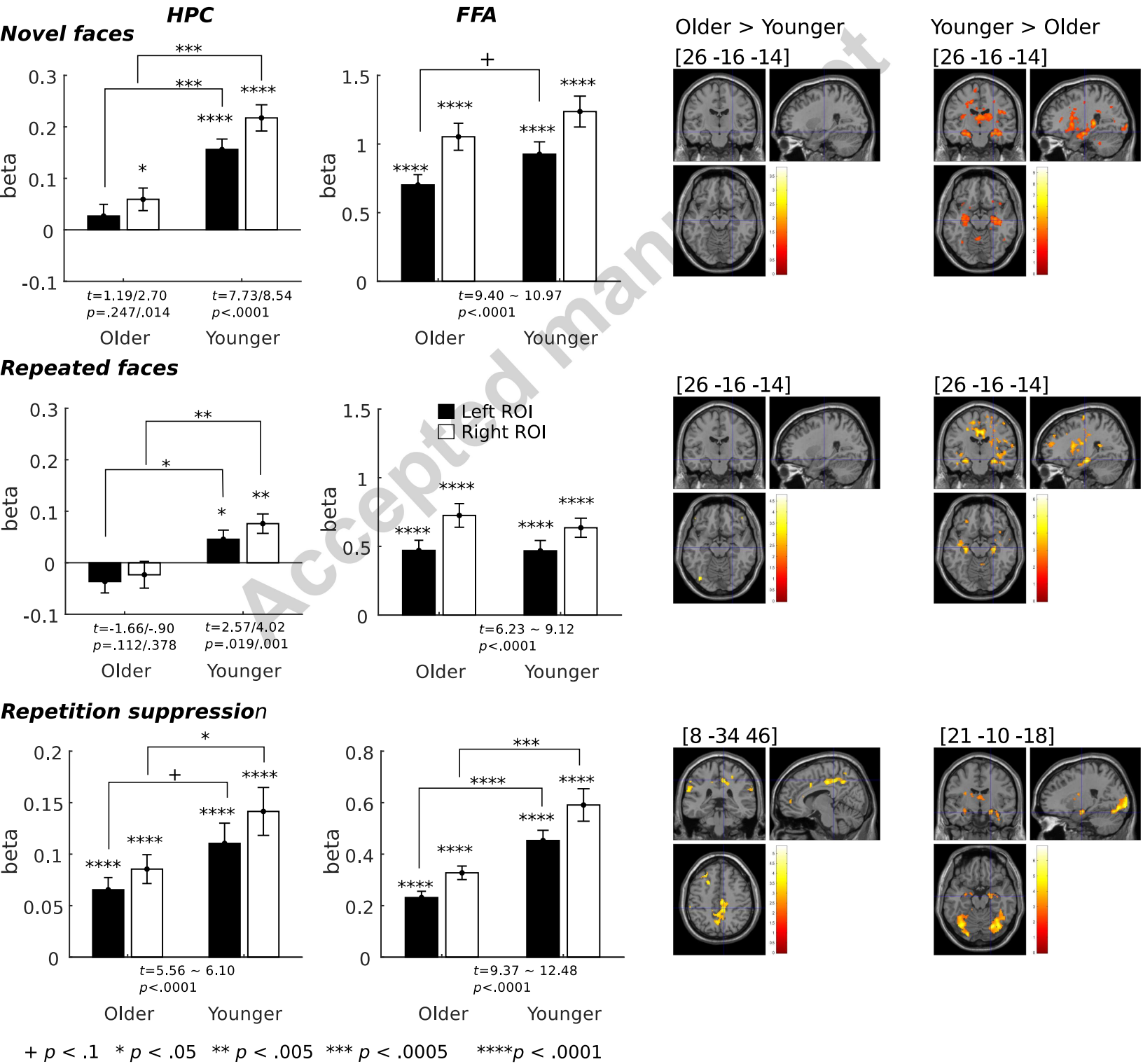
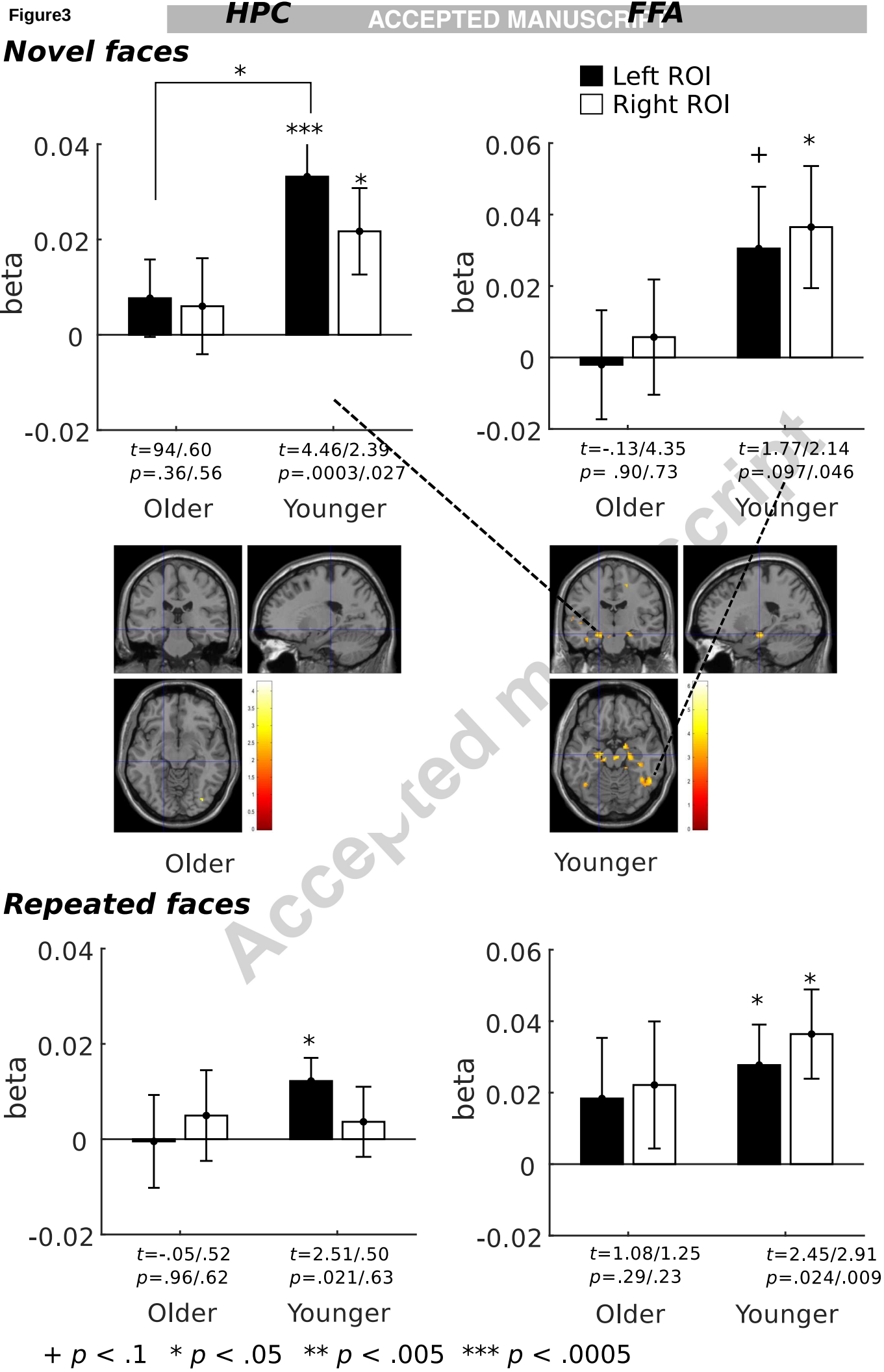
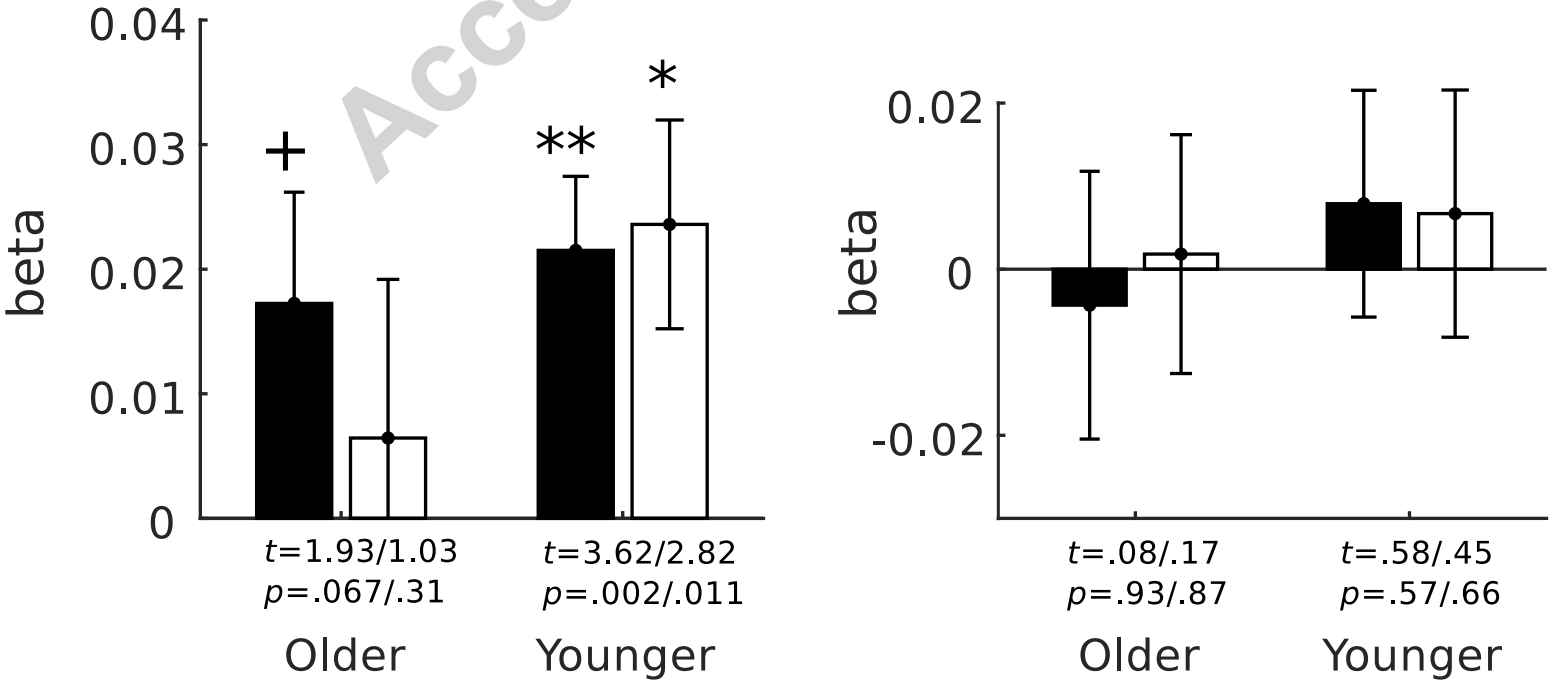


Figure3



+ $p < .1$ * $p < .05$ ** $p < .005$ *** $p < .0005$



+ $p < .1$ * $p < .05$ ** $p < .005$