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Age-related declines in neural selectivity manifest differentially during encoding and recognition

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ABSTRACT

One important factor contributing to age-related memory decline is the loss of distinctiveness with which information is represented in brain activity. This loss in neural selectivity may be driven by neural attenuation (i.e., reduced activation to preferred stimuli) or neural broadening (i.e., increased activation to non-target stimuli). In this fMRI study, we investigated age differences in neural selectivity during first encoding, repeated encoding, and recognition, as well as the underlying pattern (broadening vs. attenuation). We found lower neural selectivity in older compared to younger adults during all memory stages. Crucially, while reduced selectivity in older adults was due to neural broadening during first encoding, it was driven by neural attenuation during recognition, but revealed no clear pattern during repeated encoding. Our findings suggest that intrinsic differences between memory stages may interact with neural activity to manifest as either neural broadening or attenuation. Moreover, despite these differential patterns, neural selectivity was highly correlated across memory stages, indicating that one common mechanism may underlie expressions of age-related neural dedifferentiation.

1. Introduction

A hallmark of cognitive aging is the decline in episodic memory function (Nyberg et al., 2012). Neurobiological models have proposed that an age-related reduction in the fidelity of neuronal signal transmission underlies cognitive decline (Li et al., 2001). In particular, recent studies suggest that neural representations of information are less distinctive in older adults – a phenomenon termed age-related neural dedifferentiation (for reviews, see Koen & Rugg, 2019; Koen et al., 2020).

Supporting neuroscientific evidence of age-related neural dedifferentiation has been provided by studies that took advantage of the functional specializations of regions within the ventral visual cortex (VVC), including the parahippocampal place area (PPA) and fusiform face area. In younger adults, these regions are known to respond with increased neural activity preferentially to visual house and face stimuli, respectively (Epstein & Kanwisher, 1998; Kanwisher et al., 1997). Age comparative studies have found that the selectivity with which these regions respond to their preferred stimuli is reduced in older adults compared to younger adults (D.C. Park et al., 2004; J. Park et al., 2012). Further evidence for an age-related functional decline in visual processing comes from studies finding that the multivariate patterns of activation across visual cortices are less distinctive in older adults for both categorical representations (Carp et al., 2011; Koen et al., 2019; Trelle et al., 2019) and item-specific representations (Zheng et al., 2018; Bowman et al., 2019; Hill et al., 2021; Kobelt et al., 2021; but, see Deng et al. (2020) for enhanced item representations in older adults). Senescent declines in neural selectivity are frequently associated with declines in memory performance (Zheng et al., 2018; Bowman et al., 2019; Koen et al., 2019; Hill et al., 2021; Kobelt et al., 2021; for review, see Koen et al., 2020).

In order to unpack age differences in neural selectivity at the population level, J. Park et al. (2012) demonstrated that reduced category selectivity, defined as the difference in activation in response to a region's preferred and non-preferred stimulus type, may be driven by a few possible mechanisms. First, older adults

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may have a similar response to preferred stimuli (e.g., houses in the PPA) compared to younger adults, but have a heightened response to the non-preferred stimulus (e.g., faces in the PPA) compared with younger adults. This process is commonly termed neural broadening, referring to the broadening of neuronal tuning curves, a concept initially reported in animal models of age-related neural dedifferentiation (Leventhal et al., 2003; Schmolesky et al., 2000). Second, older adults may exhibit a reduced response to the preferred stimulus of a region, but have a similar response to the younger adults for the nonpreferred stimulus, a pattern termed neural attenuation. At the neuronal level, neural attenuation reflects reduced sensitivity, which leads to decreased neuronal firing when presented with a preferred stimulus (Schmolesky et al., 2000). Finally, since neural broadening describes the response to the nonpreferred stimulus and neural attenuation describes the response to the preferred stimulus, these processes are not mutually exclusive. Thus, older adults may exhibit a combination of both neural attenuation and neural broadening. The initial findings of J. Park et al. (2012) revealed that an age-related decline in face selectivity was driven by region-specific mechanisms, namely neural broadening in the fusiform face area and neural attenuation in the extended face network. Thus, the authors identified age-related processing deficits both within the VVC as well as in regions outside of the VVC. They concluded that age-related neural dedifferentiation may not be a static construct, but may depend on regional processing differences.

Since this seminal work by J. Park et al. (2012), only few studies have investigated these intricacies and those yielded mixed evidence: There has been evidence for neural broadening (Kobelt et al., 2021; Hill et al., 2021), neural attenuation (Koen et al., 2019), and a combination of both (Srokova et al., 2020). In addition to the mixed results, these studies quantified underlying mechanisms of neural dedifferentiation based solely on data from memory encoding tasks. Note that one recent study by Hill et al. (2021) reported age differences in neural selectivity during both encoding and retrieval, however, it was unclear whether this effect was driven by neural broadening, neural attenuation, or both. As such, it remains unknown how cognitive and neural processes that differ between memory stages influence manifestations of neural dedifferentiation.

In our view, the narrow focus of previous studies on memory encoding misses the fact that inherent differences between memory encoding and other memory stages (e.g., repeated encoding or retrieval) are known to influence neural activity (Grill-Spector & Malach, 2001; Grill-Spector et al., 2006; Larsson et al., 2016; Cabeza & Nyberg, 2000; Daselaar et al., 2009; Huijbers et al., 2009, 2011; Kim et al., 2010). For example, repeated encoding and retrieval have been shown to be associated with altered neural activity in comparison to first encoding of a given event. Repeated study of the same stimulus is widely known to improve memory performance (Glenberg et al., 1980; Hanson, 2003). On the neural level, stimuli presented multiple times are often subject to repetition effects, particularly repetition suppression, in which the activation to subsequent presentations of a stimulus is reduced (Grill-Spector & Malach, 2001; Grill-Spector et al., 2006; Larsson et al., 2016). Repetition suppression has been demonstrated in both young and older adults (Goh et al., 2010; Sommer et al., 2021). Consequently, repeated encoding is likely to affect measures of neural selectivity and the underlying pattern of neural dedifferentiation.

In addition, cognitive processing differences between memory encoding and retrieval have been attributed to a multitude of factors. First, it has been suggested that passive memory encoding is less cognitively demanding than memory retrieval (Favila et al., 2020). Age differences in neural selectivity have previously been shown to be influenced by cognitive load (Carp et al., 2010), suggesting that differences in cognitive demands between encoding and retrieval may shape manifestations of neural dedifferentiation. Additionally, it has been argued that while memory encoding relies on directing attention externally in order to process novel stimuli (Chun & Turk-Browne, 2007), memory retrieval requires orienting attention to internal mnemonic representations (Wagner et al., 2005). Accordingly, differences in neural activity supporting encoding and retrieval have been observed in a broad range of studies (Cabeza & Nyberg, 2000; Daselaar et al., 2009; Huijbers et al., 2009, 2011; Kim et al., 2010). Importantly, these activation differences may affect the processing of preferred and not-preferred stimuli differentially, potentially leading to differential expressions of neural dedifferentiation between encoding and retrieval.

Finally, in order to understand the relevance of neural dedifferentiation for age-related decline in memory performance, it seems important to acknowledge how these manifestations might lead to distinct cognitive impairments during each memory stage. For example, one might speculate that during encoding, both neural broadening and neural attenuation reduce the precision with which to-be-remembered information is represented in the brain. However, during retrieval, neural broadening and neural attenuation may expose unique processing features. Here, neural attenuation may reflect failure to activate the target representation, while neural broadening may reflect an overactivation of competing, but irrelevant representations. Further, it is crucial to note that cognitive processes during different memory stages do not operate in isolation. As previously mentioned, neural dedifferentiation might lead to a less precise representation of the to-be-remembered material already during encoding. This less precise representation might pose particular challenges for later retrieval attempts (Sander et al., 2021). Similarly, dedifferentiation occurring during retrieval may impair memory by increasing interference between competing memory traces, even in light of sufficient encoding of each mnemonic representation (Fandakova et al., 2020). Hence, an understanding of the effects of neural dedifferentiation during encoding and retrieval is required for a mechanistic description of the roots of age differences in memory performance. However, to date, no studies have been able to directly compare the mnemonic significance of expressions of neural dedifferentiation across the memory stages, thus, it is unclear whether one may be particularly influential for senescent cognitive decline.

Together, age-related declines in neural selectivity have been attributed to neural broadening, neural attenuation, and a combination of both. However, these patterns have only been investigated during memory encoding tasks. Hence, it is unknown whether age differences in neural selectivity express differentially across memory processing stages, such as repeated encoding and retrieval. Therefore, we predicted that neural selectivity would be reduced in older adults compared with young adults across all memory stages, and further sought to investigate whether the corresponding manifestations of age-related neural dedifferentiation, vary between first encoding, repeated encoding, and recognition.

2. Materials and methods

Parts of these data were previously published in Kobelt et al. (2021). Relevant methods and analyses to the current study are restated here. Importantly, the present analyses assessed a smaller sample of participants as well as adjusted regions of interest (ROIs) as compared to Kobelt et al. (2021; details reported below). Furthermore, Kobelt et al. (2021) focused on the first encoding run, whereas we incorporate both the second encoding run and recognition into our analyses.

2.1. Participants

Data were collected from a total of 76 healthy adults. The initial sample comprised 39 younger adults (18–27 years) and 37 older adults (64–76 years). Twelve participants were excluded due to too much motion in the scanner (1 young adult and 2 older adults), memory performance below chance level (2 young adults and 1 older adult) and category-selective clusters below threshold (2 young adults and 4 older adults; for the definition of category-selective clusters, see Section 2.6 below). The final sample consisted of 34 young adults (M_{age} = 22.2, SD_{age} = 2.6 years; 15 females, 19 males) and 30 older adults (M_{age} = 70.8, SD_{age} = 2.3 years; 17 females, 13 males). Participants were screened via telephone interview for mental and physical illness, metal implants, and current medications. Additionally, all older adults were screened using the Mini-Mental State Examination (Folstein et al., 1975) and all exceeded the threshold of 26 points. The study was approved by the ethics committee of the German Society for Psychological Research (DGPs) and written informed consent was obtained from each participant prior to testing.

2.2. Stimuli

Stimuli consisted of 300 gray-scale images from 3 different categories: 120 neutral faces (adapted from the FACES database; Ebner et al., 2010), 120 houses (some adapted from D.C. Park et al., 2004, and some obtained from the internet), and 60 scrambled images (30 faces and 30 houses, constructed from randomly selected face and house images) serving as control stimuli. Three additional stimuli (one face, one house, and one scrambled image) were selected to serve as target images for the encoding target-detection task. Face and house stimuli were randomly divided into two sets of 120 images (60 faces and 60 houses). One stimulus set was presented during both encoding and recognition (old images) and the other stimulus set was presented only during recognition (new images). The stimulus sets were defined once and were used for all participants.

2.3. Paradigm

The following work was completed within a larger overall study spanning 2 days of data collection. This study focuses only on the face-house task, which consisted of an intentional encoding phase and a surprise recognition test, both performed inside the fMRI scanner on the same day with a delay of approximately 30 minutes (see Fig. 1). The encoding phase consisted of 2 identical runs each comprised of nine blocks. For all blocks, each trial was presented for 2000 ms with a centered fixation cross shown between trials ranging from 2000 to 8000 ms. Stimuli were randomly distributed in 18 blocks, such that each block had 20 images from the same category (faces, houses, or scrambled) plus the category's corresponding target stimulus. The order of the blocks was alternating and counterbalanced across participants, either starting with a face or house block. Stimulus order was pseudo-randomized with the restriction that the target image was presented neither in the first 4 nor last 4 trials of a block. Due to a technical issue, the same stimulus order was used for all participants starting with a face block and in 36 participants starting with a house block. In order to keep the participants attentive to the stimuli, participants were asked to perform a target-detection task in which they pressed a button when one of the three target images was presented. Prior to entering the scanner for the encoding task, participants completed 5 practice trials of each stimulus category, including each of the target stimuli in order to verify that they understood the instructions for the target-detection task. The nontarget training stimuli were excluded from the main experiment. The second encoding run was presented identically to the first run; thus, participants were exposed to each image twice during encoding. In total, the encoding phase lasted 22 minutes.

Following encoding, participants remained briefly in the scanner while structural scans were collected (see below for details). Participants had a break outside of the scanner while they received instructions for the surprise recognition test and then returned to the scanner to complete the recognition test. The recognition test was divided in 2 runs, in each of which 3 face and 3 house blocks were presented in alternating order. Each block consisted of 20 old images (seen during encoding) and 20 new images from the same stimulus category. For each trial, participants were asked whether the image was old or new. Each trial was presented for 1200 ms and followed by a gray screen for 2000 ms, in which participants had the opportunity to respond via button press. Jittered fixation crosses separated the trials ranging from 2000 to 8000 ms. Trial order was pseudo-randomized to ensure that no more than three old or new images were presented successively. Due to a technical issue, the same stimulus order was used for 13 participants starting with a face block and 14 participants starting with a house block. In total, the recognition task lasted 22 minutes.

2.4. fMRI data acquisition and preprocessing

MR imaging was conducted on a Siemens Magnetom TrioTim 3T MRI scanner with a 32-channel head-coil. A T1-weighted (T1w) magnetization prepared rapid acquisition gradient echo (MPRAGE) pulse sequence image (voxel size = 1 × 1 × 1 mm^3; TR = 2.5 ms; TE = 4.77 ms; flip angle = 7°; TI = 1.1 ms) was collected following the encoding phase. Functional blood oxygenation level dependent (BOLD) scans were acquired using an echo planar imaging sequence in 2 runs in both encoding and recognition phases. Encoding runs consisted of 270 volumes each and recognition runs consisted of 372 volumes each (voxel size = 3 × 3 × 3.3 mm^3; TR = 2 s; TE = 30 ms). Additionally, turbo spin-echo proton density images (PDs), diffusion tensor images (DTIs), and fluid attenuation inversion recovery images (FLAIRs) were acquired, but not included in the following analyses. Experimental stimuli were displayed on a projector using the Psychtoolbox (Psychophysics Toolbox) for MATLAB (Mathworks Inc., Natick, MA), which participants were able to view via a mirror mounted on the head-coil.

Data preprocessing was performed using *fMRIPrep* (version 1.4.0; Esteban et al., 2019) using the standard settings. The T1w image was corrected for intensity nonuniformity and used as the T1w-reference image for the rest of the workflow. This reference image was then skull-stripped and spatially-normalized to the *ICBM 152 Nonlinear Asymmetrical template version 2009c* using nonlinear registration. Functional scans were corrected for motion and slice time and finally co-registered to the normalized T1w reference image. Preprocessed functional data were spatially smoothed with a 4-mm full width half maximum kernel.

2.5. Behavioral data analyses

Behavioral data were analyzed using custom MATLAB scripts. As previously reported in Kobelt et al. (2021), recognition memory performance (*Pr*) was calculated as the difference between the hit rate (proportion of correctly identified old items) and the false alarm rate (proportion of new items incorrectly identified as old items; Snodgrass & Corwin, 1988). Age differences in memory performance were assessed with an independent-samples *t* test. Age differences in response bias were assessed with independent-samples *t* tests comparing the hit rates and false alarm rates across

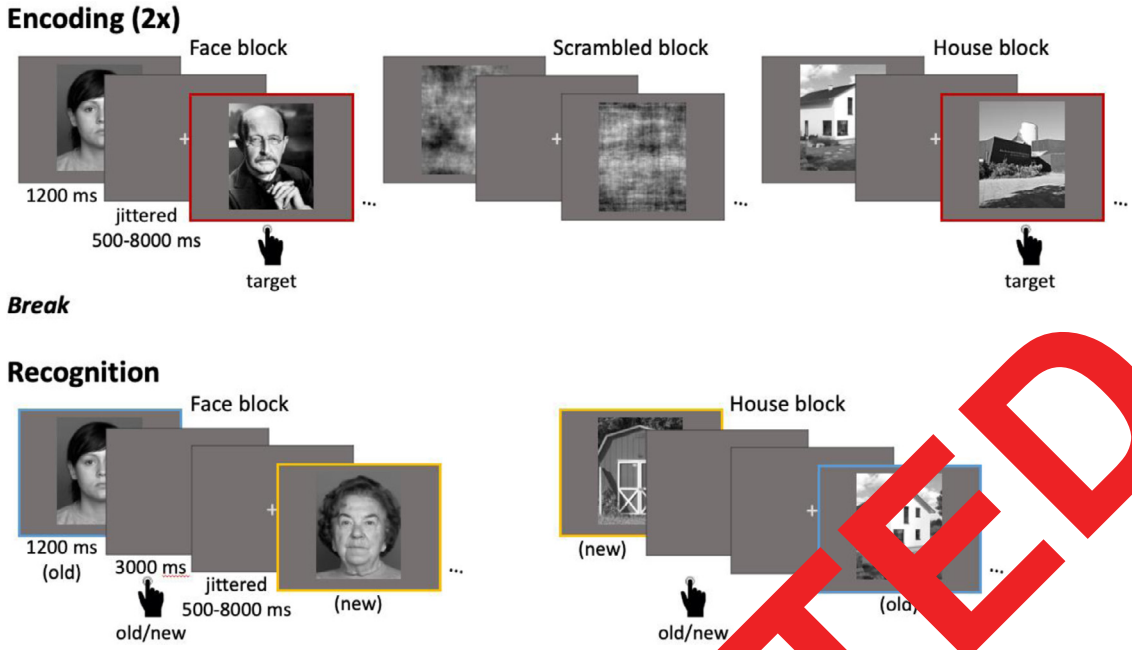

Fig. 1. Face-house task. The fMRI paradigm consisted of an incidental encoding phase (top) and a surprise recogniti[on] t (bottom). During encoding, 2 identical runs of house, face, and scrambled baseline images were presented in a block design. Each encoding run w[as] ised of 9 stim[uli] locks (3 alternating blocks from each stimulus category) with 21 trials per block. Participants were instructed to complete a target-detection ta[sk] [in] which they pressed a b[utt]on when 1 of 3 pre-learned stimuli (outlined in red) was presented. Following a short break, participants completed a surprise recognition m[em]ory test in which they indicated via button press whether each image was old (previously seen during encoding; outlined in blue) or new (not seen before; outlined in [yel]low). The rec[ogni]tion phase was divided into 6 alternating face and house blocks with 40 trials (20 old and 20 new) per block. Figure adapted from Kobelt et al. (2021). [For] interpretati[on] f the references to color in this figure legend, the reader is referred to the Web version of this article.)

age groups. Dependent-samples t tests were conducted to det[ermine] differences in the number of voxels included in the face ([t]0.07, $p = 0.95$) or house ($t(62) = -0.96$, $p = 0.34$) clusters.

mine whether memory performance differed between face an[d] house stimuli and whether memory performance exce[eded] chance level.

2.6. Defining category-selective ROIs

In order to identify participant-spe[cific] ROIs pre[ferentially] active during face and house processi[ng] and hous[e] coding blocks were contrasted to scramb[led] blo[cks] for each participant in a block GLM design as in K[obelt] et al. (2[021]). Using a cluster-based approach, adjacent vo[xels] exceeding an u[ncorr]ected threshold of $p < 0.005$ were d[efin]ed as cluster (for robustness, the analyses were replicated u[sing] u[ncorr]ected thresholds of $p < 0.001$ and $p < 0.01$; see Supplem[entary] Materi[als]). For each participant, the cluster with [the] highest [aver]age [t-v]alue for faces compared to scrambled i[mag]es [in the] desig[n] the face-selective ROI and the cluster [with] the h[ighe]st averag[e] t-value for houses compared to scramble[d] [im]age[s] [was] ated as the house-selective ROI. To limit the s[earch] space to [ca]tegory-selective regions (see D.C. Park et al., 2004), [on]ly voxels within the bilateral VVC as defined by the automated [an]atomical labeling (AAL) atlas were considered. The VVC mask included the fusiform gyrus, parahippocampal gyrus, and inferior temporal gyrus. Furthermore, as an additional step to Kobelt et al. (2021), voxels lost to signal drop-out during recognition were removed from the clusters in order to keep face and house clusters congruent within participants across the subsequent analyses on both encoding and recognition data (Olman et al., 2009). Only participants with at least 10 voxels in both their face and house clusters were included in the analysis (leading to the exclusion of 2 young adults and 4 older adults, as stated in Section 2.1; $M_{\text{FaceVoxels}} = 80$, $\text{Range}_{\text{FaceVoxels}} = 13–278$; $M_{\text{HouseVoxels}} = 78$, $\text{Range}_{\text{HouseVoxels}} = 10–264$). There were

Additionally, we explored the possibility that category-selective [re]gions outside of the VVC may be susceptible to age-related neural dedifferentiation (see Carp et al., 2011; J. Park et al., 2012). Therefore, we identified all face and house clusters in the whole brain in which adjacent voxels exceeded an uncorrected threshold of $p < 0.005$ during the encoding contrast. We visually inspected the sum of the instances in which a given voxel appeared in either a face or house cluster across all participants (see Fig. 2). This revealed considerable agreement across participants for high category selectivity in both the VVC and regions of the occipital cortex. Correspondingly, we added an occipital mask and defined an additional face- and house-selective ROI for each participant which had the highest average t-value for faces or houses compared to scrambled images, respectively. Voxels lost to signal drop-out during recognition were subsequently removed from the clusters. An additional 4 participants (3 young adults and 1 older adult) were excluded from this analysis because their clusters were smaller than 10 voxels, however, since this analysis was not the main focus of the study, these participants were not excluded from any other analyses.

2.7. Assessing neural selectivity and underlying patterns of neural dedifferentiation

Evidence for age differences in neural selectivity has been previously established using both univariate (Kobelt et al., 2021; Hill et al., 2021; Srokova et al., 2020; D.C. Park et al., 2004; J. Park et al., 2012) and multivariate (Kobelt et al., 2021; Chamberlain et al., 2021; Hill et al., 2021; Srokova et al., 2020; Koen et al., 2019) methods. Since the focus of this analysis

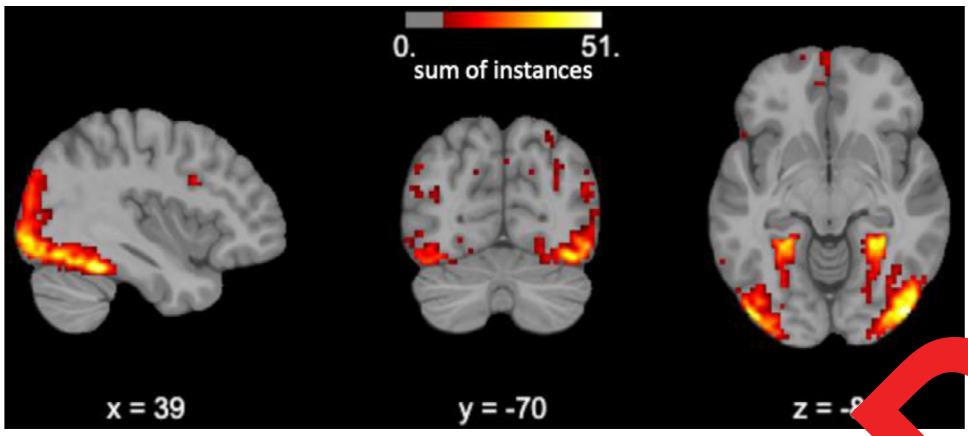

Fig. 2. Sum of instances in which a given voxel was included in either a face or house cluster across all participants (i.e., den erated n eural sele ity). Only voxels that appeared in at least 10 clusters are displayed. Upon visual inspection of this figure, we decided to assess the occipit rtex in addi th C due to the high neural selectivity across participants in both of these regions.

is to understand the underlying patterns of these age differences (i.e., broadening or attenuation), which are distinctly univariate measures assessed by the magnitude of neural activation (Schmolesky et al., 2000), a univariate approach was adopted. Thus, in order to assess mean BOLD activation for each participant, 2 block GLMs were constructed, one model for encoding and one model for recognition. For each encoding run, 3 separate regressors modeled face, house, and scrambled blocks and an additional 6 regressors modeled motion confounds. For each recognition run, 2 separate regressors' modeled face and house blocks with t ditional 6 motion regressors. The resulting voxel-wise beta s were then averaged separately for faces and houses within the and house clusters. The mean beta responses for the 2 recogniti runs were collapsed. Mean beta for preferred s g., face in the face cluster) and non-preferred stimuli g., ho s in the face cluster) were then averaged across stim resulti n av- erage beta response to preferred and no refe tively for each participant at the first second ding runs as well as at recognition. Selectivity were com d by subtracting the response to nonpref d li from the sponse to preferred stimuli within each participant.

A two-way mixed facto analysis of nce (ANOVA) was then used to analyze m beta values during ch memory stage separately with the b en fa "age group" (older vs. younger) and the within-factor "fa ness" (p ferred vs. nonpreferred). Significant interactions w ubsequ y investigated using independent sam ts wit oni-corrected p values. Zero-order cor ions e comp across participants as well as within g s usi rson's r in order to assess the relationship of neural emory stages. The resulting correlation coefficie ere Fisher z-transformed and a z-test was performed to assess differences in correlation strength.

Prior studies ha investigated the idea that age differences in neural selectivity during encoding may have downstream effects for other memory stages, but have found contradicting results (cf., St-Laurent et al., 2014; Hill et al., 2021). In order to assess whether age differences in neural selectivity during repeated encoding and recognition were related to neural selectivity during first encoding, we computed 2 linear model comparisons, one predicting neural selectivity during repeated encoding and one predicting neural selectivity during recognition. For each model comparison, one linear model was computed using age group as a single predictor and the other model used both age group and neural selectivity during first encoding redictors. Th s were compared using the *anova()* fun n

Additionally, ther s been evidence demonstrating that age-relate ral dediffer tion may vary between visual stimulu tegories (Voss et al. 008; Koen et al., 2019; Srokova et al., 2). Therefore we investigate whether faces and houses may be d rentially su ptible to age-related declines in neural selectivity the Supp entary Materials.

2.8. Analyzing repetition effects

stimuli were presented twice during the encoding phase, we suspected repetition suppression may have influenced mean beta values during the repeated encoding run. Therefore, we examined whether there were general activation differences between the 2 encoding runs. Repetition suppression has been shown to primarily affect regions in response to their preferred stimulus category (Barron et al., 2016). Thus, a 2 (age group) × 2 (encoding run) mixed factorial ANOVA was computed on the mean beta values of the preferred stimuli in order to assess age differences in repetition effects.

2.9. Determining the relationship between neural selectivity and memory performance using partial least squares correlation

Finally, we implemented a partial least squares correlation (PLSC) analysis in order to understand the common impact of neural selectivity across the different memory stages on memory performance as well as to delineate the weights of the individual contributions of neural selectivity at each memory stage (Keresztes et al., 2017; Kobelt et al., 2021; Krishnan et al., 2011; McIntosh et al., 1996). First, a between-participant correlation matrix was calculated between an n-element vector containing memory performance (Pr) and a $n \times 3$ matrix of selectivity scores from the 3 memory stages. This correlation matrix was then decomposed using singular value decomposition, producing a single estimate latent variable (LV) that optimally represents the association between neural selectivity and memory performance and depicts the memory stages showing the strongest relationship to memory performance. The significance of the LV was tested using 10,000 permutation tests of the singular value corresponding to the LV. Robustness estimates were measured using a bootstrapping procedure across 10,000 resamples of the data. Bootstrap ratios (BSRs;

normalized robustness estimates) were then calculated by dividing the neural selectivity weights from the singular value decomposition by the standard errors of their robustness estimates. Similar to z values, BSRs are considered reliably robust with values above or below ±1.96. A selectivity-memory score was calculated for each participant by multiplying the neural selectivity weights by the empirical selectivity scores. This selectivity memory score reflects the comprehensive impact of neural selectivity on memory performance within each participant.

3. Results

3.1. Behavioral results

We repeated t tests as in Kobelt and colleagues (2021) in order to re-examine possible age differences in recognition memory performance (i.e., Pr = hit rate – false alarm rate) in the current sample of participants, which slightly differed from that in Kobelt et al. (2021). We corroborated that memory performance did not differ between age groups (M_{young} = 0.24, SD_{young} = 0.12, M_{older} = 0.20, SD_{older} = 0.12, $t(62)$ = 1.45, p = 0.15) and that memory performance exceeded chance in both young ($t(33)$ = 11.93, p < 0.001) and older adults ($t(29)$ = 9.02, p < 0.001). Furthermore, memory performance did not differ between face and house stimuli in either young ($t(33)$ = −0.88, p = 0.39) or older adults ($t(29)$ = −1.61, p = 0.12). Older adults demonstrated a strong response bias, responding "old" more often than young adults to both old stimuli (M_{young} = 0.50, SD_{young} = 0.14, M_{older} = 0.62, SD_{older} = 0.12, $t(62)$ = -3.67, p < 0.001) and new stimuli (M_{young} = 0.26, SD_{young} = 0.11, M_{older} = 0.42, SD_{older} = 0.13, $t(62)$ = −5.35, p < 0.001).

3.2. Age differences in neural selectivity

3.2.1. First encoding

The following analysis of the first encoding run was reported in Kobelt et al. (2021). Due to differences in the participant sample and voxels included in the face and house selectivity maps, we re-analyzed the data here to ensure the results are corroborated. During the first encoding run, results of a 2 (age group) × 2 (preferredness) mixed factorial ANOVA on mean activation in the VVC revealed a main effect of preferredness demonstrating category selectivity ($F(1,62)$ = 7[illegible]4, p < 0.001), but no main effect of age ($F(1,62)$ = 1.02, p = 0.32). Furthermore, we found an interaction between age group and preferredness ($F(1,62)$ = 13.85, p < 0.001), indicating greater neural selectivity in young adults (M_{young} = 1.48, SD = 0.4[illegible] than in older adults (M_{older} = 1.12, SD_{older} = 0.37; see Fig. 3A left). Pairwise comparisons revealed no significant age differences in the mean beta response to preferred stimuli ($t(62)$ = 0.1[illegible] but an age difference in the mean beta response to nonpreferred stimuli ($t(62)$ = 1.86, p = 0.067) with older adults (M = 0.70, SD = 0.67) demonstrating greater activation to nonpreferred stimuli than younger adults (M = 0.31, SD = 0.96) in line with the neural broadening hypothesis (see Fig. 3B left). Thus, these results are in agreement with the findings of Kobelt et al. (2021), and the shift in significance is likely a power issue related to the smaller sample size.

In the occipital clusters, results of a 2 (age group) × 2 (preferredness) mixed factorial ANOVA on mean activation revealed a main effect of preferredness demonstrating category selectivity ($F(1,58)$ = 730.91, p < 0.001), but no main effect of age ($F(1,58)$ = 0.36, p = 0.55). Furthermore, we did not find an interaction between age group and preferredness ($F(1,58)$ = 0, p = 0.99), indicating no age differences in neural selectivity between young adults (M_{young} = 1.10, SD_{young} = 0.30) and older adults (M_{older} = 1.10, SD_{older} = 0.33).

3.2.2. Repeated encoding

During the repeated encoding run, results of a 2 (age group) × 2 (preferredness) mixed factorial ANOVA on mean activation in the VVC revealed a main effect of preferredness demonstrating category selectivity ($F(1,62)$ = 611.57, p < 0.001), but no main effect of age ($F(1,62)$ = 0.003, p = 0.96). We found an interaction between age group and preferredness ($F(1,62)$ = 7.14, p = 0.01), indicating greater neural selectivity in young adults (M_{young} = 1.39, SD_{young} = 0.40) than in older adults (M_{older} = 1.12, SD_{older} = 0.41; see Fig. 3A middle). Pairwise comparisons revealed no significant age differences in the mean beta response to preferred stimuli ($t(62)$ = −0.62, p = 0.[illegible] or in the mean beta response to nonpreferred stimuli ($t(62)$ = [illegible]3, p = 0.6[illegible] see Fig. 3B middle). Therefore, despite the observed age-related decline in neural selectivity during repeated encoding, there was no clear evidence for neural broadening or attenuation.

In the occipital clusters, results of a 2 (age group) × 2 (preferredness) mixed factorial ANOVA on mean activation revealed a main effect of preferredness demonstrating category selectivity ($F(1,58)$ = [illegible] p < 0.00[illegible] but no main effect of age ($F(1,58)$ = 0.8[illegible] p = [illegible]. We did not find an interaction between age group and preferredness ($F(1,58)$ = 0.24, p = 0.63), indicating no age differences in neural selectivity between young adults (M_{young} = 1.09, SD_{young} = 0.40) and older adults (M_{older} = 1.04, SD_{older} = 0.37).

3.2.3. [illegible]gnition

During [illegible]tion, results of a 2 (age group) × 2 (preferredness) mixed factorial ANOVA on mean activation in the VVC revealed a main effect of preferredness demonstrating category selectivity ($F(1,62)$ = 171.20, p < 0.001), but no main effect of age ($F(1,62)$ = 2.92, p = 0.09). We found an interaction between age group and preferredness ($F(1,62)$ = 12.87, p < 0.001), indicating greater neural selectivity in young adults (M_{young} = 0.82, SD_{young} = 0.43) than in older adults (M_{older} = 0.46, SD_{older} = 0.33; see Fig. 3A right). Pairwise comparisons revealed a significant age difference in the mean beta response to preferred stimuli ($t(62)$ = −2.23, p = 0.029) with older adults (M = 1.59, SD = 1.00) demonstrating lower activation to preferred stimuli than younger adults (M = 2.21, SD = 1.20; see Fig. 3B right). No age differences were found in the mean beta response to nonpreferred stimuli ($t(62)$ = −1.07, p = 0.29). The pattern exhibited at recognition is in line with the neural attenuation hypothesis.

In the occipital clusters, results of a 2 (age group) × 2 (preferredness) mixed factorial ANOVA on mean activation revealed a main effect of preferredness demonstrating category selectivity ($F(1,58)$ = 186.35, p < 0.001), but no main effect of age ($F(1,58)$ = 0.05, p = 0.82). We did not find an interaction between age group and preferredness ($F(1,58)$ = 0.03, p = 0.87), indicating no age differences in neural selectivity between young adults (M_{young} = 0.48, SD_{young} = 0.27) and older adults (M_{older} = 0.47, SD_{older} = 0.27). Due to the absence of age differences in neural selectivity in the occipital cortex in all 3 memory stages, further analyses followed up only on the VVC.

3.3. Stability of interindividual differences in neural selectivity across memory stages

We sought to elucidate whether interindividual differences in neural selectivity remained stable across the memory stages. Thus, Pearson correlations were computed to investigate how measures of neural selectivity were related within individuals across memory

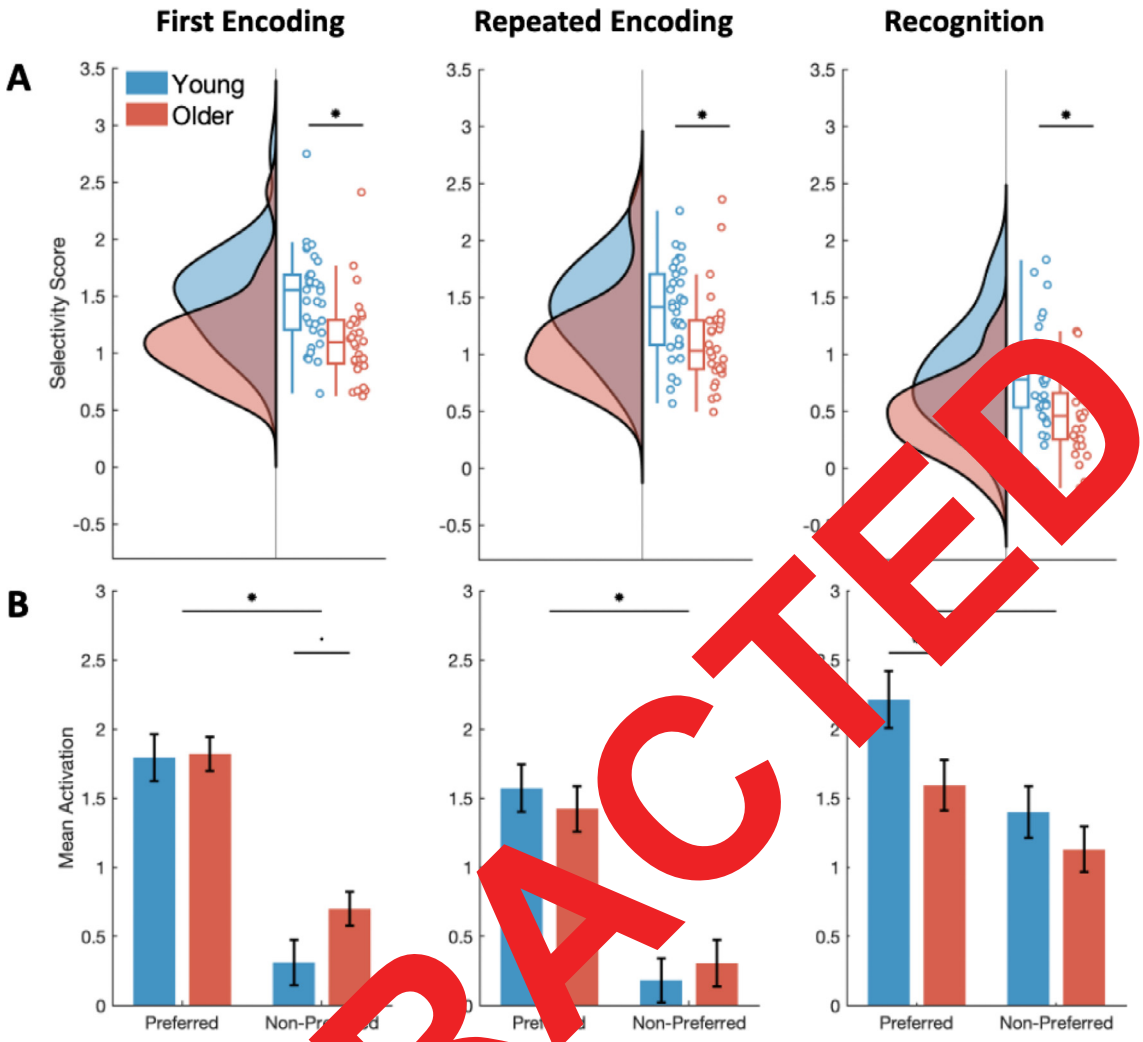

Fig. 3. Age differences in neural selectivity (A) and [illegible] (B). Young adults (blue) demonstrated greater neural selectivity than older adults (red) during first encoding (left), repeated encoding [illegible], and [illegible]nition (right). Group distributions are displayed in unmirrored violin plots and boxplots with medians and 95% confidence intervals with whiskers repre[illegible]ng the 2nd [illegible]8th percentiles (Allen et al., 2019). Selectivity scores of individual participants are reflected in jittered data points. Error bars in the bar charts de[illegible]dard error of t[illegible]an. Significant group differences ($p < 0.05$) are indicated by asterisks and marginal group differences are indicated by periods. (For interpreta[illegible]of t[illegible]erences to colo[illegible] this figure legend, the reader is referred to the Web version of this article.)

stages. Neural selecti[illegible]wa[illegible]ositively correlated between first encoding and repeated e[illegible]g ($r = 0$[illegible], $p < 0.001$, $r_{young} = 0.87$, $p_{young} < 0.001$, $r_{older} = 0.$[illegible], $p_{older} < 0.001$), first encoding and recognition [illegible] $= 0.$[illegible], $p < 0$[illegible], $r_{young} = 0.86$, $p_{young} < 0.001$, $r_{older} = 0$[illegible], $p_{older} < 0.001$), and repeated encoding and recognition ($r =$ [illegible] p[illegible] $= 0.77$, $p_{young} < 0.001$, $r_{older} = 0.36$, $p_{older} = 0.0$[illegible]ese findings indicate that interindividual differences in neura[illegible]lectivity were strongly related across memory stages (see Fig. 4).[illegible]nificant age differences in the strength of the correlations of neural selectivity were found between first encoding and repeated encoding ($z = 2.25$, $p = 0.02$) and between repeated encoding and recognition ($z = 2.45$, $p = 0.01$), but not between first encoding and recognition ($z = 1.58$, $p = 0.11$). It should also be noted that the sizes of the ROIs were moderately correlated with neural selectivity during first encoding ($r = -0.28$, $p = 0.02$) and repeated encoding ($r = -0.27$, $p = 0.03$), but not during recognition ($r = -0.10$, $p = 0.42$). However, this relationship did not mediate the neural selectivity correlations.

3.4. Age-related variance in neural selectivity during repeated encoding and recognition attributed to neural selectivity during first encoding

A linear model comparison revealed a significantly better model fit on neural selectivity during repeated encoding when including neural selectivity during first encoding as a predictor ($R^2 = 0.71$) compared to age group alone ($R^2 = 0.17$; $F(62) = 58.38$, $p < 0.001$). A linear model comparison also revealed a significantly better model fit on neural selectivity during recognition when including neural selectivity during first encoding as a predictor ($R^2 = 0.62$) compared to age group alone ($R^2 = 0.10$; $F(62) = 43.71$, $p < 0.001$). Additionally, the main effect of age group was eliminated by adding neural selectivity during first encoding as a predictor in both models ($ps > 0.14$). These findings suggest that age differences in neural selectivity during both repeated encoding and recognition are largely attributable to age differences in neural selectivity during first encoding.

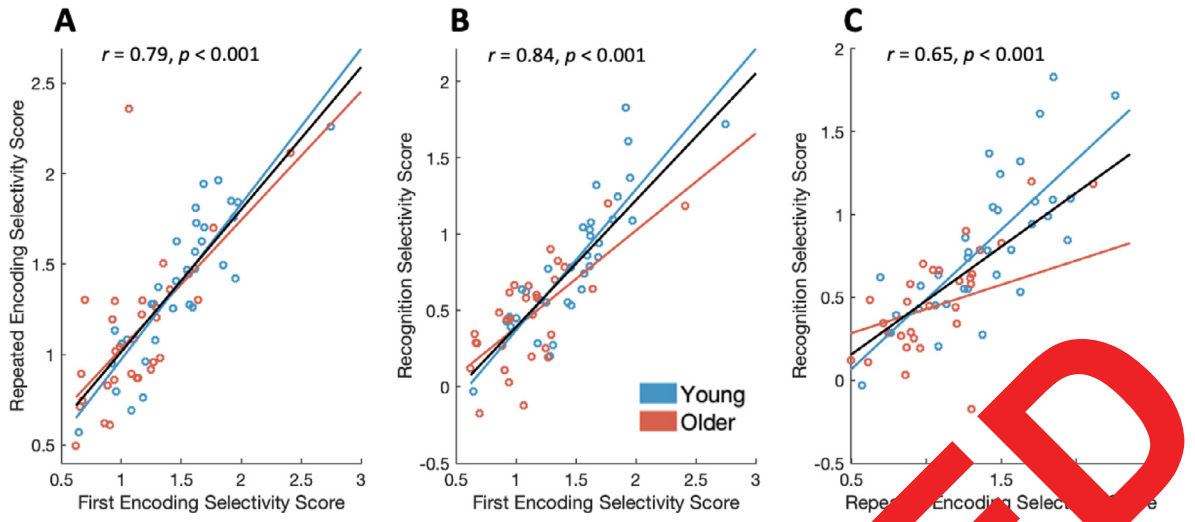

Fig. 4. Neural selectivity was strongly correlated between first encoding and repeated encoding (A), first encoding and rec[illegible]n (B), and repeated encoding and recognition (C). Young adults shown in blue and older adults in red. Black lines and corresponding Pearson correlation values reflect co[illegible]s for both groups combined. Note: axis scale varies between plots. (For interpretation of the references to color in this figure legend, the reader is refer[illegible] the Web [illegible]on of th[illegible]ticle.)

3.5. Repetition effects between first and repeated encoding

A 2 (age group) × 2 (encoding run) mixed factorial ANOVA on preferred mean beta values revealed no main effect of age group ($F(1,62) = 0.13$, $p = 0.72$), but a main effect of encoding run ($F(1,62) = 4.27$, $p = 0.04$). No interaction was found between age group and run ($F(1,62) = 0.34$, $p = 0.56$). Mean comparisons show that the repeated encoding run ($M = 1.50$, $SD = 0.5$[illegible]) demonstrated lower preferred activation than the first encoding run ($M = 1.80$, $SD = 0.85$). In sum, we found evidence for repetition suppression between the first and repeated [illegible] runs, but no evidence for age differences therein.

3.6. Relation to memory performance

In order to disentangle the relative [illegible]tribution of [illegible]l selectivity during each memory stage to [illegible]erformance, we performed a PLSC analysis to extract a single co[illegible]site score that depicts individual differences in [illegible]ural selectivity. [illegible]s analysis identified a marginally reliable [illegible]ent variable (LV; p [illegible]0.051) that optimally represents the r[illegible]onshi[illegible]tween neural selectivity and memory ($r = 0.25$; see Fig[illegible] P[illegible] revealed higher neural selectivity during first encoding (BS[illegible].49) a[illegible]ecognition (BSR = 2.19) as the 2 stable c[illegible]ts of t[illegible]V[illegible]aining the largest amount of informati[illegible]ommo[illegible]to mem[illegible]performance and the multivariate pa[illegible] of n[illegible]selectivity. Note, if neural selectivity is standardized [illegible]ach ag[illegible]oup in order to control for age differences, the LV [illegible]longer reliable ($p = 0.12$).

4. Discussion

Evidence for age-related neural dedifferentiation has been established as a reduction in the distinctiveness of categorical visual processing in the VVC in older adults (Carp et al., 2011; Kobelt et al., 2021; Koen & Rugg, 2019; D.C. Park et al., 2004; J. Park et al., 2012). Studies often explore these differences as a possible mechanism for age-related memory decline (Kobelt et al., 2021; Koen et al., 2019, 2020). Importantly, age differences in neural selectivity are typically investigated using data collected during passive viewing or encoding tasks despite the fact that age-related neural d[illegible] have also [illegible] expressed during retrieval processing ([illegible]as & Duarte, 2012; J[illegible]nson et al., 2015; St-Laurent et al., 201[illegible] Therefore, we expanded the scope of this research line by asse[illegible]ng measur[illegible]of age-related neural dedifferentiation across diffe[illegible] memory [illegible]ocessing stages (i.e., initial encoding, repeated encodi[illegible]d r[illegible]gnition) in a group of young and older adults.

We rep[illegible]d the results of previous studies by demonstrating [illegible]lder adults exhibit reduced neural selectivity in the VVC duri[illegible]g compared to younger adults (Kobelt et al., 2021; D.C. [illegible]k et al., 2004), and expanded the literature by showing that this age deficit in neural selectivity is also salient during repeated encoding. Furthermore, we found evidence for reduced neural selectivity in older adults during recognition, supporting findings that age-related neural dedifferentiation also manifests during memory retrieval processing (Dulas & Duarte, 2012; Johnson et al., 2015; St-Laurent et al., 2014). In addition, a multivariate measure of neural selectivity showed a significant relationship with memory performance, in line with the idea that neural dedifferentiation is associated with poorer episodic memory (Kobelt et al., 2021; Koen et al., 2019; for review, see Koen et al., 2020), though this relationship was not independent of age as suggested in a recent review (Koen & Rugg, 2019). Our results also revealed that neural broadening and neural attenuation, as found during first encoding and recognition, respectively, are similarly detrimental to memory processing, indicating that both manifestations significantly contribute to senescent cognitive decline. Our findings support the idea that high fidelity neural representations are crucial in facilitating memory encoding and retrieval processes (Koen et al., 2020).

Importantly, age differences in neural selectivity can manifest as one of three possible underlying patterns: neural broadening, neural attenuation, or both (J. Park et al., 2012). The underlying pattern can be determined by examining the average BOLD activation in response to preferred and non-preferred stimuli. Using this method, we have previously determined that the pattern driving age differences in neural selectivity during first encoding resembled neural broadening (Kobelt et al., 2021). This finding is also in line with several other studies which established neural broadening during encoding (J. Park et al., 2012; Hill et al., 2021; but see Koen et al., 2019). Expanding on the findings reported by Kobelt et al. (2021), we investigated neural broadening and

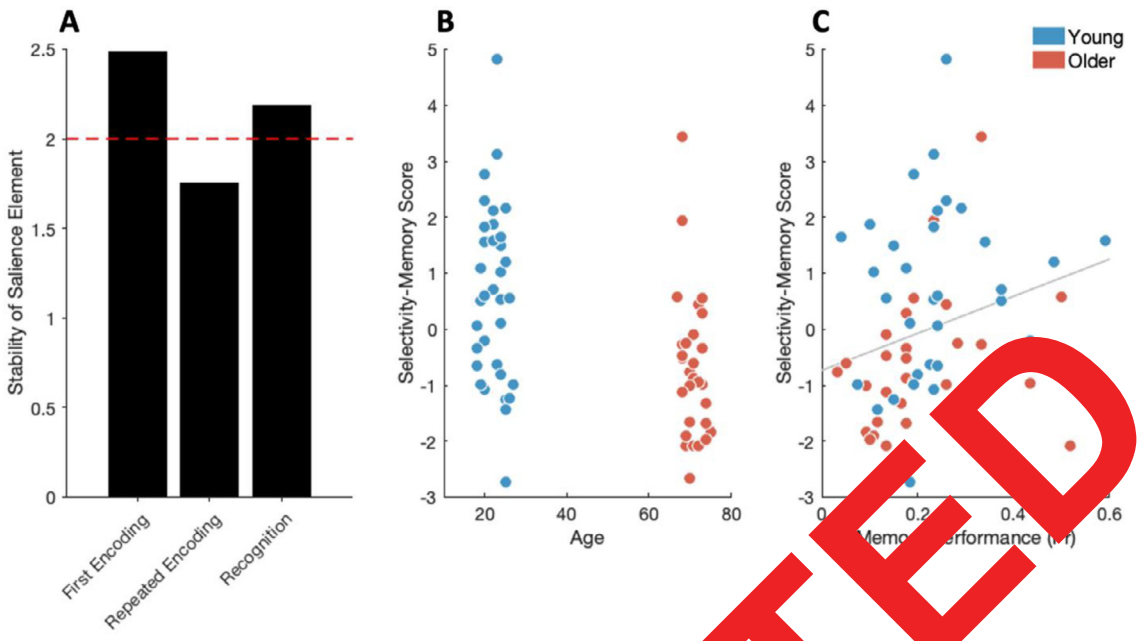

Fig. 5. Association between neural selectivity and memory identified by PLSC. Bootstrap ratios of the LV profile si[illegible]st encoding and recognition as the stable components with the robustness cutoff indicated by the dashed red line (A). Selectivity-memory scores were lower in older a[illegible] compared with younger adults (B) and positively correlated with memory performance (C). Blue denotes young adults and red denotes older [illegible]or interpretatio[illegible]he references to color in this figure legend, the reader is referred to the Web version of this article.)

attenuation during subsequent memory stages, namely repeated encoding and recognition. Interestingly, although we observed age differences in neural selectivity during repeated enc[illegible] the underlying pattern did not clearly indicate either broad[illegible]g or attenuation. During recognition, we found evidence promo[illegible]g neural attenuation as the pattern driving age differences in neu[illegible] selectivity. Hence, our results provide rare eviden[illegible]fferenti[illegible] mechanisms underlying age-related neural ded[illegible]ential[illegible]n across memory processing stages (i.e., neural broad[illegible]g duri[illegible]ncoding and neural attenuation during retrieval).

Considering that neural selectivity w[illegible] assess[illegible] the same region at all three timepoints, the di[illegible]nces in the[illegible]erved pattern likely arose from processing[illegible]es between [illegible] memory stages. Comparing first and repe[illegible]ed enc[illegible]g, we found evidence of repetition suppression, w[illegible]h may explai[illegible]ese differential observed patterns. We did[illegible] find age differen[illegible]in the repetition effect, but a similar o[illegible]all red[illegible]on in neural activation during repeated encoding in[illegible]h [illegible] groups. Interestingly, a previous study has reported that [illegible] adults e[illegible]hibited broader repetition effects than [illegible]adult[illegible]h [illegible]., 2010). In that study, the authors as[illegible]ed ag[illegible]differen[illegible] the repetition effect for pairs of identi[illegible]faces p[illegible]ented one after another as well as pairs of faces in w[illegible]e had been slightly morphed. They found that y[illegible]er adults demonstrated the repetition effect only for identical fac[illegible]ut older adults demonstrated the repetition effect for both ident[illegible]and morphed faces, indicating an age-related reduction in neural selectivity in line with the neural broadening hypothesis. Note that Goh et al. (2010) evaluated the repetition effect at a single trial level, whereas we utilized a block design. It thus remains an intriguing possibility that age differences in repetition suppression effects can themselves serve as neural markers for age differences in neural differentiation (see Sommer et al., 2021), which potentially influenced the observed underlying pattern of age differences in neural selectivity.

We further identified differences in the pattern of activation between first encoding and recognition. Differences between encodi[illegible]nd retrieva[illegible]ave been previously observed in mean activity (Ca[illegible]& Ny[illegible], 2000; Daselaar et al., 2009), functional connectivity ([illegible] et al., 2011; Simons & Spiers, 2003), and object representations (Long & Kuhl, 2021). These discrepancies may reflect [illegible]es in the utility of the tasks (Simons & Spiers, 2003) or [illegible] differences in orienting attention between the memory stages (Chun & Turk-Browne, 2007; Wagner et al., 2005), which may be represented in neural activity leading to differential manifestations of neural dedifferentiation.

Another explanation for the observed differences in activation patterns between encoding and recognition may be differences in task demands. It has been suggested that task demands may modulate expressions of age-related neural dedifferentiation (Koen & Rugg, 2019) and that memory retrieval imposes greater task demands than passive memory encoding (Favila et al., 2020). In this study, the task demands were implicitly varied, with a passive encoding task employing few cognitive resources, but an active recognition task requiring higher cognitive resources. This subtle modulation of cognitive engagement may have interacted with the neural representations of categorical information leading to differences in activation. Age differences in neural selectivity have previously been shown to be highly susceptible to variation in cognitive load (Carp et al., 2010). Carp et al. (2010) provided evidence for greater neural differentiation in older adults compared to younger adults under low cognitive load, but greater neural differentiation in younger adults compared to older adults under high cognitive load. These findings demonstrate the malleability of measures of neural dedifferentiation under changing task demands, which may offer an additional explanation for the differences we observe between encoding and recognition.

We found that age differences in neural selectivity during both repeated encoding and recognition could be mostly attributed to age differences in neural selectivity during first encoding. These findings are in line with a recent study by Hill et al. (2021), which showed that age-related dedifferentiation of reinstated neural patterns during retrieval was largely explained by encoding-related

dedifferentiation. Therefore, poor formation of memory representations during encoding likely has downstream consequences for subsequent memory stages (Sander et al., 2021). As a result, our evidence for neural attenuation during retrieval may reflect an inability to activate the correct target representations amid concurrent, highly similar memory traces. Together, this suggests that age-related impairments in memory processing may stem from information degradation during initial encoding and not during retrieval (but, see St-Laurent et al., 2014).

It is an open question whether neural broadening and neural attenuation are manifestations of distinct underlying mechanisms or different manifestations of a singular underlying mechanism. We found that reduced neural selectivity in older adults was driven by neural broadening during first encoding, but by neural attenuation during recognition. Furthermore, neural selectivity across all memory stages was highly correlated, despite exhibiting differential activation patterns. These findings suggest that the participants who demonstrated greater neural broadening during encoding also demonstrated greater neural attenuation during recognition, indicating that these distinct manifestations are likely related. It is thus possible that a "common cause" (see Lindenberger & Baltes, 1994), underlies both neural broadening and neural attenuation. One plausible "common cause" contributing to the expression of age-related neural dedifferentiationare age differences in neurotransmitter availability that act globally on neural activation. According to Li et al. (2001), deficient neuromodulation reduces both excitatory and inhibitory neural signals, which may explain how neural attenuation and broadening manifest, respectively. Early research using simulations of neurotransmitter systems pointed to an age-related decline in the integrity of dopaminergic pathways as the potential mechanism leading to cognitive decline (Li & Lindenberger, 19 Li et al., 2001). Although the role of reduced dopaminergic activity in memory decline has been substantiated (Abdulrahman et al 2017; Bäckman et al., 2006, 2010; Rieckmann et al., 2 studies exploring the relationship between dopamine and dedifferentiation of functional brain activation reveal mixed sults, with some findings indicating a dopamine-related reduction in neural selectivity (Abdulrahman et al., 2017) and others suggesting no relationship (Rieckmann et al., 2018). More recently, age differences in gamma-aminobutyric acid (GABA) have come into the research focus. Reduced GABA levels have been associated with lower neural selectivity in visual (Chamberlain et al., 21) and auditory (Lalwani et al., 2019) regions. In particular relevance to our study, Chamberlain and colleagues (2021) found a decrease in neural selectivity in the VVC in response visual face and house stimuli, which coincided with crease in GABA concentration. Thus, a reduction in neurotransmitter availability (e.g., dopamine and GABA) is a likely candidate for a common cause of age-related neural dedifferentiation.

As an exploratory analysis, we also investigated age differences in neural selectivity in the occipital cortex. However, we found no evidence for age-related decline in neural selectivity in this region, indicating that both young and older adults demonstrated high neural selectivity in the occipital cortex. This finding suggests that age differences in neural selectivity for category information may influence higher-order perceptual networks and not lower-level perceptual processing regions. Furthermore, this finding is in line with a recent study by Koen et al. (2019), which also identified evidence for age-related neural dedifferentiation in ventral visual regions, but not in occipital regions. Interestingly, several studies have found age differences in neural selectivity in brain regions outside of the VVC (Carp et al., 2010, 2011; Kobelt et al., 2021; J. Park et al., 2012), however, they differ from the present analysis in that they did not identify participant-specific ROIs and, with the exception of J. Park et al. (2012), they used a multivariate approach to assess neural selectivity. Note that the Kobelt et al. (2021) finding of age differences in neural selectivity in the occipital cortex was only identified by their item-level analysis, not in their category-level analysis, indicating that aging may impact fine-grained neural representations in the occipital cortex, which our analysis does not detect. Future research should seek a better understanding of how age-related neural dedifferentiation manifests across different brain regions.

We would like to point out 2 limitations with the present study. First, the face and house clusters were defined exclusively using data from encoding, but used for both encoding and retrieval analyses. The intent was to avoid "double di by defining the clusters using the same data as the m analys However, recent studies have demonstrated a s d shift fro coding to retrieval, in which highly selective re are found be more anterior during retrieval than oding (bridge al., 2021; Steel et al., 2021). Since the esent datase d scrambled images during the encod phase was n possible to define phase-specific cluster us may not have captured the full extent of the a iffer in neu electivity during retrieval. Although s unclear the ese spatial shifts may be less pronou uring recogn tasks compared with free or cued reca tasks. ond, the use of a memory recognition task does not allow us distinguish whether the observed age-related dedifferenti during retrieval was due to dedifferen tion of reinstated encoding information or dedifferentiated rep entations of e perceptual input of the test stimuli. Age-rela declines i eural selectivity have been observed during both al perce al input (Carp et al., 2011; Kobelt et al., 2021; Koen & ; D.C. Park et al., 2004; J. Park et al., 2012) as ll as during reinstatement of encoding-related neural activity (man et al., 2017; Hill et al., 2021; St-Laurent et al., 2014). ce re ognition stimulates both reinstatement as well as active erception, it is not possible to disentangle these 2 processes in he present study. These two points should be considered when lanning future studies targeting age-related neural dedifferentiation during memory retrieval.

Collectively, our findings demonstrate age-related declines in neural selectivity during first encoding, repeated encoding, and recognition, supporting the idea that aging affects neural representations of categorical information across memory stages. The underlying patterns of functional activation revealed that age differences in neural selectivity were driven by neural broadening during encoding, but neural attenuation during recognition, indicating how memory stages and possibly related task demands interact with neural activation. Importantly, neural selectivity was strongly associated across memory stages, suggesting that neural broadening and attenuation are unique manifestations of a common mechanism responsible for dedifferentiated neural responses in older age.

Author statement

Claire Pauley: Formal analysis, Software, Writing - Original Draft. Verena R. Sommer: Conceptualization, Investigation, Writing – Review & Editing. Malte Kobelt: Software, Writing – Review & Editing. Attila Keresztes: Investigation, Writing – Review & Editing. Markus Werkle Bergner: Conceptualization, Writing – Review & Editing. Myriam C. Sander: Conceptualization, Project administration, Supervision, Writing – Review & Editing.

Disclosure statement

The authors declare no competing financial interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.12.001.

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