THE RELATIONSHIP BETWEEN AGE, COGNITIVE PERFORMANCE, AND THE NEURAL

CORRELATES OF EPISODIC MEMORY ENCODING AND RETRIEVAL

by

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Cognitive aging is associated with a disproportionate decline in episodic memory, the ability to recollect contextual details of previously experienced events. Understanding the mechanisms which underlie age-related episodic memory decline is a critical precursor to developing interventions aimed at ameliorating memory deficits in healthy and pathological aging. Considerable empirical evidence suggests that age-related episodic memory deficits arise from numerous factors which differentially impact multiple neural processes and brain regions. The present work focuses on examining some contributors which have been proposed under this framework. Study 1 investigates age-related neural dedifferentiation, a phenomenon characterized by age-related reductions in the neural selectivity of category-selective cortical regions. Our analyses reveal robust age effects on neural differentiation for scene, but not for face stimuli, adding to prior evidence indicating that age-related neural dedifferentiation is not a ubiquitous phenomenon. Study 1 also reveals that the strength of neural differentiation during encoding is predictive of subsequent memory performance independently of age. The work in Study 1 is complemented by Study 4 in which neural dedifferentiation is operationalized at the level of individual exemplars (as opposed to stimulus categories). To examine item-level neural differentiation, we framed our analyses in terms of age differences in repetition suppression effects, which revealed null effects of age. Collectively, Studies 1 and 4 highlighting the functional significance of age-related neural dedifferentiation and emphasize the urgent need to advance our understanding of the factors that lead to age differences in neural selectivity and specificity.

Moving on to Study 2, the work described therein examines age differences in retrieval gating, the ability to regulate the retrieval of mnemonic information according to behavioral goals. Study 2 provides the first evidence that older adults do not engage in retrieval gating, indicating that episodic memory decline may arise as consequence of a decline in the engagement of goal-dependent retrieval strategies. Lastly, Study 3 reveals novel evidence for age differences in the retrieval-related anterior shift, the phenomenon whereby the peak neural activity at retrieval occurs in more anterior portions of single cortical regions relative to encoding. Our analyses show that the shift is greater in older than younger adults, and that greater shift is associated with worse memory performance independently of age. In line with prior empirical work proposing a posterior (perceptual) to anterior (conceptual) gradient in the brain, these findings indicate that the age-related increase in anterior shift may be reflective of an increased reliance on gist-based low-fidelity retrieval in older age. Taken together, the studies comprising this dissertation enhance our understanding of the behavioral and neural correlates of cognitive aging and advance the collective knowledge in the field cognitive neuroscience of age-related episodic memory decline.

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CHAPTER 1

INTRODUCTION: BACKGROUND AND SIGNIFICANCE

1.1   Theoretical Framework of Episodic Memory

Episodic memories are consciously accessible memories for personally experienced past events which are bound to a specific time and place (Tulving, 1983, 2002). Episodic memory processing involves three functionally distinct and critical stages: encoding, storage, and retrieval. Encoding is the first stage by which the information pertaining to an experienced event is transformed into a cohesive mnemonic representation. The representations of the encoded memories are then stabilized during the storage stage. Storage is not merely a passive 'archive' of past memories: memory for an experienced event becomes consolidated and modified via cellular and synaptic processes which occur minutes to hours following encoding (Wincour & Moscovitch, 2011; Dudai et al., 2015). Further modification or forgetting of the stored memory may occur through interference caused by previously learned information (proactive interference; Underwood, 1957) or by our continued interaction with the environment and consequent formation of new memories (retroactive interference; Jenkins & Dallenbach, 1924). The last stage, episodic retrieval, involves processes which are engaged to prompt the reactivation of a stored memory. Importantly, the retrieved contents of the episode may be differentially emphasized or further modified by our prior experiences or current behavioral goals and biases. Therefore, episodic retrieval should be thought of as an imperfect reconstructive process as opposed to a mirror replay of prior events.

The studies described in this dissertation focus on the mechanisms underlying encoding and retrieval in the context of cognitive aging. Major emphasis is placed on the notion that encoding and retrieval are highly interactive processes and should not be thought of as being independent of one another (for review see Renoult et al., 2019). Current theories of episodic memory function conjecture a considerable overlap and interdependence in the processes which underlie episodic encoding and retrieval. In the field of experimental psychology, this notion became known as the principle of Transfer Appropriate Processing (TAP; Morris et al., 1977; for review see Roediger et al., 2002). TAP argues that successful retrieval is dependent on the overlap

in the cognitive operations engaged at encoding and subsequent retrieval, and it assumes that retrieval involves the reactivation of the cognitive processes which had been active at encoding. Indeed, greater overlap between encoding- and retrieval-related processing has been shown to result in a greater likelihood of successful retrieval (Weldon et al., 1989; for review see Rugg et al., 2015). TAP has been neurobiologically validated by the evidence supporting retrieval-related *cortical reinstatement*, a phenomenon characterized by a partial retrieval-related reactivation of neural patterns which had been initially observed at encoding (for reviews see Danker and Anderson, 2010; Rissman and Wagner, 2012; Rugg et al., 2015; Xue, 2018). As will be discussed later, the current theories of cortical reinstatement assume that the specificity and fidelity with which an event is represented at encoding are direct determinants of the quality of the retrieved representation (Trelle et al., 2020; Hill et al., 2021). It should be emphasized that although encoding and retrieval are often studied in separation, understanding the mechanisms that underlie one stage are also in part informative of the other stage.

1.2 Episodic Memory from the Perspective of Cognitive Aging

1.2.1 Episodic Memory Decline

Relative to other forms of memory, such as semantic memory (memory for general knowledge), episodic memory is known to decline substantially with increasing age (Nilsson, 2003; Nyberg et al., 2012). Episodic memory abilities are a critical component of cognitive functioning in older age. Even in the absence of pathology, cognitive aging has a detrimental impact on one's quality of life and every-day functioning (Mather, 2006; Young & Bunce, 2011). Episodic memory function is not only useful for the retrieval of previously experienced events, but it is also critical when relying on prior experiences to guide behavioral goals. Understanding the factors that contribute to episodic memory decline is an essential precursor to developing interventions which ameliorate the impact of aging and prevent or delay the onset of neurodegenerative disease.

Although it is well established that behavioral performance on episodic memory tasks declines with age, not all types of tests and forms of episodic memory appear to be affected equally (Naveh-Benjamin, 2000; Old & Naveh-Benjamin, 2008; Luo & Craik, 2008; Koen & Yonelinas,

2014, 2016). Research demonstrates that older adults exhibit deficits on free recall as well as in tasks requiring retrieval of associations between event items (associative memory) or retrieval of the item's contextual information (source memory). In contrast, item recognition tasks requiring binary old/new judgements (item memory) often appear relatively impervious to increasing age.

From a dual-process perspective, recognition memory is held to be supported by two distinct memory signals: recollection and familiarity (for reviews see Yonelinas 2002; Aggleton & Brown, 2006; Diana et al., 2007). Recollection reflects the retrieval of qualitative information and the context of the experienced event, and as such it is thought to support associative and source memory judgements. Familiarity manifests as a scalar signal of varying memory strength for a previously experienced memory but in the absence of qualitative information about the event (i.e., spatiotemporal context of a recognized item). In line with the observations in the cognitive aging literature, it has been proposed that increasing age is associated with selective declines in recollection but with relatively preserved performance on tasks that rely on familiarity (Koen & Yonelinas, 2014, 2016; but see Parks, 2007; Wang et al., 2012).

Associative and source memory retrieval tasks typically require participants to select between two or three response options when making their memory judgement. For example, the Remember / Know procedure (Tulving, 1985) requires participants to respond 'remember' if they subjectively judge that they have recollected the details associated with the cued item, and 'know' if their response is based on a sense of familiarity in the absence of qualitative detail. In source memory paradigms (Duarte et al., 2005; Yu et al., 2012), participants commonly judge which of the provided alternative categorical contexts had been paired with a recognized item (e.g., determining whether a cued test word had been paired with an image of a face or a scene at encoding). Although older adults tend to demonstrate a decline in recollection, these approaches are based on a dichotomy between 'recollected' vs 'not recollected' outcomes, and as a result may fail to account for potential age differences in the quality of the successfully recollected episode. Studies employing a continuous behavioral measure to probe precision of retrieval (such as tasks with a continuous 360-degree response dial) have demonstrated that older adults exhibit declines in the precision for mnemonic details even when the response is accompanied by successful recollection (Nilakantan et al., 2018; Korkki et al., 2020). This finding would suggest that memory

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decline may arise from a reduction in the quality and specificity of mnemonic information, consistent with the observation that age differences are more likely to be detected on tasks requiring retrieval of specific episodic detail (Luo & Craik, 2008). Age-related decline in the ability to retrieve precise detail supports the proposal that age-related memory decline results from an increased reliance on gist-like representations of previous events (Koustaal & Schacter, 1997; Dennis et al., 2007; 2008, Gallo et al., 2019; Srokova et al., 2022 [Chapter 4]).
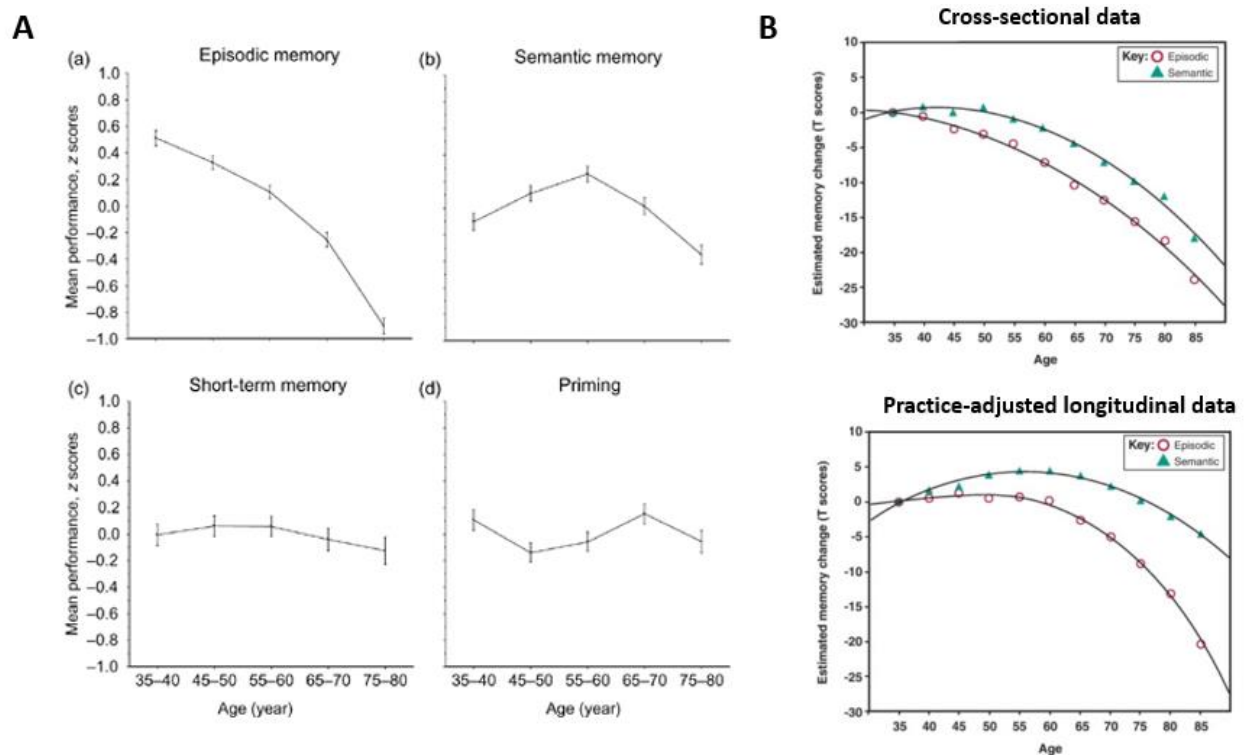
Figure 1.1. Episodic memory declines substantially with increasing age. **(A)** Cross-sectional data demonstrate a linear decline in episodic memory across the adult lifespan while other types of memory remain relatively stable. *Figure in panel A reproduced with permission from Nilsson, 2003* **(B)** Longitudinal data suggests that the linear decline observed in cross-sectional studies is overestimated. Episodic memory function remains relatively intact throughout young to middle age, and the age-related decline onsets approximately at the age of 60. *Figure in panel B reproduced with permission from Nyberg et al., 2012*. See *1.2.3. Methodological Considerations in the Field of Cognitive Aging* for a discussion on cross-sectional versus longitudinal research in the field of cognitive aging.

1.2.2 Causes of Episodic Memory Decline

Several decades of empirical research have been dedicated to uncovering the factors that contribute to episodic memory decline in healthy aging. One of the first major theories, the 'common cause hypothesis' of cognitive aging, posits that age-related decline in the sensory, cognitive, and sensorimotor domains is attributable to a common domain-general neurobiological mechanism (Lindenberger & Baltes, 1994; Baltes & Lindenberger, 1997; Christensen et al., 2001). The hypothesis originated from findings demonstrating an age-related increase in the across-participant correlations between measures on psychometric tests and sensorimotor abilities, a phenomenon which had been termed cognitive or 'static' dedifferentiation (for review see Tucker-Drob et al., 2019). According to the cognitive dedifferentiation hypothesis, cognitive decline is attributed to a single 'common factor' which itself is sensitive to increasing age. The consequent age-related increase in correlations and a reduction in scores on psychometric tests reflects a byproduct of the shared variance between the common factor and different cognitive and sensory measures. However, evidence for a single common factor has been weak and only equivocal at best (Zelinski & Lewis 2003; La Fleur et al., 2018; Tucker-Drob et al., 2019).

Multiple factor theories posit that effects of age are process-specific, and as such different cognitive abilities and processes are differentially and independently sensitive to age (Buckner 2004). Considerable behavioral and neurobiological evidence suggests that age-related episodic memory decline may arise from numerous factors which differentially impact multiple brain regions or networks and their associated functions. Numerous contributing factors have been proposed under this framework, including but not limited to reduced 'binding' efficiency at encoding (Old and Naveh-Benjamin 2008; Craik & Rose, 2012; Friedman and Johnson 2014), reduction in executive functioning and abilities to allocate attentional resources (Dennis & Cabeza, 2008; Diamond, 2013), or age differences in the engagement of goal-dependent strategies (Morcom & Rugg, 2004; Duverne et al., 2009; Srokova et al., 2021 [Chapter 3]). Another such factor is age-related neural dedifferentiation, a neural counterpart of the aforementioned cognitive dedifferentiation hypothesis. Neural dedifferentiation is characterized by an age-related decline in the neural selectivity and specificity in category-selective cortical regions (for reviews see Koen & Rugg, 2019; Koen et al., 2020). Unlike cognitive dedifferentiation, neural dedifferentiation has

received substantial empirical support over the last decade or so, and the phenomenon will be discussed in detail below (see *1.3.2. Age-related Neural Dedifferentiation*).

1.2.3   Methodological Considerations in the Field of Cognitive Aging

An important methodological consideration in the field of cognitive aging is the distinction between cross-sectional and longitudinal designs (for review see Rugg, 2016). Cross-sectional studies employ designs which enable the examination of differences in a variable between two or more age groups at a specific point in time. For example, a cross-sectional study may sample two subsets, one of younger and one of older adults, in order to compare their memory performance, thus providing insights into *age differences* or *effects of age* on memory function. In contrast, longitudinal designs examine long-term change in a variable across several points in time. A longitudinal study of cognitive aging involves a group of participants who return for one or more follow-up sessions several months or years later. The advantages of a longitudinal design constitute the ability to track within-subject change, thus informing us of the *effects of aging* on memory function.

Examining the effects of aging on memory is the ideal approach to understanding how growing old affects our ability to successfully encode, store, and retrieve mnemonic information. Unfortunately, longitudinal studies are often costly and require years if not decades of data collection. As a result, the cross-sectional approach is often relied on primarily for pragmatic reasons. The preliminary and proposed experiments described in this dissertation proposal employ a cross-sectional design with two extreme age groups and consequently the interpretation of any findings is qualified by critical caveats inherent to cross-sectional research.

Chronological age is confounded with birth cohort, and as such any effects of age observed in the studies described below may reflect generational differences. Younger adults in the 21st century live in a very different environment compared to the world their older counterparts lived in during their early adulthoods. Over the past several decades, the world has witnessed major technology advancements, easier access to education, and improvements in diet and nutrition. The 'Flynn effect', a phenomenon characterized by a rapid increase in test scores on psychometric tests of fluid and crystallized intelligence observed throughout the 20th century, can be attributed to

these environmental changes (Trahan et al., 2014). It is thus essential to consider that any effects of age may potentially be explained by age differences in life experiences in childhood and adulthood.

Another source of variance which may contribute to age differences in memory function is survivor bias. The exclusion and inclusion criteria commonly employed in cross-sectional studies of healthy aging are tailored to minimize the likelihood of recruiting older adults with mild cognitive impairment or early dementia. Although these criteria ensure that the older adults are aging 'successfully', it is unknown what proportion of the younger adult volunteers will undergo a healthy aging trajectory. It is difficult if not impossible to accurately predict whether a younger adult will live long enough to reach their 60's or 70's, let alone whether they will or will not develop dementia. Thus, just as we do not know whether an 18-year-old would be eligible for a study of healthy aging in 50 years, we also do not know how a 68-year-old would have performed 50 years ago.

Although cohort and survivor effects are major weaknesses of cross-sectional design, this does not imply that examining age differences is not important or informative. Cross-sectional data inform theoretical models of memory and aging, enables the rapid implementation of manipulations aimed at ameliorating the impacts of cognitive decline, and motivate hypotheses necessary for the development of more time- and financially-consuming longitudinal research.

1.3   Examining Effects of Age on Episodic Memory using fMRI
1.3.1   Episodic Encoding and Neural Differentiation

Single cells and broader neuronal populations exhibit a preferential response (selectivity) to certain stimulus types and categories relative to others (e.g., Hubel & Wiesel, 1959; Rose & Blakemore, 1974). Consequently, neuronal cells are thought to *differentiate* between stimulus categories, a phenomenon termed *neural differentiation*. Neural differentiation is foundational to the empirical work demonstrating the existence of functional networks of cortical regions which are differentially recruited to support a variety of cognitive processes.

Interest in scene-selectivity was sparked by a seminal paper by Epstein & Kanwisher (1998) who demonstrated evidence for a scene-selective region within the parahippocampal and

fusiform gyri, a region which they termed the parahippocampal place area (PPA). The authors also reported a second locus of scene-selectivity in the medial parietal retrosplenial area, a region which was later confirmed by O'Craven & Kanwisher (2000) and has since been termed the retrosplenial complex (RSC; also sometimes referred to as the medial place area (MPA)). A third scene-selective region was identified in the medial occipital lobe, a region labeled as the occipital place area (OPA; Nakamura et al., 2000). Similar category-specific regions within the occipito-temporal regions have been identified for other categories of visual stimuli, such as the fusiform face area (FFA; Kanwisher et al., 1997) and the occipital face area (OFA; Pitcher et al., 2007) responsible for face processing, and object-selective regions such as the lateral occipital complex (LOC; Grill-Spector et al., 2001) and the perirhinal cortex (PRC; Murray et al., 1999).

From an evolutionary perspective, the existence of functionally specialized cortical regions is perhaps not surprising. Scene perception is critical when navigating or identifying one's spatial environment, and object recognition is necessary when deciding how to act upon an item. Likewise, also from an evolutionary perspective, face processing is an important part of social cognition which allows us to communicate and understand other people's identity or emotions. In the context of memory research, studies often employ images of scenes, objects, or faces as the to-be-encoded stimuli, leading to robust neural responses in the associated category-selective cortical regions during encoding. Neural activity in the sensory cortices is modulated by numerous factors, such as properties and complexity of the stimulus features (for review of scene-selective cortices see Aminoff et al., 2013; Epstein & Baker, 2019) or task demands, whereby relatively low-demand passive viewing of visual stimuli results in a reduced response in the visual occipito-temporal cortex (Gazzaley et al., 2005; Zanto et al., 2010; Baldauf & Desimone, 2014). Consequently, neural differentiation within category-selective cortical regions may be thought of as being related to the depth of processing of visual stimuli and the fidelity and specificity of the neuronally-represented perceptual information.
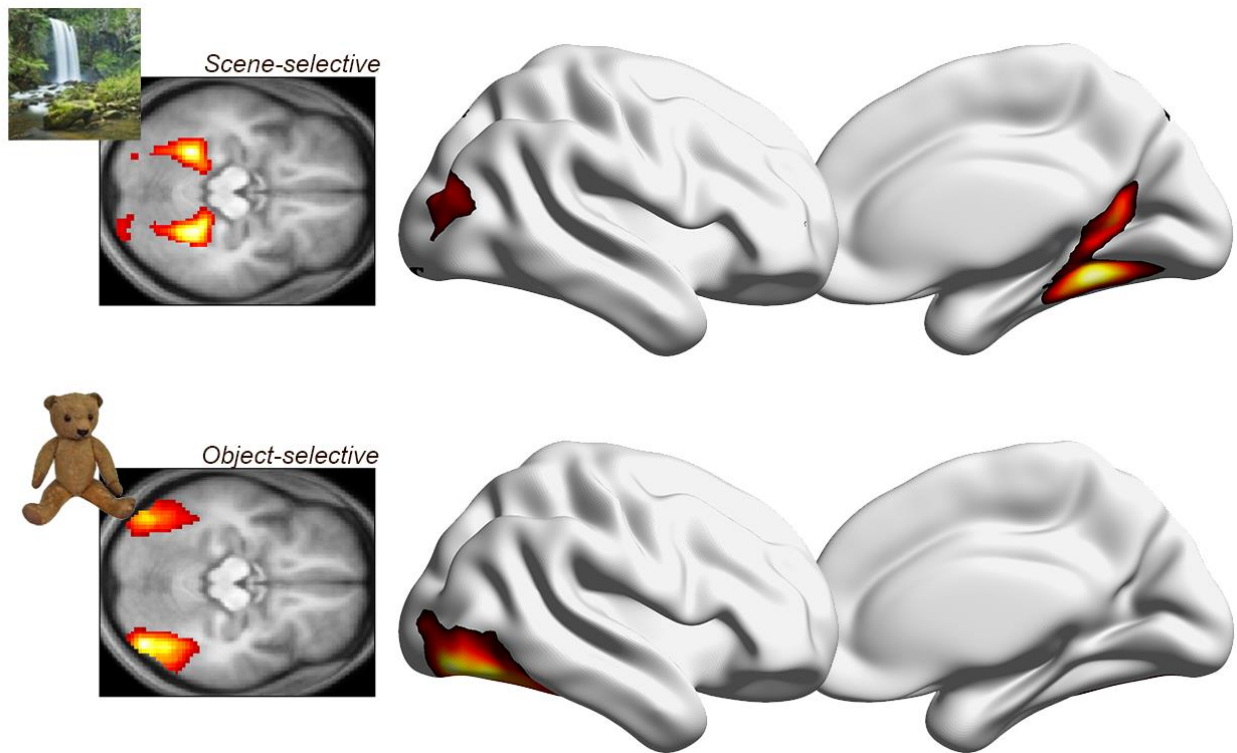
Figure 1.2. The brain is functionally specialized. Processing of visual scenes is associated with an enhanced activity in the scene-selective parahippocampal place area, retrosplenial cortex, and the transverse occipital gyrus (top; scene > object GLM contrast). On the other hand, viewing of objects is associated with an increase in activity within the lateral occipital complex. (bottom; object > scene contrast). *Functional localizer data described in Srokova et al., 2021.*

1.3.2 Age-related Neural Dedifferentiation

Current theories of cognitive aging posit that episodic memory decline arises from numerous factors, such as reduced efficiency to bind episodic features into a coherent episode at the time of encoding (Old and Naveh-Benjamin 2008; Craik & Rose, 2012; Friedman and Johnson 2014), or a decline in the ability to engage goal-dependent strategies which align retrieval with task goals (Morcom & Rugg, 2004; Duverne et al., 2009; Srokova et al., 2021). Another such factor reflects the phenomenon termed *age-related neural dedifferentiation*. Age-related neural dedifferentiation is characterized by reductions in the neural selectivity (differentiation) of category-selective cortical regions with increasing age, a phenomenon which given its apparent

relationship with cognition is thought to be functionally significant in the context of age-related cognitive decline (for reviews see Koen & Rugg, 2019; Koen et al., 2020; Figure 1.3).

Computational models of neural dedifferentiation proposed by Li and colleagues (Li et al., 2001; Li and Rieckmann, 2014) posit that the phenomenon of neural dedifferentiation reflects an age-related reduction in neural efficiency driven by decreased integrity of ascending neuromodulatory systems. The computational models place emphasis on the proposal that neural dedifferentiation is at least in part caused by reduced dopaminergic availability which in turn compromises the fidelity of neural representations and neural signal-to-noise ratios. On a similar theme, neural dedifferentiation has also been hypothesized to arise from an age-related decline in inhibitory γ-aminobutyric acid (GABA) neurotransmission (Lalwani et al. 2019; Cassady et al., 2019, 2020; Chamberlain et al., 2021). In non-human primates, the application of a GABA receptor agonist in senescent macaque monkeys restores orientation selectivity of neurons within the visual cortex to the same levels observed in younger macaques (Leventhal et al., 2003). In line with this research, magnetic resonance spectroscopy (MRS) in human subjects suggests that age-related reductions in GABA are associated with an age-related decline in neural specificity within the auditory cortex (Lawlani et al., 2019) and the ventral visual cortex (Chamberlain et al., 2021). MRS-acquired GABA levels have also been found to be associated with lower resting state motor network segregation (a proxy for network-level neural dedifferentiation) and concurrently with lower performance on a motor task (Cassady et al., 2019; Cassady et al., 2020).

Age-related neural dedifferentiation has been characterized in terms of reduced neural specificity and fidelity of perceptual representations in older age. Given the importance of high-fidelity information and processing for successful episodic encoding, neural differentiation has understandably received much attention from cognitive aging researchers. Several studies have demonstrated that neural differentiation is associated with poorer performance on memory tests for experimental items (Berron et al., 2018; Koen et al., 2019; Sommer et al., 2019; Srokova et al., 2020; Kobelt et al., 2021) and on offline neuropsychological tasks tapping fluid processing (Park et al., 2010; Koen et al., 2019), as well as with lower strength of cortical reinstatement at retrieval (Hill et al., 2021; see *1.3.5. Age differences in Cortical reinstatement*). Importantly, neural differentiation is predictive of cognitive performance and cortical reinstatement in an age-invariant

manner, that is, the relationship appears to not be moderated by age (Koen et al., 2019; Srokova et al., 2020; Kobelt et al., 2021). Although the absence of moderating effects of age implies that higher fidelity and specificity of mnemonic information processing confers benefits on memory across the entire lifespan, the findings should not imply that neural dedifferentiation does not play a critical role in cognitive aging (Koen et al., 2020). Recent evidence indicates that neural dedifferentiation is augmented in seemingly cognitively healthy older adults who exhibit high levels of cortical Tau, a neuropathological marker of Alzheimer's disease (Maass, 2019), highlighting a potential functional role of neural differentiation in Alzheimer's disease and related dementias. Given the relationship with memory performance, understanding the factors which contribute to reduced neural differentiation with increasing age is essential to understanding memory decline in both healthy and abnormal aging.

Of importance, age-related neural dedifferentiation appears to not be a ubiquitous phenomenon. As is discussed in detail in Chapter 2, neural dedifferentiation is most consistently observed within scene-selective regions (Voss et al., 2008; Carp et al. 2011; Zheng et al., 2018; Koen et al., 2019; Srokova et al., 2020), whereas several studies report null effects of age for objects and words (Chee et al., 2006; Voss et al., 2008; Zheng et al., 2018; Koen et al., 2019) and mixed results in face-selective regions (age effects reported in: Park et al., 2004, 2012; Voss et al., 2008; null effects of age: Payer, et al., 2016; Srokova et al. 2020). Numerous factors have been proposed to explain why scene-selective regions are most sensitive to aging, including task and attentional demands and cumulative life experience with different stimulus categories (Koen & Rugg, 2019). It is also worth pointing out that given that neural dedifferentiation appears relatively less region-general, these mixed findings challenge hypotheses that posit that age-related neural dedifferentiation is primarily attributable to cortex-wide reduction in dopaminergic drive or cortical GABA levels. Needless to say, the determinants of the phenomenon remain unclear.
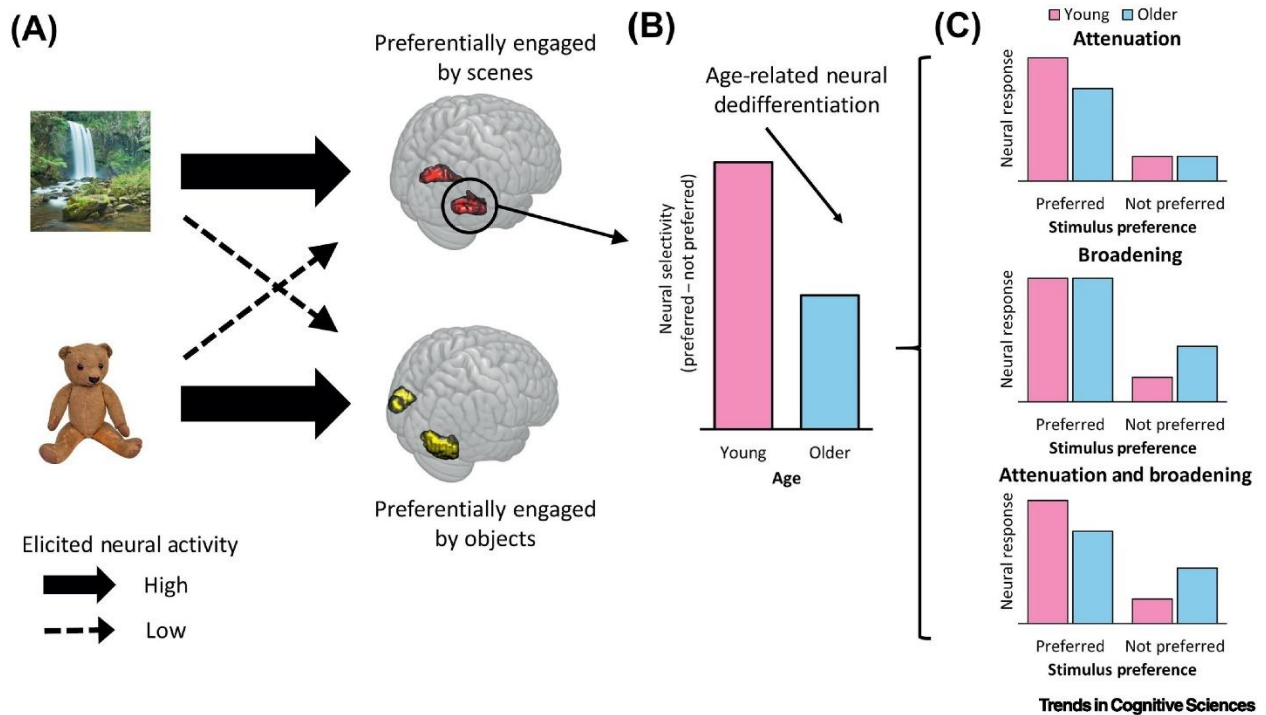
Figure 1.3. A schematic explaining the phenomenon of age-related neural dedifferentiation. **(A)** A given cortical region is differentially engaged by object and scene stimuli. For example, a scene-selective region shows higher selectivity for scenes (preferred category) relative to objects (non-preferred category). **(B)** Neural differentiation is computed as the difference between the region's response to the preferred versus non-preferred category. Age-related neural dedifferentiation is defined by the finding whereby neural differentiation is lower in older relative to younger adults. **(C)** Age-related neural dedifferentiation may arise due to an attenuated response to the region's preferred stimulus category, or a broadened (enhanced) response to the region's non-preferred category, or due to a combination of the two phenomena. *Figure reproduced with permission from Koen & Rugg, 2019.*

1.3.3   Neural Dedifferentiation at Different Levels of Analysis [1]

There are several approaches that can be used to quantify neural differentiation (for review, see Koen & Rugg, 2019, Koen et al., 2020). At the single cell level, neural differentiation may be operationalized in terms of the tuning functions of a single neuronal cell. For example, orientation selectivity of a cell reflects preferential tuning for a bar of light stimulus presented in a specific orientation or degree (Hubel & Weisel, 1959). In this case, age-related neural dedifferentiation

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[1] The contents of this section are closely based on a previously published manuscript which I co-authored: Koen, J. D., **Srokova, S.**, & Rugg, M. D. (2020). Age-related neural dedifferentiation and cognition. *Current Opinion in Behavioral Sciences*, *32*, 7-14.

manifests as reduced selectivity of the cell for its preferred orientation and in turn an enhanced firing to non-preferred orientation (i.e., broadened tuning curves). FMRI or scalp EEG may be employed to examine neural differentiation at the level of cell populations. Neural differentiation may be operationalized in fMRI data using univariate and multivoxel (multivoxel pattern analysis; MVPA) approaches at the level of perceptual categories (Figure 1.3) or at the individual item-level (Figure 1.4).

At the categorical level, the univariate differentiation index quantifies the difference between the mean trial-wise blood-oxygen-level-dependent (BOLD) response to the region's preferred stimulus category (e.g., scenes in the PPA) and the mean trial-wise BOLD response to a non-preferred category (e.g., objects in the PPA), divided by their pooled standard deviation (Voss et al., 2008; Zebrowitz et al., 2016; Koen et al., 2019; Srokova et al., 2020). This approach is preferrable over unscaled differences in fMRI BOLD amplitude given that the scaling function controls for individual differences in the gain of the hemodynamic response function (Liu et al., 2013; see below for age differences in neural differentiation).

Multivoxel Pattern Similarity Analysis (PSA) quantifies the similarity of voxel-wise BOLD profiles as a means of examining the 'specificity' with which the stimulus is neurally represented in a given region (Zheng et al., 2018; Koen et al., 2019; Srokova et al., 2020). This approach assumes that more similar patterns of activity between trials reflect greater selectivity for the stimulus category. Multivariate classification analyses are based on a similar assumption. In this approach, a classifier is trained to differentiate between trials of two or more stimulus categories. Performance of the classifier is then evaluated in terms of its success in classifying a different set of trials into the appropriate trial bins (Park et al., 2010; Carp et al., 2011). More stable and categorically distinct patterns of activity manifest in form of greater classifier performance, and thus imply greater 'specificity' of the perceptual representations within the category-selective cortex.

Several studies have also examined neural dedifferentiation at the level of individual exemplars (Figure 1.4). One univariate approach is based on the phenomenon of repetition suppression effects (also termed 'adaptation') which manifests as a reduction in the neural response elicited by a repeated presentation of a previously experienced stimulus (Henson & Rugg,

2003). Age-related neural dedifferentiation manifests as relatively greater repetition suppression effects in older adults for items that are highly perceptually similar but not identical. The logic behind this approach lies in the assumption that repetition suppression for similar items reflects the re-engagement of neuronal populations which overlap with the populations active during the presentation of a similar, but different exemplar. For example, Goh and colleagues (2010) demonstrated that repetition suppression in the FFA for identical faces was equal in younger and older adults, whereas greater suppression effects were evident in older adults when the faces were morphed to appear visually similar to the first-presented faces (Figure 1.4B).

An alternative approach quantifies item-level differentiation in terms of the similarity between the neural patterns elicited by consecutive re-presentations of an item relative to other items. In this approach, age-related neural dedifferentiation is reflective of a reduced within – between similarity of neural patterns – i.e., the difference in the similarity between an item and its repetition versus the similarity between the item and other items. The literature using this approach provides mixed results, often reporting null effects of age (St-Laurent, 2014; 2019; Zheng et al., 2018), with one study reporting age-related reductions in the item-level similarity metric for scene and object stimuli (Zheng et al., 2018; although note the result was based on whether or not the similarity metric was significantly above zero as opposed to directly contrasting the two age groups).

A multivariate classification analysis may also be employed for item-level measures of neural dedifferentiation. In a recent study, Bowman and colleagues (2019) trained a classifier to discriminate between memory recognition trials according to whether they had been presented previously (targets), trials which were perceptually similar to previously presented items (item lures; e.g., images of two similar pigeons), or objects which were thematically but not perceptually related to one another (thematic rules; e.g., an image of a pigeon and a crow). Accuracy in classifying trials into targets vs item lures was above chance for younger but not older adults, indicating that the fidelity of neural representations was lower in older relative to younger adults (see also Trelle et al., 2019).
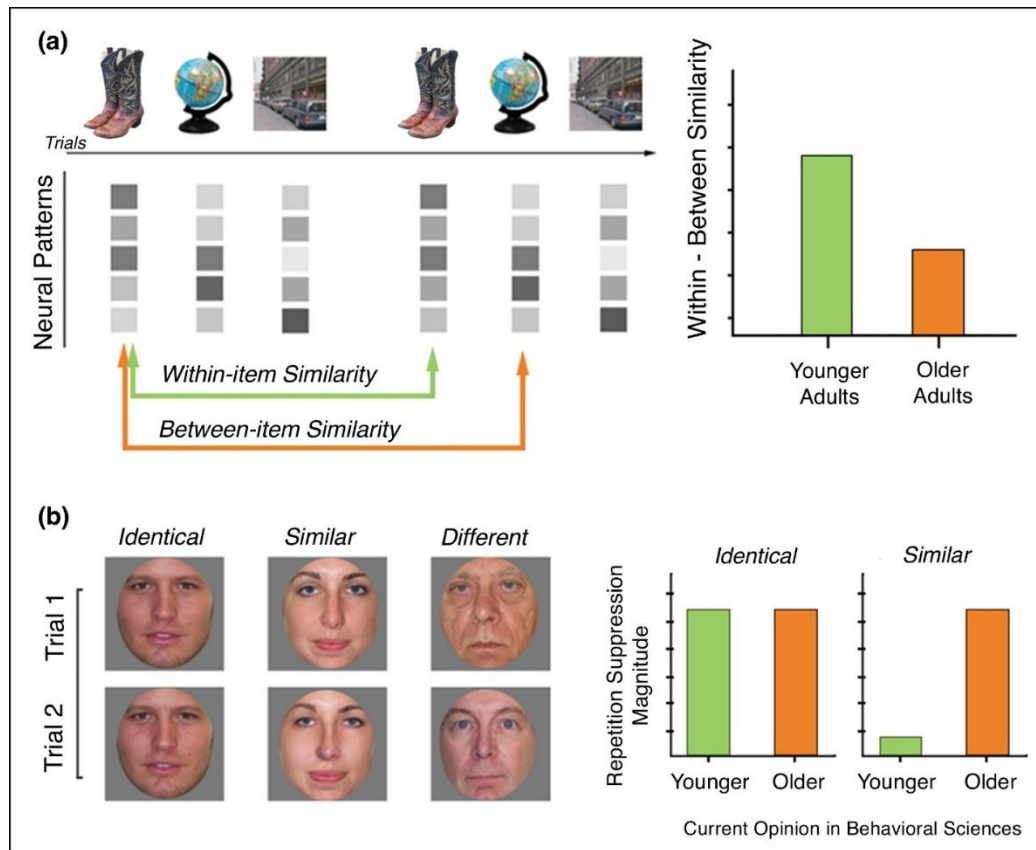
Figure 1.4. Item-level differentiation can be operationalized using univariate as well as multivoxel approaches. **(A)** Pattern similarity analysis can be employed to contrast the neural similarity between consecutive presentations of identical or perceptually similar items (the difference between within- and between-item similarity). Age-related neural dedifferentiation manifests as a reduced within-between similarity. **(B)** Univariate approaches benefit from the phenomenon of 'repetition suppression' whereby a consecutive re-presentation of an identical item results in a reduction in the elicited neural activity. Age-related neural dedifferentiation takes the form of an age-related increase in the repetition suppression effects of perceptually similar (but not identical) items. The logic behind this approach is based on the assumption that repetition suppression for similar but not identical items is reflective of reduced fidelity of neural representations. *Figure reproduced with permission from Koen, Srokova, & Rugg, 2020.*

Although not discussed further in this dissertation, it is also worth briefly noting that neural dedifferentiation may also be evident at the level of large-scale brain networks (see Koen et al., 2020 for a more detailed discussion). Graph theoretical approaches on resting-state connectivity data allows the quantification of the extent to which brain regions (nodes) can be categorized into distinct functional networks. The younger adult brain is characterized by well-segregated networks

whereby a strong connectivity is maintained between the nodes belonging to the same network (high within-network connectivity), accompanied by relatively weaker connectivity between the nodes belonging to other networks (low between-network connectivity). The difference between the within- and between-network connectivity has been termed 'modularity' or 'segregation'. Numerous studies employing this approach have shown that increasing age is associated with reduced segregation of networks.

In conclusion, the studies reviewed above demonstrate that age-related neural dedifferentiation can be identified at the level of perceptual categories, individual exemplars, as well as brain networks. In this dissertation, Chapter 2 employs univariate and multivoxel approaches to examine age differences in neural differentiation for scene and face categories. Chapter 5 speaks directly to potential age differences in repetition suppression effects for perceptually similar objects and scene exemplars.

1.3.4   Episodic Retrieval and Cortical Reinstatement

In line with the TAP framework described above (see 1.1. *Theoretical Framework of Episodic Memory*), episodic memory retrieval is thought to be accompanied by the 'reactivation' of processes which were engaged when the episode was originally experienced. The neurobiological extension of TAP reflects the retrieval-related *cortical reinstatement*, a phenomenon which is characterized by a partial overlap in the neural activity observed at encoding and subsequent retrieval (for reviews see Danker and Anderson, 2010; Rissman and Wagner, 2012; Rugg et al., 2015; Xue, 2018). The framework of cortical reinstatement posits that the neural populations active at encoding are stored in the hippocampus as indices which code for activity of neural populations as opposed to perceptual content per se. This is achieved by hippocampally-mediated pattern separation processes which store similar episodic events as non-overlapping and orthogonal memory representations. At retrieval, a retrieval cue elicits a pattern of neural activity which overlaps with the original encoding-related activity, and hippocampal pattern completion processes 'complete' the mnemonic representation by reactivating the neural pattern originally elicited at encoding (for review see Rugg et al, 2008; 2015; Yassa & Stark, 2011; Figure 1.4).

From a methodological perspective, just as is the case of neural differentiation, measures of cortical reinstatement can be operationalized using univariate and multivoxel approaches. The univariate approach is similar to the operationalization of neural differentiation with the main difference being that the analyses of cortical reinstatement are focused on retrieval trials. Cortical reinstatement within an ROI may be operationalized by comparing the mean across-voxel parameter estimate for retrieval trials of one category and contrasting it against parameter estimates associated with a different trial or stimulus type (e.g., Woodruff et al., 2005; Johnson & Rugg, 2007). For example, for the scene-selective PPA, cortical reinstatement of visual scenes can be computed by extracting the mean BOLD parameter estimates for trials which had been studied with scene stimuli at encoding, minus the mean parameter estimate for retrieval trials for trials which had been paired with images of scrambled pixelated backgrounds (c.f., Elward & Rugg, 2015; Elward et al., 2021). A reinstatement index can also be computed from trial-wise GLM data in the same way as the aforementioned differentiation index: mean across-trial BOLD response to ROI's preferred stimulus category at retrieval minus the mean BOLD response to ROI's non-preferred stimulus category, divided by pooled standard deviation as to control for group differences in the hemodynamic response function (c.f., Srokova et al., 2021).

MVPA metrics of cortical reinstatement can be computed employing approaches such as classification analyses or PSA, where a metric of cortical reinstatement quantifies the relationship between the patterns of encoding-related neural activity and the patterns observed at retrieval. For example, in a study reported by Johnson and colleagues (2009), participants viewed a series of words presented in one of three encoding tasks, and their memory for the words was subsequently tested using a 'Remember/Know/New' procedure. A neural network classifier was trained on the encoding data to differentiate between the three contexts, and the classifier's performance was then evaluated on the retrieval data. The classifier demonstrated above chance performance in successfully discriminating between retrieval trials according to their encoding context, thus indicating that the retrieval of the word was associated with the reinstatement of the context in which it was experienced at encoding. Similar findings were observed by Wang and colleagues (2016) where a classifier performed significantly above chance in determining whether a test cue was studied in one of two study contexts (see also Thakral et al., 2017).

PSA metrics of cortical reinstatement are typically operationalized in terms of Pearson's correlations between encoding and retrieval patterns of neural activity (e.g., Ritchey et al., 2013; Kuhl & Chun, 2014; Favila et al., 2018; Folville et al., 2020; Hill et al., 2021). Here, reinstatement may be assessed at the level of an entire stimulus category or at the level of a single item. A recent study by Hill and colleagues (2021) operationalized category-level reinstatement for visual scenes by computing the average Fisher Z-transformed Pearson's correlation (i.e., similarity) between all encoding scene trials and all retrieval scene trials minus the average Fisher Z correlation between all encoding scene trials and all retrieval trials of the other stimulus category (in this case trials associated with images of faces). On the other hand, item-level reinstatement would be operationalized as the average similarity between a given encoding trial and its associated retrieval trial minus the average similarity between that trial and all retrieval trials of the same image category. Here, a greater similarity metric reflects stronger cortical reinstatement effects.

Cortical reinstatement has been held to reflect the amount and content of retrieval, and therefore the reinstatement hypothesis predicts that more complete reinstatement of encoded neural patterns should result in better memory performance. In line with this prediction, research has shown that stronger cortical reinstatement effects accompany more accurate and confident memory judgements (e.g., Gordon et al., 2014; Johnson et al., 2009; Thakral et al., 2015; Trelle et al., 2020; Srokova et al., 2021). However, findings also suggest that successful recollection of contextual information is not a prerequisite for detecting reinstatement effects, and in fact reinstatement may be observed even in the absence of recollective experience (Thakral et al., 2017). A recent study by Elward and colleagues (2021) demonstrated that patients with developmental amnesia exhibit reinstatement effects equivalent to those of healthy younger adults, despite marked impairments in memory performance. These findings imply that although the strength of cortical reinstatement may reflect the amount and fidelity of retrieved content, reinstatement is not the sole determinant of whether retrieved mnemonic information is available for conscious recollection.
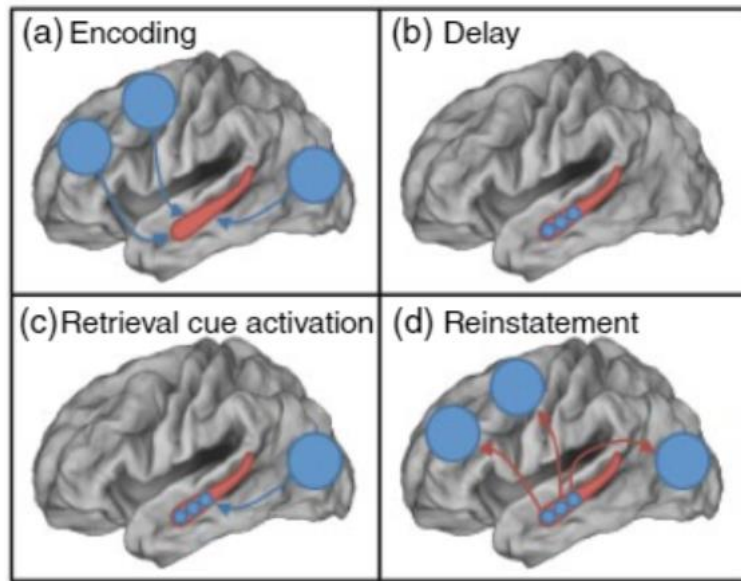
Figure 1.5. The theoretical framework of cortical reinstatement. Neural activity at encoding is indexed and stored by the hippocampus. A retrieval cue which partially overlaps with the activity at encoding leads to the engagement of hippocampal pattern completion processes which reinstate the encoding-related neural pattern. *Figure reproduced with permission from Rugg et al., 2015.*

1.3.5 Age Differences in Cortical Reinstatement

Given the well-established memory decline in older age, the proposal that the strength of cortical reinstatement reflects the amount and fidelity of retrieved information has motivated empirical research examining potential age differences in cortical reinstatement. This work was based on the hypothesis that, given the decline in episodic memory, older adults should exhibit weaker cortical reinstatement effects relative to their younger counterparts. The story is however not entirely straightforward, and although some studies report reduced cortical reinstatement effects in older adults (McDonough et al., 2014; St-Laurent et al., 2014; 2019; Abdulrahman et al., 2017; Bowman et al., 2019; Folville et al., 2020; Hill et al., 2021), null effects of age have also been reported (Wang et al., 2016; Thakral et al., 2017, 2019; Srokova et al., 2021).

Recent findings suggest that age differences in cortical reinstatement relate to age differences in selectivity observed at encoding. Using a PSA metric of cortical reinstatement, Hill and colleagues (2021) observed lower scene-selectivity in older than younger adults at both encoding and retrieval. Neural differentiation at encoding predicted the strength of cortical reinstatement at retrieval for both scene and face stimuli. Of importance, the age differences in

scene-related cortical reinstatement were absent when covarying out scene selectivity at encoding, suggesting that age-related decrease in the strength of cortical reinstatement may largely be attributable to the fidelity with which the information is processed at encoding. Given the ongoing debate in the field as to whether age-related memory decline is primarily attributable to declines in mnemonic processing at encoding or retrieval, this study emphasizes the importance of considering age differences in processes active at encoding as potential contributors to age differences in behavioral and brain measures at retrieval.

However, as mentioned previously, age effects in cortical reinstatement are not ubiquitous and null effects of age have been reported (Wang et al., 2016; Thakral et al., 2017, 2019). In light of the aforementioned analyses, which reveal that the strength of cortical reinstatement may largely be determined by neural selectivity at encoding, it is possible that inconsistencies in age effects at retrieval may parallel those observed for age-related neural differentiation at encoding. As discussed above (see *1.3.2 Age-related Neural Dedifferentiation*) age differences in neural selectivity at encoding appear more robust for images of scenes, but much less so for object, words, or face stimuli (Chee et al., 2006; Voss et al., 2008; Zheng et al., 2018; Koen et al., 2019). In the analyses described by Wang and colleagues (2016) and Thakral and colleagues (2017, 2019), participants actively encoded words and images of objects. Given that objects and words are perceptual categories which are less likely to elicit demonstrable age differences in neural selectivity at encoding, the null effects of age at retrieval may potentially be explained by null effects in selectivity at encoding. Indeed, returning to the study described by Hill and colleagues, their analyses revealed robust age differences in category-level cortical reinstatement for scenes, but null effects of age for face stimuli. These findings paralleled the analyses at encoding demonstrating that neural differentiation was moderated by age in the scene- but not face-selective regions (see also Srokova et al., 2020). Therefore, the factors which contribute to age differences in neural differentiation may share variance with the factors which drive the observed age effects in cortical reinstatement.

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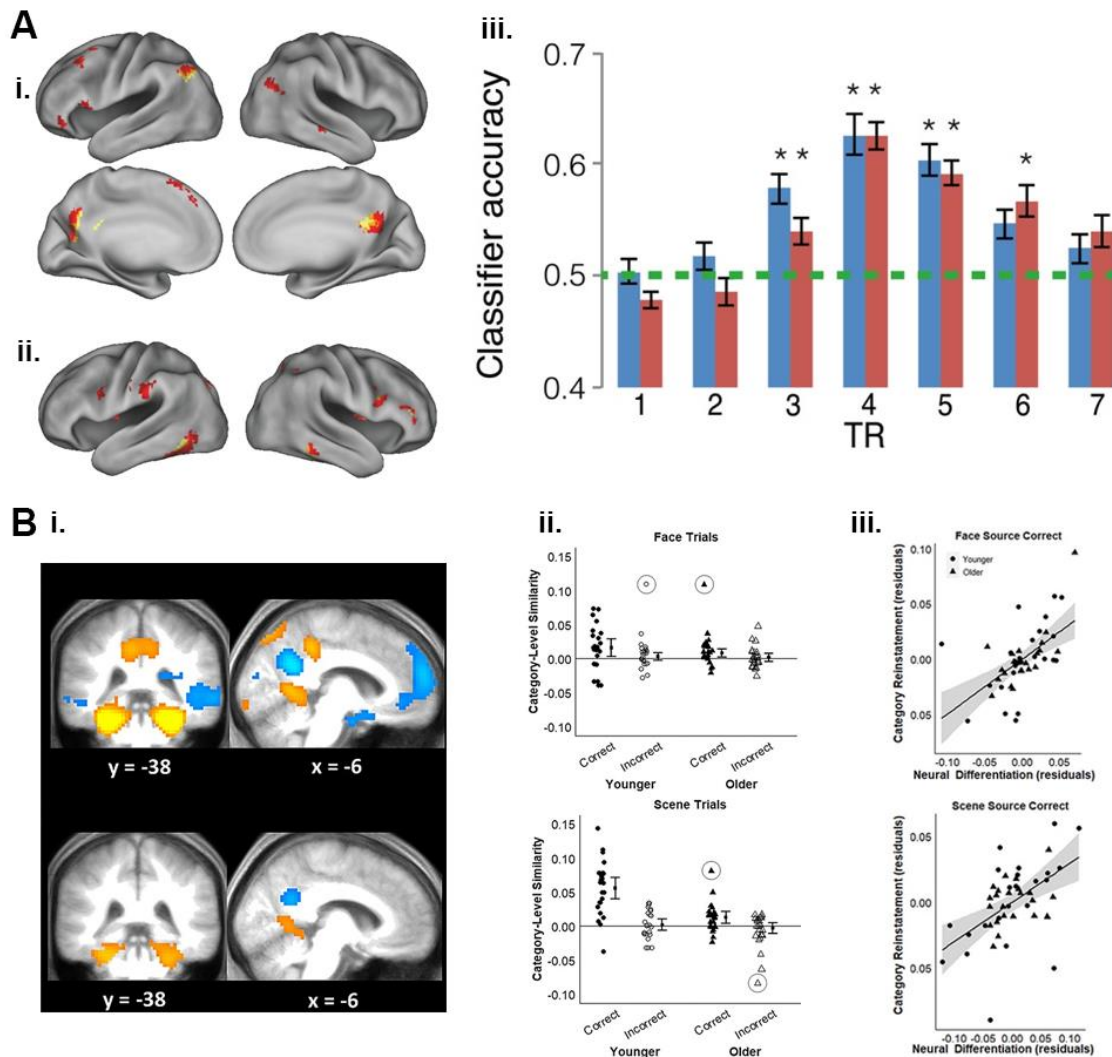
Figure 1.6. (A) Age-invariant reinstatement effects for words **(i)** and images **(ii). (iii)** Retrieval-related MVPA classification accuracy for correctly recollected words and images. The classifier was trained on study data to classify retrieval trials according to their study category (words vs images). Blue bars denote classification accuracy in younger adults and red bars denote older adults. The dotted green line signifies chance performance of the classifier. Reliable reinstatement effects (i.e., classifier performance significantly above chance) were observed in the 3rd to 6th TRs in both age groups, and also the 7th TR in the older age group. There was no evidence for reduced reinstatement effects in older age. *Figures in panel A reproduced with permission from Wang et al., 2016* **(B) (i)** Scene-selective (orange) and face-selective (blue) effects at encoding (top) and retrieval (bottom). **(ii)** Encoding-retrieval PSA demonstrated reduced category-level cortical reinstatement effects in older adults for scene trials (bottom) but null effects of age for faces (top). **(iii)** The strength of neural differentiation at encoding was predictive of the strength of cortical reinstatement at retrieval for both face and scene trials. These relationships were age-invariant. *Figures in panel B reproduced with permission from Hill et al., 2021.*

CHAPTER 2

NEURAL DIFFERENTIATION IS MODERATED BY AGE IN

SCENE-SELECTIVE, BUT NOT FACE-SELECTIVE CORTICAL REGIONS

This chapter includes a manuscript which has been published in *eNEURO* by me (Sabina Srokova) as the first author, along with co-authors Drs. P.F. Hill, J.D. Koen, D.R. King, & M.D. Rugg who provided substantial input via their comments and edits of the presented text.

Srokova, S., Hill, P. F., Koen, J. D., King, D. R., & Rugg, M. D. (2020). Neural differentiation is moderated by age in scene-selective, but not face-selective, cortical regions. *ENeuro, 7*(3).

2.1 Introduction

Increasing age has been reported to be associated with reduced specificity and distinctiveness of neural representations, a phenomenon known as age-related neural dedifferentiation (for review, see Koen & Rugg, 2019; Koen et al., 2020). Computational models of cognitive aging suggest that neural dedifferentiation plays a role in age-related cognitive decline (Li et al., 2001; Li & Rieckmann, 2014). Specifically, the phenomenon has been proposed to arise from age-related reductions in neuromodulation, compromising the fidelity of neural representations (see Abdulrahman et al., 2017).

In an early fMRI study of age-related neural dedifferentiation, Park et al. (2004) reported that older adults demonstrated lower neural selectivity in voxels selective for four perceptual categories (houses, chairs, pseudowords and faces). Although subsequent studies have reported convergent findings, the data suggest that age-related dedifferentiation is not ubiquitous. For example, whereas dedifferentiation is frequently reported in scene-selective (Voss et al., 2008; Carp et al. 2011; Zheng et al., 2018; Koen et al., 2019) and face-selective cortical regions (Park et al., 2004; Voss et al., 2008; Park et al., 2012; Zebrowitz et al., 2016), null findings for both of these stimulus classes have also been reported (for scenes: Berron et al., 2018; for faces: Payer, et al., 2006). The evidence is also divergent for object and word stimuli. Although Park et al. (2004)

reported age-related dedifferentiation for objects and orthographic stimuli, subsequent studies have found null age effects for both stimulus classes (objects: Chee et al., 2006; Zebrowitz et al., 2016; Zheng et al., 2018; Koen et al., 2019; words: Voss et al., 2008, see also Wang et al., 2016; Abdulrahman et al., 2017).

Numerous factors likely account for these inconsistent reports, and one such factor might be the attentional demands imposed by the experimental task. Whereas prior studies that employed relatively 'passive' viewing tasks have typically reported age-related neural dedifferentiation for both faces (Park et al., 2004, 2012; Voss et al. 2008; Zebrowitz et al., 2016) and object stimuli (Park et al., 2004, but see Chee et al., 2006), studies that employed tasks requiring discriminative judgements on the experimental items have tended to report little or no evidence for neural dedifferentiation (faces: Payer et al., 2006, objects: Koen et al., 2019). In line with reports suggesting that neural selectivity in category-selective cortical regions is modulated by selective attention (Gazzaley et al., 2005, 2008; Baldauf and Desimone, 2014), findings of neural dedifferentiation in the context of passive viewing might have been confounded by age differences in attentional deployment. Therefore, here we examined whether the prior findings of Koen at al. (2019) of null age effects of neural differentiation of objects during an active encoding task extended to faces.

Metrics of neural differentiation have been reported to predict both memory performance for the experimental stimuli (e.g. Yassa et al., 2011; Berron et al., 2018; Bowman et al., 2019; Koen et al., 2019; Sommer et al., 2019; for related findings, see Du et al., 2016) and measures of performance on psychometric tests tapping 'fluid' processing (Park et al., 2010; Koen et al., 2019). The findings are consistent with the possibility that age-related cognitive decline is driven by neural dedifferentiation. Of importance, however, recent findings suggest that the relationship between neural differentiation and cognitive performance is age-invariant (Koen et al., 2019; Koen and Rugg, 2019), that is, the strength of the relationship does not vary with age. Although an age-invariant relationship does not rule out a role for dedifferentiation in mediating age-related cognitive decline, it does suggest that the contribution of neural selectivity to cognitive performance is stable across the lifespan (see Rugg, 2016, for further discussion).

In the present study, participants underwent fMRI while studying word-face and word-scene stimulus pairs prior to a memory test. Neural differentiation was operationalized by a univariate differentiation index (Voss et al., 2008; Zebrowitz et al., 2016; Koen et al., 2019) and multi-voxel pattern similarity (Zheng et al., 2018; Koen et al., 2019; Sommer et al., 2019, Trelle et al., 2019) in two face-selective (Fusiform face area, FFA; Occipital Face Area, OFA) and two scene-selective (Parahippocampal place area, PPA; Retrosplenial cortex, RSC) regions of interest (ROIs). One aim of the current study was to examine whether the null effects of age in neural differentiation of objects (Koen et al., 2019) extend to face stimuli in the context of an attentionally demanding task. Additionally, we aimed to replicate and extend prior findings regarding age-related neural dedifferentiation for scene stimuli, and the relationship between neural differentiation of scenes with subsequent memory performance and measures of fluid processing.

2.2 Materials and Methods

The experimental procedures described below were approved by The Institutional Review Boards of the University of Texas Southwestern Medical Center and the University of Texas at Dallas. All participants provided informed consent prior to taking part in the experiment.

2.2.1 Participants

Twenty-seven younger and 33 older adult volunteers were recruited from local communities surrounding The University of Texas at Dallas and the greater Dallas metropolitan area, and were compensated $30/h. All volunteers were right-handed, had normal or corrected-to-normal vision, and were fluent English speakers before the age of five. Participants were excluded if they self-reported a history of cardiovascular or neurological disease, diabetes, substance abuse, use of medication affecting the central nervous system, or showed evidence of cognitive impairment based on their performance on a neuropsychological test battery (see below).

Three younger and three older adult participants were excluded from subsequent analyses for the following reasons: voluntary withdrawal from the study (N = 2), behavioral performance which resulted in not having enough trials (< 10) in a critical memory bin (N = 2), technical malfunction of the equipment (N = 1), and an incidental MRI finding (N = 1). Additionally, six

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older participants were excluded due to chance source memory performance, according to our pre-determined cutoff score (probability of source recollection, pSR < 0.1). The final sample therefore consisted of 24 young (age range: 18 – 28 years, 15 female) and 24 older adult (age range: 65 – 75 years, 14 female) participants. Demographic data and neuropsychological test performance are reported in Table 2.1.

Several of the participants in the present study had previously participated in one or more studies reported by our laboratory. Specifically, 4 older adults participated in the event related potential study reported by Koen et al. (2018), 1 older adult participated in a prior fMRI study reported by Koen et al. (2019), and 4 older adults took part in an fMRI experiment first reported by de Chastelaine et al. (2015).

2.2.2 Neuropsychological Testing

All participants completed our standard neuropsychological test battery consisting of the Mini-Mental State Examination (MMSE), The California Verbal Learning Test-II (CVLT; Delis et al., 2000), Wechsler Logical Memory Tests 1 and 2 (Wechsler, 2009), The Trail Making tests A and B (Reitan and Wolfson, 1985), the Symbol Digit Modalities test (SDMT; Smith, 1982), the F-A-S subtest of the Neurosensory Center Comprehensive Evaluation for Aphasia (Spreen and Benton, 1977), the Wechsler Adult Intelligence Scale–Revised subtests of forward and backward digit span (Wechsler, 1981), Category fluency test (Benton, 1968), Raven's Progressive Matrices (List 1, Raven et al., 2000) and the Wechsler Test of Adult Reading (WTAR; Wechsler, 1981). Potential participants were excluded prior to the fMRI session if they scored < 27 on the MMSE, > 1.5 SD below age norms on any standardized memory test, > 1.5 SD below age norms on two or more standardized non-memory tests, or if their estimated full-scale IQ was < 100.

The neuropsychological test scores were reduced to four components based on the outcome of a principal component analysis applied to a prior large dataset from our laboratory. The dataset comprised scores from younger, middle aged and older adults (total N=154) (de Chastelaine et al. 2016). Four principal components with eigenvalues greater than 1, accounting for 64.1% of the variance, were retained and subjected to the Varimax rotation (Kaiser, 1958). The rotated components (RC) correspond roughly to processing speed (RC1), memory (RC2), crystallized

intelligence (RC3), and fluency (RC4). The neuropsychological tests included in the analysis, their corresponding rotated factor weights, and the proportions of variance accounted for by the rotated components are presented in Table 2.2.

Table 2.1. Demographic data and results of the neuropsychological test battery (mean, SD) for younger and older adults.

	Younger Adults	*Older Adults*	*p-value*
N	24	24	
Age	22.42 (3.24)	70.00 (3.46)	
Years of Education	15.46 (2.65)	16.71 (2.44)	NS
MMSE	29.25 (0.90)	29.33 (0.70)	NS
CVLT Short Delay – Free	13.75 (2.00)	11.88 (2.86)	0.012
CVLT Short Delay – Cued	13.83 (2.32)	13.08 (2.15)	NS
CVLT Long Delay – Free	14.13 (2.11)	12.79 (2.62)	NS
CVLT Long Delay – Cued	14.38 (1.93)	13.46 (2.13)	NS
CVLT recognition – Hits	15.71 (0.46)	15.25 (1.07)	NS
CVLT recognition – False alarms	0.33 (0.70)	1.67 (1.61)	0.001
Logical Memory I	33.00 (4.76)	28.00 (4.11)	< 0.001
Logical memory II	32.00 (4.80)	25.83 (5.49)	< 0.001
SDMT	62.33 (11.27)	49.29 (7.91)	< 0.001
Trails A (s)	20.20 (5.26)	25.11 (6.46)	0.006
Trails B (s)	44.12 (10.18)	62.48 (16.77)	< 0.001
Digit Span Total	19.71 (4.14)	18.79 (3.49)	NS
Category fluency	23.71 (4.91)	22.46 (5.35)	NS
F-A-S	49.17 (12.85)	46.29 (12.75)	NS
WTAR	42.42 (3.46)	44.54 (4.06)	NS
Raven's	11.04 (0.86)	9.50 (1.89)	0.001
Speed Factor (RC1)	-1.47 (2.01)	1.56 (1.68)	< 0.001
Memory Factor (RC2)	1.53 (1.94)	-1.62 (2.42)	< 0.001
Crystallized intelligence Factor (RC3)	0.30 (1.42)	-0.39 (1.79)	NS
Fluency Factor (RC4)	0.20 (1.18)	-0.10 (1.45)	NS

Digit Span total corresponds to the sum of forward and backward digit span.
Speed factor bears a negative number with better performance on tasks of processing speed.
NS = not significant

Table 2.2. Factor Loadings from the PCA, Varimax rotated, based on dataset previously reported by de Chastelaine et al. (2016).

	Speed (RC1)	Memory (RC2)	Crystallized Intelligence (RC3)	Fluency (RC4)
CVLT composite	-.19	.84	.08	-.15
CVLT recognition – Hits	-.20	.42	.23	-.64
CVLT recognition – False alarms	.21	-.69	.26	-.17
Logical memory composite	.10	.67	.18	.02
Trails A (s)	.91	-.09	-.05	-.14
Trails B (s)	.85	-.09	-.28	.08
SDMT	-.59	.40	.08	.30
Digit Span	-.16	.01	.80	-.08
Category fluency	-.34	.23	.14	.63
F-A-S	-.12	.06	.46	.57
WTAR	-.12	.12	.79	.21
Raven's	-.33	.48	.10	.05
Eigenvalue	3.65	1.70	1.28	1.06
Variance explained (before rotation)	.20	.14	.11	.09
Variance explained (after rotation)	.19	.19	.15	.11

2.2.3 Experimental Procedure

2.2.3.1 Experimental Materials

Experimental stimuli were presented using Cogent 2000 software (www.vislab.ucl.ac.uk/cogent_2000.php) implemented in Matlab 2012b (www.mathworks.com). The stimuli were projected onto a translucent screen attached at the rear of the MRI bore and were viewed through a mirror mounted on the scanner head coil. Participants completed two study-test cycles inside the scanner. For each cycle, study and test phases were each split into two scanning sessions, with a 30s rest period midway through each session. The critical experimental stimuli were distributed across four study and four test sub-lists, with a single sub-list per scanning session. Therefore, participants' memory for the first two study sub-lists was tested in two memory test sessions before continuing to the second cycle. The critical stimuli comprised 288 concrete nouns, 96 colored images of male and female faces (face stimuli obtained from Minear & Park (2004) database), and 96 colored images of urban and rural scenes. All images of faces and scenes were scaled at 256 x 256 pixels. An additional 68 words and 40 images were used as fillers at the

beginning of each scan session and immediately after each break or as practice stimuli. The critical stimuli were interspersed with 96 null trials (white fixation cross) in both the study and test lists (24 trials per sub-list). Stimuli were selected randomly without replacement to create twenty-four different stimulus sets for yoked younger and older adult pairs. Study and test trials were pseudorandomized such that participants were not presented with more than three consecutive trials belonging to the same image class, or more than two consecutive null trials.

2.2.3.2 Study Phase

Participants completed two scanned study-test cycles. Each cycle included two study blocks. The blocks each contained 24 null trials and 48 critical words, half of which were paired with an image of a face and a half paired with a scene image. The word was presented in the upper half of the screen with the image beneath it and a white fixation cross positioned between the two items (see Figure 2.1). Words were presented in a white font 30pt uppercase Helvetica over a black background. A study trial began with a red fixation cross for a duration of 500ms, followed by the presentation of the word-image pair for 2000ms. This was followed a white fixation cross for a further 2000ms. When a word was paired with a face, the instructions were to imagine the person depicted by the image interacting with the object denoted by the word. For word-scene trials, the task was to imagine a scenario in which the object denoted by the word is interacting with elements of the scene. To ensure adherence to task instructions, participants were asked to rate the vividness of each imagined scenario on a three-point scale: 'Not vivid, 'Somewhat vivid', to 'Very vivid'. Responses were recorded with right-hand index, middle and ring fingers using a scanner-compatible button box. Only trials on which ratings were made between 450-4500ms post-stimulus onset were included in the analyses described below. Trials attracting multiple responses were excluded from behavioral analyses and included as events of no interest in the fMRI analyses.

2.2.3.3 Test Phase

The test phase was also conducted within the fMRI scanner (the fMRI data will be reported in a separate communication). While undergoing scanning, participants' memory for the studied items was tested across two test lists (two sub-lists per study-test cycle). Each sub-list comprised

48 studied words, 24 new words, and 24 null trials. Each test trial began with a 500ms duration red fixation cross, followed by the test word, which was presented for 2000ms, and a white fixation cross for 2000ms. Participants were required to indicate whether they remembered studying the test words by making an 'Old' or a 'New' judgment. Instructions were to respond 'Old' only if they were confident the word had been studied. For test items endorsed 'Old', participants were prompted to make a source memory judgement, during which they signaled whether the word had been studied along with a face or a scene. An additional 'Don't Know' response option was available to discourage guessing. The source memory prompt was presented immediately after the 'Old'/'New' memory response had been made. Test items receiving a 'New' judgement were followed by a 2000ms duration white fixation cross. Test responses were made with the index, middle and ring fingers of the right hand on a scanner-compatible button box. The buttons were counterbalanced across participants such that the 'Old'/'New' judgment were made with the index and middle finger, while the source judgements were counterbalanced across the index, middle, and ring fingers with the constraint that the 'Don't know' response was never assigned to the middle finger. Analogously to the study phase, trials associated with responses made outside of a 500ms– 4500ms post-stimulus window were not considered in the analyses and were included as events of no interest.
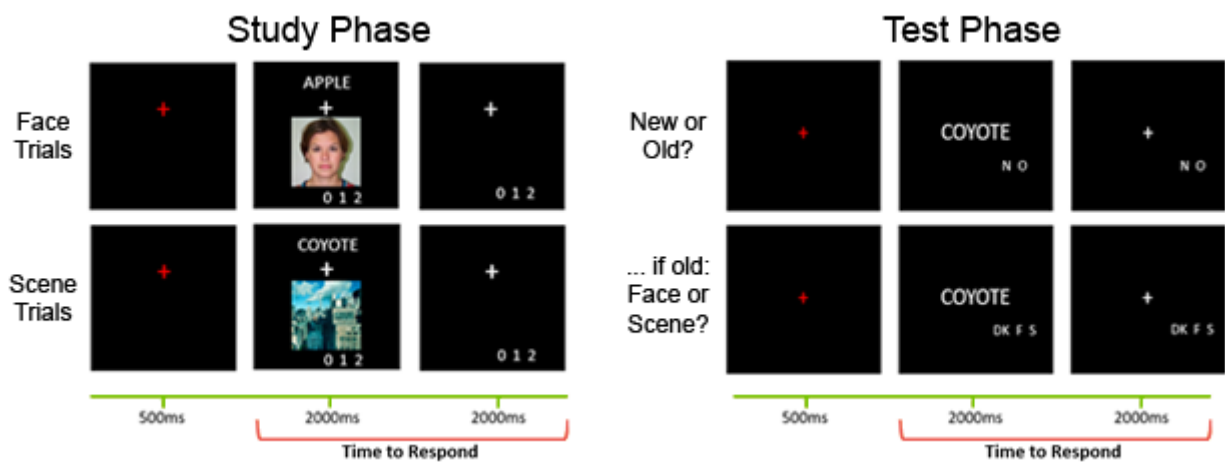
Figure 2.1. Overview of the encoding task and subsequent memory test. At encoding, participants were asked to "Imagine the person interacting with the object denoted by the word." (face trials) or to "Imagine the object denoted by the word interacting with the scene." (scene trials).

2.2.3.4 Experimental Design and Statistical Analysis

The main independent variables in the analyses described below include age group (younger vs older adults), image category of the study trials (faces vs scenes), and the two face-selective and two scene-selective regions-of-interest (ROIs): Fusiform Face Area (FFA) and Occipital Face Area (OFA) as face-selective ROIs; Parahippocampal Place Area (PPA) and Retrosplenial cortex (RSC) as scene-selective ROIs.

Statistical analyses were conducted using R Software (R Core Team, 2019) and all tests were considered significant at $p < 0.05$. Analyses of variance were performed using the *afex* package (Singmann et al., 2016) and the degrees of freedom were corrected for nonsphericity using the Greenhouse and Geisser (1959) procedure. All *t*-tests were performed as Welch's unequal variance tests using the t-test function in base R. Effect sizes are reported as partial-η^2 for the analysis of variance (ANOVA) results and the package *effsize* (Torchiano, 2019) was used for Cohen's d in pairwise comparisons (Cohen, 1988). Linear regression models were employed using the lm function in base R, and partial correlations were conducted using the function pcor.test in the *ppcor* package (Kim, 2015). Principal components analysis (Hotelling, 1933; Abdi and Williams, 2008) on the neuropsychological test scores was implemented with the *psych* package (Revelle, 2017).

2.2.3.5 Behavioral Data Analysis

Study and test trials were binned according to their subsequent memory status. We focused on item recognition performance as reflected in the initial 'Old' / 'New' judgement, and source memory performance as indexed by the subsequent 'Scene'/ 'Face' / 'Don't Know' judgement. Trials that received no response or multiple responses were excluded. Item Memory performance was computed as the difference between the overall hit rate and the false alarm rate:

$$Item\ pR = \frac{Item\ Hit}{Old\ Trials} - \frac{False\ Alarms}{New\ Trials}$$

The hit rate was calculated as the proportion of trials which were correctly endorsed as 'Old' relative to the total number of old trials, regardless of their subsequent source memory judgement.

The false alarm rate was calculated as the proportion of new trials incorrectly endorsed as 'Old' relative to all new trials. The overall item recognition accuracy was submitted to a 2 (age group) x 2 (image class) mixed factorial ANOVA.

Additionally, source memory accuracy was computed using a modified single high-threshold model (Snodgrass and Corwin, 1988) according to the following formula (see Gottlieb et al., 2010; Mattson et al. 2014):

$$pSR = \frac{pSource\ Hit - 0.5 * (1 - pSource\ Don't\ Know)}{1 - 0.5 * (1 - pSource\ Don't\ know)}$$

where 'pSource Hit' refers to the proportion of correctly recognized test items endorsed with a correct source memory judgement at test and 'pSource Don't Know' refers to items that were correctly recognized but received a 'Don't Know' source memory response. Given the design of this experiment, our source memory metric necessarily encompasses both face and scene trials. Therefore, we collapsed source memory performance across image type and compared performance between the two age groups with an independent samples t-test.

Other behavioral measures included reaction time (RT) and vividness ratings for the encoding trials. RT was calculated as the median time to make a vividness rating. Both RTs and the vividness ratings were computed separately for trials corresponding to each image class and binned according to whether or not they were associated with a correct source judgment at test. The vividness ratings and RTs were submitted to separate 2 (Age group) x 2 (image class) x 2 (subsequent memory) mixed factorial ANOVAs.

2.2.3.6 MRI Data Acquisition and Preprocessing

Functional and structural MRI data were acquired at 3T using a Philips Achieva MRI scanner (Philips Medical Systems, Andover, MA) equipped with a 32 channel receiver head coil. The functional scans were acquired with a T2*-weighted, blood-oxygen level-dependent echoplanar imaging (EPI) sequence (sensitivity encoding [SENSE] factor = 2, flip angle = 70°, 80 x 78 matrix, field of view [FOV] = 24 cm, repetition time [TR] = 2000 ms, and echo time [TE] = 30 ms). EPI volumes comprised 34 slices (1mm interslice gap) at a voxel size of 3x3x3 mm,

acquired in an ascending order and parallel to the anterior-posterior commissure line. Structural images were obtained with a T1-weighted MPRAGE sequence (FOV = 240 x 240, 1x1x1 mm isotropic voxels, sagittal acquisition).

MRI data were preprocessed and analyzed using a combination of Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK) and custom Matlab scripts. The functional images were realigned to the mean EPI image and slice-time corrected using sinc interpolation to the middle slice. The images were then subjected to reorientation and spatial normalization with respect to a sample-specific template following previously published procedures (de Chastelaine et al. 2011, 2016). Functional images were smoothed with an 8 mm full-width half maximum Gaussian kernel prior to region-of-interest (ROI) selection. Estimation of differentiation indices and PSA were conducted on unsmoothed data.

2.2.3.7 MRI Data Analysis

The analyses reported here focus on the data from the study sessions (analyses of the test data will be reported in a separate paper). The ROIs were derived from univariate fMRI analyses across the four study sessions, which were performed in two stages. In the first stage, separate GLMs were constructed for each participant by sorting the study trials into two categories depending on the trial type: scene trials and face trials. Trials belonging to each of these categories were modeled with a 2s duration boxcar function onsetting concurrently with the onset of the study word-image pair, convolved with a canonical hemodynamic response function (HRF). Filler trials, null trials, and trials which received multiple or no responses were modeled as covariates of no interest. Additional covariates of no interest included the 30s duration rest periods midway through each study session and the six regressors representing motion-related variance (three representing rigid-body translation and three for rigid-body rotation along the three axes). Trials with translational displacement greater than 1mm or with rotational displacement greater than 1° in any direction were modeled as covariates of no interest and hence removed from the analysis. In the second stage, the parameter estimates of the two events of interest were carried over to a second-level random effects 2 x 2 factorial ANOVA with age (younger, older) treated as the between-subjects factor, and trial type (scene, face) as the within-subjects factor.

For the purposes of the differentiation index analyses and the PSA, the unsmoothed data from each of the four total study sessions were concatenated using the *spm_fmri_concatenate* function and subjected to a 'least-squares-all' analysis (Rissman et al., 2004; Mumford et al., 2014) to estimate the BOLD response for each trial. Each event was modeled with a 2s duration boxcar function and convolved with a canonical HRF. The covariates of no interest included the 6 motion regressors described above and the four session specific means.

2.2.3.8 Region-of-Interest Selection

Two face-selective (FFA, OFA) and two scene-selective (PPA, RSC) ROIs were empirically defined via a second-level GLM that contrasted scenes and faces, (thresholded at p < 0.01 (uncorrected)) across all participants without regard to the factor of age group. The contrasts were inclusively masked with the 'Neuromorphometrics' atlas provided in SPM12. The face > scene contrast was masked with the atlas's fusiform gyrus and parahippocampal gyrus to derive the FFA mask, and the OFA was defined by inclusively masking the contrasts with inferior occipital and occipital fusiform gyri. The scene > face contrast was masked with the fusiform and parahippocampal gyri to identify the PPA. As Neuromorphometrics does not provide a mask for the RSC, we searched the Neurosynth database using the term "retrosplenial" (search in August 2019, search results FDR-corrected at p < 0.00001; Yarkoni et al., 2011) and used the outcome to create the RSC mask. All ROIs were collapsed across the two hemispheres.

Table 2.3. The voxel size and peak MNI coordinates for each ROI

	ROI size (voxels)	Peak MNI Coordinates		
		X	Y	Z
R. Occipital Face Area	98	45	-79	-16
L. Occipital Face Area	24	-45	-85	-10
R. Fusiform Face Area	34	45	-43	-28
L. Fusiform Face Area	10	-42	-49	-25
R. Parahippocampal Place Area	219	30	-40	-19
L. Parahippocampal Place Area	249	-27	-46	-16
R. Retrosplenial Cortex	168	18	-58	14
L. Retrosplenial Cortex	211	-15	-61	11
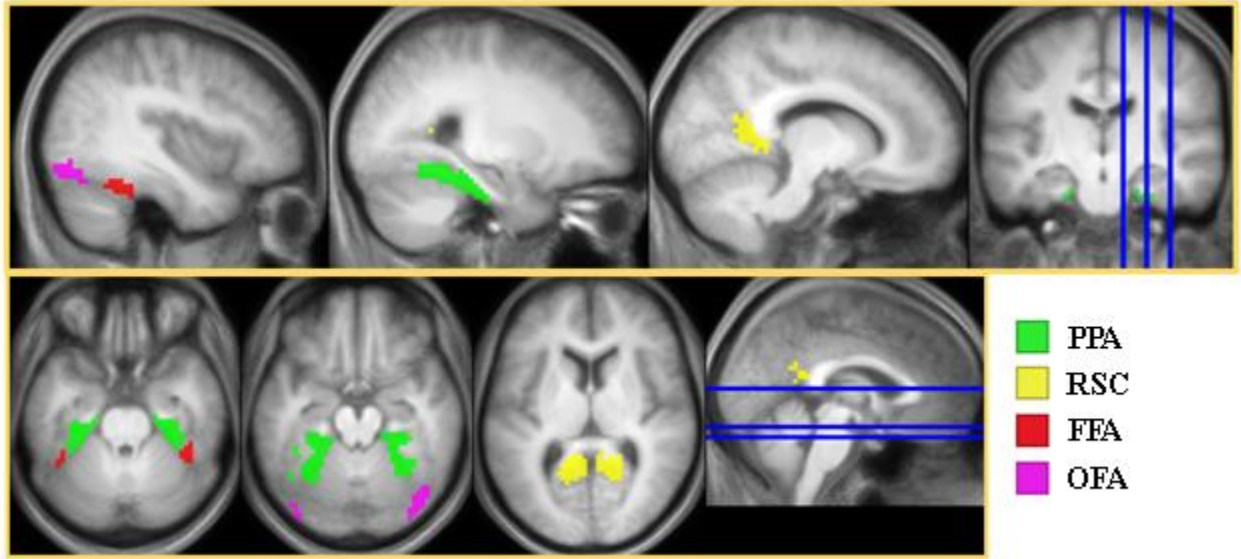
Figure 2.2. Bilateral scene- and face-selective ROIs derived using a second-level GLM contrasting faces and scenes, inclusively masked with Neuromorphometrics in SPM (PPA, FFA, OFA) or with Neurosynth (RSC).

2.2.3.9 Differentiation Index

We computed a differentiation index for each ROI as a measure of the selectivity of neural responses at the regional level (Voss et al., 2008; Zebrowitz et al., 2016; Koen et al., 2019). The differentiation index for a given ROI was computed as the difference between the mean BOLD response for trials of a preferred stimulus class and the mean BOLD response for trials of the non-preferred class, divided by pooled standard deviation:

$$Differentiation\ Index = \frac{\mu_{pref} - \mu_{non\ pref}}{\sqrt{\dfrac{\sigma_{pref}^2 + \sigma_{non\ pref}^2}{2}}}$$

Therefore, a higher differentiation index indicates greater selectivity for a given ROI (note that because of the scaling function, the differentiation index is insensitive to individual or group differences in the gain of the hemodynamic response function mediating between neural activity and the fMRI BOLD response). We computed a differentiation index for each of the four ROIs for

each participant. The resulting indices were subjected to a 2 (age group) x 4 (ROI) mixed factorial ANOVA. We conducted an additional ANOVA of the differentiation indices computed only from the trials that went on to receive a source correct memory response. The goal of this additional analysis was to ascertain whether any age differences arising from the original analysis were a reflection of the differential mixing of trial types as a function of age group (on average, young participants had a higher proportion of source correct study trials than did older adults).

Neural dedifferentiation may manifest as a reduced neuronal response to a preferred stimulus category (i.e. neural attenuation), as an elevated response to a non-preferred category (i.e. neural broadening), or as the combination of both phenomena (Park et al., 2012; Koen & Rugg, 2019). The differentiation index is insensitive to this distinction. Thus, we also examined the β-parameters, averaged across all voxels within each ROI, reflecting responses to scene and face trials in ROIs where we identified age-related neural dedifferentiation. The β-parameters were subjected to a 2 (age group) x 2 (ROI) x 2 (image class) mixed-factorial ANOVA.

Finally, to examine whether neural differentiation predicted memory performance or psychometric factor of fluency, for each ROI we constructed regression models that employed differentiation index and age-group as predictor variables, and, in parallel models, either source or item memory performance as the dependent variable. Initial versions of the models also included the interaction between differentiation index and age group as an additional predictor variable. In no case did the interaction term account for a significant fraction of the variance in performance ($p > 0.116$). Results are reported below for the reduced models that excluded the interaction term.

2.2.3.10 Multivoxel Pattern Similarity Analysis

Multivoxel pattern similarity analysis (PSA) was conducted in a similar fashion to Koen et al. (2019) to complement the univariate analyses described above. The similarity measures were derived from single-trial, voxel-wise β-parameters (see Methods above). For each participant and ROI, we first computed a within-category similarity metric. This was achieved by computing the correlations across voxels between each study trial and all other study trials belonging to the same image category, subjecting the resulting correlations to a Fisher's z transformation, and averaging them. The between-category similarity was calculated in an analogous fashion except that the

correlations were estimated between rather than within image category. The between- and within-similarity was always computed across trials of different scanning sessions to avoid potential bias arising from carry-over effects (Mumford et al. 2014). The similarity index was then computed as the difference between the within- and between-category similarity metrics. This index can be used as a metric of neural differentiation as it reflects the extent to which different perceptual categories evoke consistent patterns of neural responses within a given region of interest. As in the case of the differentiation index described above, this correlation-based metric is insensitive to individual differences in hemodynamic gain.

The similarity indices were subjected to a 2 (age group) x 4 (ROI) mixed factorial-ANOVA. As with the analyses of the differentiation indices, we also computed pattern similarity separately for trials that went on to receive a source correct memory response. Additionally, similarity indices were employed in regression analyses aimed at predicting behavioral performance. These analyses were exactly analogous to those conducted on the differentiation indices.

2.3   Results

Demographic data and the outcomes of the neuropsychological test battery are presented in Table 2.1. The groups were well-matched for years of education and MMSE but showed a typical pattern of age-related differences in cognitive performance. Thus, relative to the older group, younger adults had better performance on a subset of declarative memory tests, including the CVLT short free recall test and the logical memory subtests of the WMS. The younger adults also made significantly fewer recognition false alarms on the CVLT recognition memory test and outperformed the older group on the speeded tests (Trails A, Trails B, and Symbol Digit Modalities) and Raven's progressive matrices.

The rotated factor loadings (see Methods) were applied to each participant's neuropsychological test scores, and the resulting factor scores for the four rotated components are presented at the bottom of Table 2.2. Consistent with the individual neuropsychological tests, there were age differences in the Speed and the Memory constructs. There were no age differences in the Crystallized Intelligence or Fluency factors.

2.3.1 Behavioral Results

2.3.1.1 Study Performance

Mean study reaction times (RTs) and vividness ratings are reported in Table 2.4, separated by image category and age group. A 2 (age group) x 2 (image category) x 2 (memory: source correct vs. source incorrect/don't know and item misses) mixed factorial ANOVA on the RT data revealed a significant main effect of category, reflecting faster responses in face trials ($F_{(1,46)}$ = 5.350, p = 0.025, partial-η^2 = 0.101), but the remaining main effects and all interactions were not significant (ps > 0.100). A 2 (age group) x 2 (image category) x 2 (memory) ANOVA on the mean vividness ratings revealed a significant main effect of memory (trials rated as more vivid were associated with better source memory performance), ($F_{(1,46)}$ = 53.436, p < 0.001, partial-η^2 = 0.537). There was no effect of age ($F_{(1,46)}$ = 3.120, p = 0.084, partial-η^2 = 0.064), category ($F_{(1,46)}$ = 0.656, p = 0.409, partial-η^2 = 0.015), and no interaction effects (ps > 0.180).

Table 2.4. Mean (SD) Study phase performance in younger and older adult groups.

	Young Adults		*Older Adults*	
	Faces	*Scenes*	*Faces*	*Scenes*
Vividness Ratings				
Source Correct Memory	2.42 (.32)	2.44 (.32)	2.24 (.39)	2.18 (.43)
Incorrect Memory	2.23 (.42)	2.13 (.51)	2.06 (.46)	2.01 (.49)
Reaction Time (ms)				
Source Correct Memory	2369 (678)	2398 (628)	2130 (570)	2266 (524)
Incorrect Memory	2351 (658)	2350 (633)	2285 (605)	2327 (579)

2.3.1.2 Memory Performance

Memory performance on the experimental task is summarized in Table 2.5. A 2 (age group) x 2 (image category) mixed factorial ANOVA on item recognition identified a significant main effect of image category ($F_{(1,46)}$ = 5.443, p = 0.024, partial-η^2 = 0.106), and a main effect of age group ($F_{(1,46)}$ = 10.112, p = 0.003, partial-η^2 = 0.180). There was no significant interaction between the two factors ($F_{(1,46)}$ = 0.766, p = 0.386, partial-η^2 = 0.016). The main effect of image class reflected higher item memory performance for words paired with faces relative to scenes. Additionally, overall item recognition performance was significantly greater for younger than

older adults. An independent samples t-test on source memory performance (pSR) revealed a significant difference in favor of the younger group ($t_{(45.12)} = 3.440$, $p = 0.001$, $d = 1.010$).

Table 2.5. Mean (SD) Item and Source memory performance for younger and older adult groups.

	Young Adults		*Older Adults*	
	Faces	*Scenes*	*Faces*	*Scenes*
Item Hit Rate	0.82 (0.15)	0.81 (0.15)	0.70 (0.17)	0.66 (0.14)
False Alarm Rate	0.13 (0.10)		0.13 (0.10)	
Proportion Source Correct	0.83 (0.14)	0.79 (0.16)	0.75 (0.13)	0.68 (0.13)
Proportion Source Incorrect	0.05 (0.04)	0.06 (0.05)	0.14 (0.07)	0.18 (0.10)
Proportion Source Don't Know	0.12 (0.13)	0.16 (0.13)	0.12 (0.12)	0.14 (0.13)
Item Memory	0.69 (0.18)	0.67 (0.17)	0.56 (0.14)	0.52 (0.13)
Source Memory (pSR)	0.68 (0.18)		0.51 (0.16)	

Item memory computed as the difference between hit and false alarm rates
Source memory computed using the single high-threshold model described in Behavioral Data Analysis

2.3.2 fMRI Differentiation Index

The differentiation indices were subjected to a 2 (age group) x 4 (ROI) mixed factorial ANOVA. The ANOVA revealed a main effect of ROI ($F_{(2.11, 96.87)} = 29.498$, $p < 0.001$, partial-$\eta^2 = 0.391$), a main effect of age group ($F_{(1, 46)} = 7.389$, $p = 0.009$, partial-$\eta^2 = 0.138$), and a significant age-by-ROI interaction ($F_{(2.11, 96.87)} = 9.025$ $p < 0.001$, partial-$\eta^2 = 0.164$). Two follow-up ANOVAs were performed separately for the face-selective and scene-selective ROIs. The 2 (age group) x 2 (scene-selective ROIs) ANOVA resulted in a significant main effect of ROI ($F_{(1, 46)} = 115.71$, $p < 0.001$, partial-$\eta^2 = 0.715$), a significant main effect of age group ($F_{(1, 46)} = 24.006$, $p < 0.001$, partial-$\eta^2 = 0.343$), and a near-significant age-by-ROI interaction ($F_{(1, 46)} = 3.869$, $p = 0.055$, partial-$\eta^2 = 0.078$). As is illustrated in Figure 2.3-A, the main effect of age group is driven by reduced neural differentiation in the older age group in both ROIs: PPA ($t_{(45.50)} = 4.693$, $p < 0.001$, $d = 1.355$), and RSC ($t_{(45.95)} = 3.763$, $p < 0.001$, $d = 1.086$). An analogous 2 (age group) x 2 (face-selective ROIs) ANOVA resulted in only a weak trend toward an age-by-ROI interaction ($F_{(1, 46)} = 3.679$, $p = 0.061$, partial-$\eta^2 = 0.074$), and no main effect for ROI ($F_{(1, 46)} = 0.637$, $p = 0.429$, partial-$\eta^2 = 0.014$), or age group ($F_{(1, 46)} = 0.265$, $p = 0.609$, partial-$\eta^2 = 0.006$). Unsurprisingly, therefore, there were null effects of age on neural differentiation in both FFA ($t_{(45.81)} = 0.401$, $p =$

0.690), and OFA ($t_{(42.92)} = -1.381$, $p = 0.175$). Each of the differentiation indices illustrated in Figure 3-A differed significantly from zero in both age groups (ps < 0.002). Together, these results indicate that age group moderated neural differentiation within the scene-selective but not the face-selective ROIs.

In a follow-up analysis, the differentiation index was computed separately for stimulus pairs according to whether they went on to receive a source correct or any form of incorrect response (source incorrect/don't know and item misses) on the subsequent memory task. A 2 (age group) x 4 (ROI) x 2 (memory status) mixed factorial ANOVA revealed a main effect of ROI ($F_{(2.09, 96.21)} = 23.511$, $p < 0.001$, partial-$\eta^2 = 0.338$), a main effect of age group ($F_{(1, 46)} = 6.737$, $p = 0.013$, partial-$\eta^2 = 0.128$), a significant age-by-ROI interaction ($F_{(2,09)} = 6.250$, $p = 0.002$, partial-$\eta^2 = 0.119$), and a three-way interaction between age, ROI and memory status ($F_{(1.81, 83.16)} = 4.483$, $p = 0.017$, partial-$\eta^2 = 0.089$). However, the analysis did not identify a main effect of memory ($F_{(1, 46)} = 1.714$, $p = 0.197$, partial-$\eta^2 = 0.036$), nor a memory-by-age or memory-by-ROI interaction ($F_{(1, 46)} = 2.567$, $p = 0.116$, partial-$\eta^2 = 0.052$, and $F_{(1.81, 83.16)} = 0.605$, $p = 0.532$, partial-$\eta^2 = 0.013$, respectively). Pairwise follow-up tests failed to identify significant differences between differentiation indices computed separately for the two classes of subsequent memory judgment in any of the ROIs in either age group (ps > 0.178).

We went on the examine the differentiation indices only for trials that were later associated with a source-correct memory response to ensure that the age-differences reported above were not driven by the differential mixing of source correct and source incorrect trials (given the age differences in source memory, see above). The ANOVA identified a significant main effect of ROI ($F_{(1.89, 86.74)} = 22.401$, $p < 0.001$, partial-$\eta^2 = 0.327$), a main effect of age group ($F_{(1, 46)} = 4.890$, $p = 0.032$, partial-$\eta^2 = 0.096$), and an age-by-ROI interaction ($F_{(1.89, 86.74)} = 11.103$, $p < 0.001$, partial-$\eta^2 = 0.194$). As in the analyses of study trials collapsed across memory performance, we followed up the significant ROI-by-age group interaction with subsidiary 2 (age group) x 2 (face-selective ROIs) and a 2 (age group) x 2 (scene-selective ROIs) ANOVAs. In the scene-selective regions, we identified a significant main effect of age-group ($F_{(1, 46)} = 22.921$, $p < 0.001$, partial-$\eta^2 = 0.333$), a main effect of ROI ($F_{(1, 46)} = 133.684$, $p < 0.001$, partial-$\eta^2 = 0.744$), but only a trend towards an age-by-ROI interaction ($F_{(1, 46)} = 3.938$, $p = 0.053$, partial-$\eta^2 = 0.079$). As evident in Figure 2.3-B,

the effects of age on neural differentiation within the scene-selective regions were characterized by reduced differentiation indices in both PPA ($t_{(45.98)} = 5.281$, $p < 0.001$, $d = 1.524$), and RSC ($t_{(44.79)} = 3.359$, $p = 0.002$, $d = 0.970$). The analogous analysis in the face-selective regions revealed a significant age-by-ROI interaction ($F_{(1, 46)} = 4.172$, $p = 0.047$, partial-$\eta^2 = 0.083$), but the ANOVA did not reveal main effects of age or ROI ($F_{(1, 46)} = 2.013$, $p = 0.163$, partial-$\eta^2 = 0.042$ and $F_{(1, 46)} = 0.640$, $p = 0.428$, partial-$\eta^2 = 0.014$, respectively). Subsequent pairwise comparisons demonstrated significantly greater differentiation in older relative to younger adults in the OFA ($t_{(43.92)} = -2.204$, $p = 0.032$, $d = 0.636$), but no age differences in the FFA ($t_{(44.94)} = -0.258$, $p = 0.797$, $d = 0.075$). As in the prior analyses, each of the differentiation indices illustrated in Figure 2.3-B was significantly different from zero in both age groups ($ps < 0.019$). Overall, restricting analyses to only those encoding trials receiving a subsequent source correct response led to convergent results in scene-selective ROIs, whereby older adults demonstrated lower neural selectivity relative to younger adults.
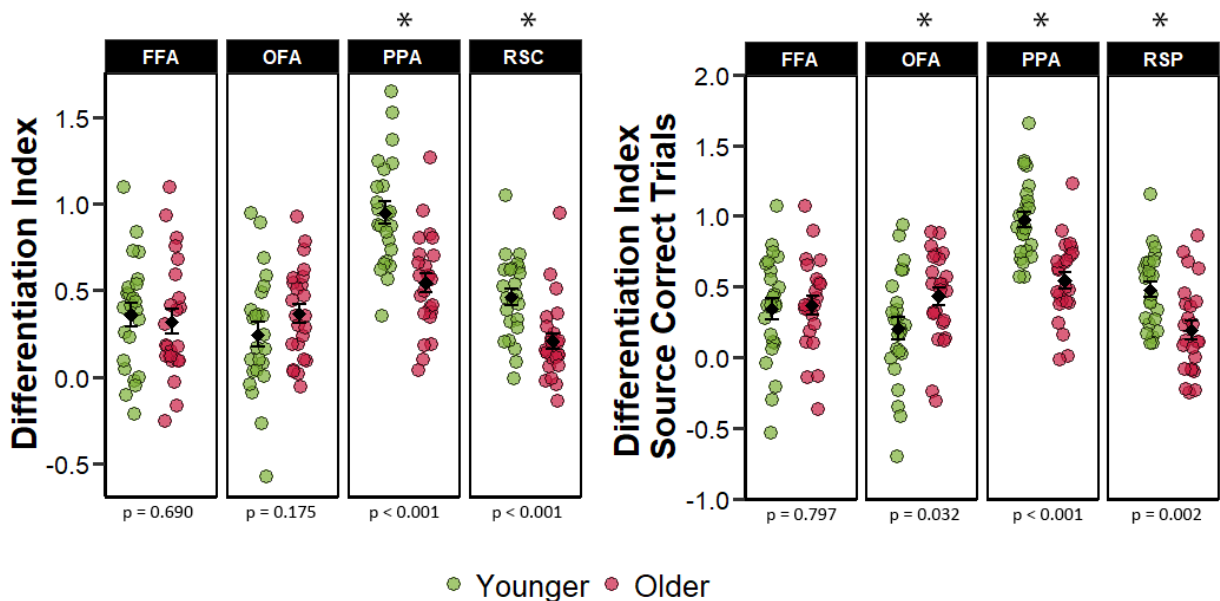
Figure 2.3. (A) Univariate differentiation indices collapsed across all trials regardless of subsequent memory performance. **(B)** Differentiation indices computed for only those trials that went on to receive a source-correct response at subsequent retrieval. The error bars around the group means denote ± 1 SEM. The p-values represent the t-tests comparing younger and older adults in each ROI with * denoting a statistically significant age difference.

To further examine age-related dedifferentiation effects in scene-selective regions, we examined whether reduced neural selectivity in older adults resulted from a reduction in BOLD signal for the preferred image category (neural attenuation) or an increase in BOLD signal to the non-preferred category (neural broadening). A 2 (age group) x 2 (scene-selective ROIs) x 2 (image class) mixed factorial ANOVA on the extracted β-parameters revealed a significant main effect of ROI ($F_{(1, 46)} = 125.677$, $p < 0.001$, partial-$\eta^2 = 0.732$), and a main effect of stimulus category ($F_{(1, 46)} = 223.252$, $p < 0.001$, partial-$\eta^2 = 0.829$), but a null effect of age group ($F_{(1, 46)} = 0.591$, $p = 0.445$, partial-$\eta^2 = 0.013$), and a null age-by-ROI interaction ($F_{(1, 46)} = 0.032$, $p = 0.859$, partial-$\eta^2 = 0.001$). However, the ANOVA revealed a 2-way interactions between stimulus category and age group ($F_{(1, 46)} = 25.859$, $p < 0.001$, partial-$\eta^2 = 0.360$), and stimulus category and ROI ($F_{(1, 46)} = 65.59$, $p < 0.001$, partial-$\eta^2 = 0.588$). The 3-way interaction was not significant ($F_{(1, 46)} = 1.553$, $p = 0.219$, partial-$\eta^2 = 0.033$). As is evident from Figure 2.4-A, there was an attenuated BOLD response to scenes in older participants across both scene ROIs ($t_{(44.94)} = -2.894$, $p = 0.005$, d = -0.591$), accompanied by an elevated response to face stimuli ($t_{(44.94)} = 2.659$, $p = 0.009$, d = 0.543$). Thus, age-related neural dedifferentiation in the scene-selective ROIs was driven by a combination of attenuated BOLD response to scenes and increased responses to faces.

Although no age differences in neural differentiation were observed in the face-selective ROIs, we performed an analysis analogous to that described in the preceding paragraph. Figure 2.4-B illustrates the mean BOLD response to face and scene stimuli in these regions. We employed an analogous 2 (age group) x 2 (ROIs) x 2 (image class) ANOVA on the extracted β-parameters. The ANOVA identified main effects of category ($F_{(1, 46)} = 64.107$, $p < 0.001$, partial-$\eta^2 = 0.582$) and age group ($F_{(1, 46)} = 5.775$, $p = 0.020$, partial-$\eta^2 = 0.112$), and a null effect of ROI ($F_{(1, 46)} = 0.382$, $p = 0.540$, partial-$\eta^2 = 0.008$). Unlike in the analysis reported for the scene-selective ROIs, the ANOVA did not identify a significant interaction between age group and category ($F_{(1, 46)} = 0.132$, $p = 0.711$, partial-$\eta^2 = 0.003$), and the interaction between age group and ROI was also not significant ($F_{(1, 46)} = 1.241$, $p = 0.271$, partial-$\eta^2 = 0.026$). Lastly, the 3-way interaction between age group, category, and ROI also failed to attain significance ($F_{(1, 46)} = 3.016$, $p = 0.089$, partial-$\eta^2 = 0.062$). The null effects for the interactions involving the factors of age groups and stimulus

category are consistent with the outcome of the analysis of the dedifferentiation indices derived from the face-selective ROIs described previously.
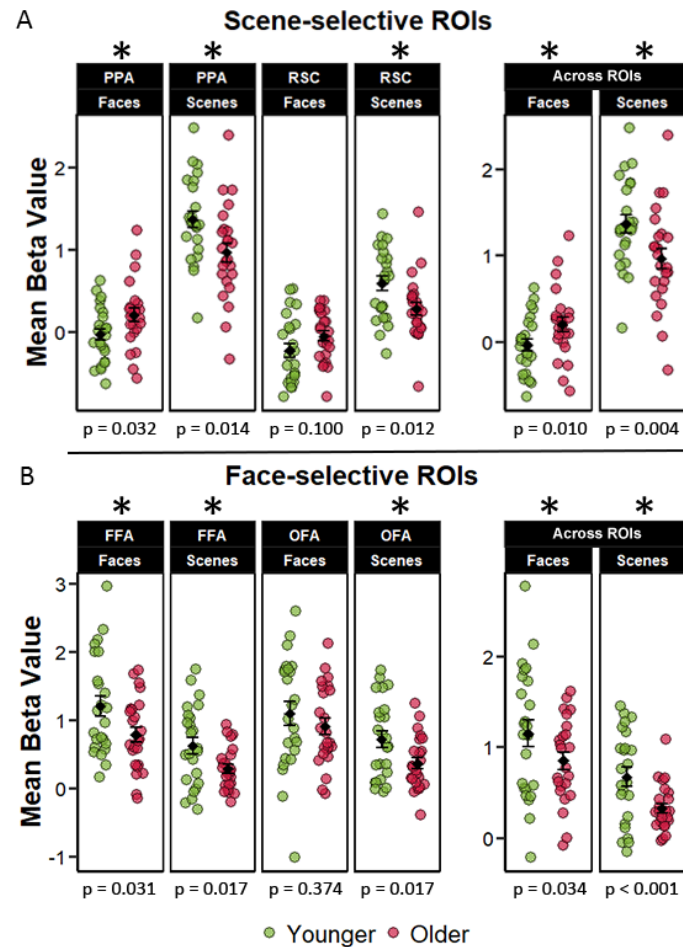
Figure 2.4. **(A)** Across-trial mean β-parameters for face and scene trials in the scene-selective ROIs, including the mean β-parameters collapsed across the scene ROIs. The figure illustrates that age-related neural dedifferentiation in these regions was driven by both broadened responses to faces and attenuated responses to scenes in the older group. **(B)** Across-trial mean β-parameters for face and scene trials in the face-selective ROIs, including the mean β-parameters across the face ROIs. The error bars around the group means denote ± 1 SEM. The p-values represent the t-tests comparing younger and older adults in each ROI with * denoting a statistically significant age difference. Unlike in the scene ROIs, parameter estimates were consistently greater for the young relative to the older group.

2.3.3   Pattern Similarity Analysis

Multivoxel PSA (Kriegeskorte et al., 2008) was employed as a complement to the analysis of the differentiation index described above. We computed a within-between similarity metric in each ROI as an index of selectivity to the ROI's preferred relative to the non-preferred stimulus class (see Methods). Analogous to the analyses of the differentiation index, the initial 2 (age group) x 4 (ROI) mixed factorial ANOVA was employed on the within-between similarity indices computed across all trials regardless of subsequent memory status. This revealed significant main effects of ROI ($F_{(2.35, 108.24)} = 11.924$, $p < 0.001$, partial-$\eta^2 = 0.206$), and age group ($F_{(1, 46)} = 12.855$, $p < 0.001$, partial-$\eta^2 = 0.218$), along with a significant two-way interaction ($F_{(2.35, 108.24)} = 4.981$, $p = 0.006$, partial-$\eta^2 = 0.098$). A subsequent 2 (age group) x 2 (ROI) mixed ANOVA focusing on just the scene-selective ROIs yielded a significant main effect of ROI ($F_{(1, 46)} = 71.020$, $p < 0.001$, partial-$\eta^2 = 0.607$), a main effect of age ($F_{(1, 46)} = 20.273$, $p < 0.001$, partial-$\eta^2 = 0.306$), and a significant age-by-ROI interaction ($F_{(1, 46)} = 19.077$, $p < 0.001$, partial-$\eta^2 = 0.293$). An analogous 2 (age group) x 2 (ROI) ANOVA on the data from the face-selective ROIs failed to identify a significant age-by-ROI interaction ($F_{(1, 46)} = 0.191$, $p = 0.174$, partial-$\eta^2 = 0.040$), nor did it reveal significant main effects of ROI ($F_{(1, 46)} = 0.575$, $p = 0.452$, partial-$\eta^2 = 0.012$), or age group ($F_{(1, 46)} = 3.091$, $p = 0.085$, partial-$\eta^2 = 0.063$). Follow-up pairwise comparisons examining age differences in each of the four ROIs revealed significantly lower similarity metrics for scenes in both the PPA ($t_{(40.50)} = 5.191$, $p < 0.001$, $d = 1.498$), and RSC ($t_{(37.66)} = 2.290$, $p = 0.027$, $d = 0.660$). We did not however detect any age differences in similarity indices for faces within face-selective ROIs: FFA ($t_{(33.06)} = 1.939$, $p = 0.061$, $d = 0.560$), OFA ($t_{(45.46)} = 0.626$, $p = 0.534$, $d = 0.181$), (Figure 2.5-A). The similarity indices differed significantly from zero in all ROIs in both age groups ($ps < 0.001$). These results indicate that, when computed across all encoding trials, within – between pattern similarity was moderated by age in the scene- but not the face-selective ROIs.

As with the analyses of the differentiation index, the pattern similarity indices were also computed separately for trials binned into two categories depending on if the trial received a correct source memory response or not at retrieval. A 2 (age group) x 4 (ROI) x 2 (memory status) mixed factorial ANOVA resulted in a main effect of age group ($F_{(1, 46)} = 12.894$, $p < 0.001$, partial-$\eta^2 = 0.219$), a main effect of ROI ($F_{(2.34, 107.47)} = 10.873$, $p < 0.001$, partial-$\eta^2 = 0.191$), an age-by-

ROI interaction ($F_{(2.34, 107.47)}$ = 4.480, p = 0.010, partial-η^2 = 0.089), and a three-way interaction between age, ROI and memory status ($F_{(2.39, 109.99)}$ = 3.542, p = 0.025, partial-η^2 = 0.071). The analysis did not identify a main effect of memory ($F_{(1, 46)}$ = 3.074, p = 0.098, partial-η^2 = 0.063), nor any two-way interactions between memory and age group or ROI (ps > 0.213). Subsequent pairwise comparisons demonstrated that the pattern similarity indices computed separately for the two classes of memory judgment were not significantly different from each other in either ROI in either age group (ps > 0.140).

For the reasons described above, we repeated the foregoing analyses using only those trials that went on to give rise to a correct source memory judgment, allowing an assessment of whether age-differences in pattern similarity were driven by age-differences in the number of successful memory trials contributing to the similarity metrics. A 2 (age group) x 4 (ROI) mixed ANOVA revealed significant main effects of age ($F_{(1, 46)}$ = 12.071, p = 0.001, partial-η^2 = 0.208), and ROI ($F_{(2.34, 107.43)}$ = 10.550, p < 0.001, partial-η^2 = 0.187), along with significant age by ROI interaction ($F_{(2.34, 107.43)}$ = 5.325, p = 0.004, partial-η^2 = 0.104). A follow-up ANOVA on the data for the scene-selective ROIs revealed significant main effects of age group ($F_{(1, 46)}$ = 20.830, p < 0.001, partial-η^2 = 0.312), and ROI ($F_{(1, 46)}$ = 58.860, p < 0.001, partial-η^2 = 0.561), as well as an age-by-ROI interaction ($F_{(1, 46)}$ = 16.221, p < 0.001, partial-η^2 = 0.261). ANOVA of the face-selective ROIs failed to identify any significant effects: age ($F_{(1,46)}$ = 1.647, p = 0.206, partial-η^2 = 0.035); ROI ($F_{(1,46)}$ = 0.320, p = 0.574, partial-η^2 = 0.007); age-by-ROI interaction ($F_{(1, 46)}$ = 0.558, p = 0.459, partial-η^2 = 0.012). As Figure 2.5-B illustrates, the similarity indices demonstrated age-related reductions in both the PPA and RSC ($t_{(41.62)}$ = 5.543, p < 0.001, d = 1.600, and $t_{(37.12)}$ = 2.328, p = 0.025, d = 0.672, respectively), while age effects were absent in the two face-selective ROIs ($t_{(33.53)}$ = 1.230, p = 0.226, d = 0.356 and $t_{(45.54)}$ = 0.575, p = 0.568, d = 0.166; in the FFA and OFA respectively). Similarity indices were however significantly different from zero in all ROIs and age groups (ps < 0.001). Thus, as with the differentiation index, when pattern similarity analysis was restricted to encoding trials associated with a correct subsequent source memory judgment robust age effects were evident in scene- but not face-selective ROIs.
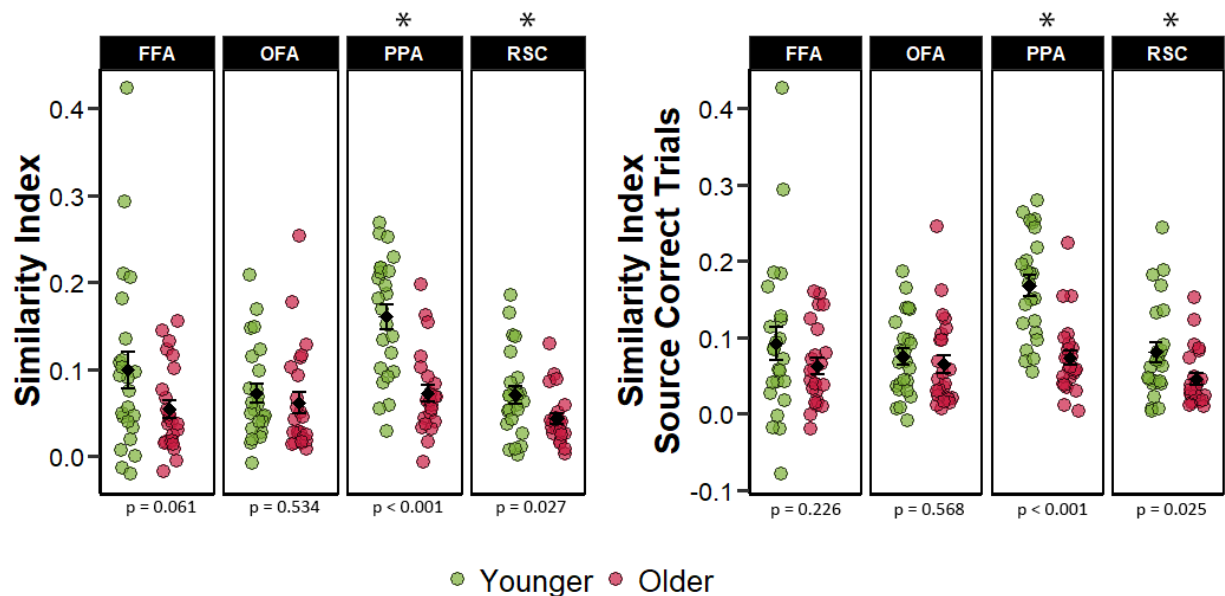
Figure 2.5. **(A)** Within – Between similarity indices computed collapsing across memory performance**. (B)** Within – Between similarity indices computed for only those trials that went on to receive a source-correct response at subsequent retrieval. The error bars around the group means denote ± 1 SEM. The p-values represent the t-tests comparing younger and older adults in each ROI with * denoting a statistically significant age difference.

2.3.4 Relationship Between Neural Differentiation and Subsequent Memory Performance

In light of prior findings (Koen et al., 2019), and as described in the methods, we ran a series of multiple regression analyses in which age group and the differentiation indices from each ROI were employed as predictors of subsequent source and item memory performance. As described in Methods, the initial multiple regression models included the ROI-by-age interaction terms, however, in no case was the interaction significant ($p > 0.116$). Therefore, Table 2.6 presents the partial correlations between neural differentiation and performance after controlling for age group. As is evident from the table, the partial correlations between differentiation indices and source memory performance achieved significance only in the PPA. This was the true both when computing the differentiation index collapsing across memory performance and when selecting only the source-correct trials. Moreover, these relationships between differentiation in the PPA and source memory performance remained significant after controlling for both age and item memory performance (collapsed across all trials: $r_{partial} = 0.334$, $p = 0.023$; source-correct trials:

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$r_{partial}$ = 0.314, p = 0.033). The partial relationships controlling for age group are illustrated in Figure 2.6. Analogous analyses were conducted for the pattern similarity indices: no significant relationships between similarity indices and memory performance were identified (p > 0.092, data and figures available from first author upon request).

Table 2.6. Partial correlations (p-values) between item memory and source memory performance and differentiation index when controlling for age group. The differentiation indices were computed either across all encoding trials (first two columns) or only for those encoding trials that were associated with a source-correct memory response (second two columns).

	Collapsed across all trials		Source-correct trials	
	Item Memory	Source Memory	Item Memory	Source Memory
FFA	-0.145 (0.330)	-0.117 (0.432)	-0.083 (0.581)	-0.010 (0.945)
OFA	0.071 (0.635)	0.086 (0.567)	0.149 (0.318)	0.08 (0.565)
PPA	0.140 (0.347)	0.335 (0.022)	0.180 (0.225)	0.347 (0.017)
RSC	0.096 (0.519)	0.155 (0.299)	0.037 (0.805)	0.101 (0.498)
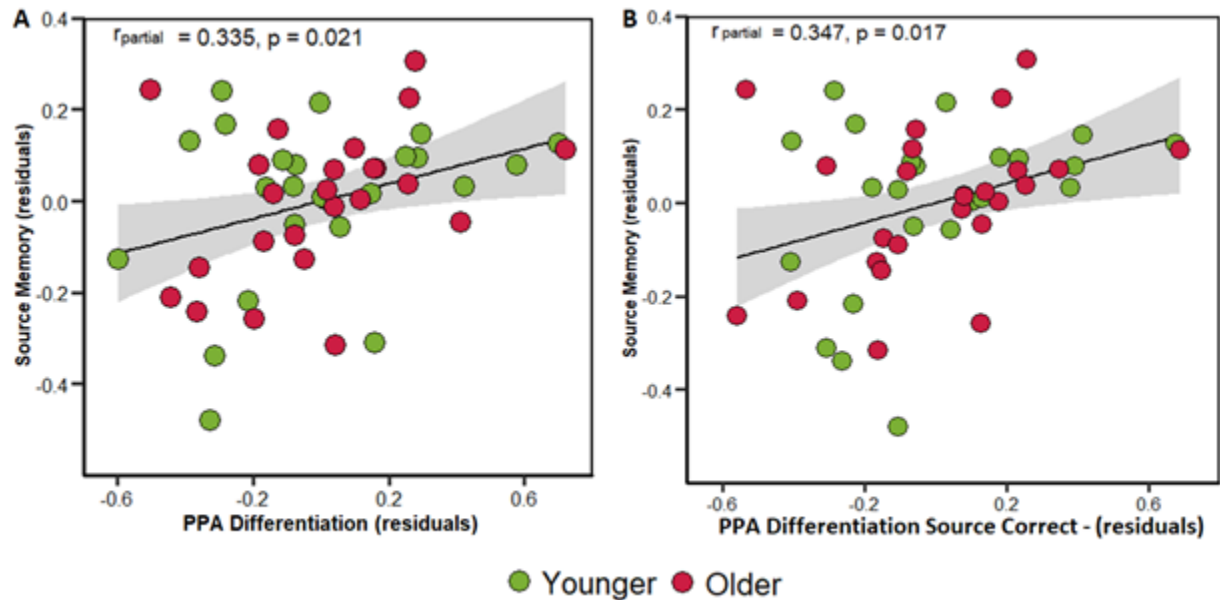
Figure 2.6. Scatterplots illustrating the partial correlations (controlling for age group) between PPA differentiation indices with source memory performance. Plot in (**A**) illustrates the relationship between source memory and differentiation index collapsed across all encoding trials. Plot in (**B**) illustrates the same relationship but restricted only to the trials that went on to receive a source correct memory response.

2.3.5 Relationship Between Neural Differentiation and Neuropsychological Performance

Given prior findings of a positive, age-invariant, relationship between the PPA differentiation index and the fluency component derived from the neuropsychological test battery (see Introduction), we examined whether a similar relationship was evident in the present study. When collapsed across all trials regardless of subsequent memory, the partial correlation (controlling for age) between the differentiation index and fluency factor scores was not significant in either the PPA ($r_{partial} = -0.009$, $p = 0.951$) or the RSC ($r_{partial} = 0.112$, $p = 0.454$). The relationship was also absent when the differentiation index was derived from source correct trials only (PPA: $r_{partial} = 0.105$, $p = 0.482$; RSC: $r_{partial} = 0.170$, $p = 0.255$).

2.4 Discussion

The current study employed a combination of univariate and multi-voxel analyses to examine age effects on category-level neural selectivity (neural differentiation) during the encoding of images of faces and scenes prior to a subsequent memory test. Neural selectivity was examined in two scene- and two face-selective ROIs. The univariate and pattern similarity measures yielded convergent results indicating that scene-, but not face-selective, regions demonstrated reduced category-level selectivity with older age – that is, age-related neural dedifferentiation. The findings add to the already large literature describing age-related neural dedifferentiation effects (for review, see Koen and Rugg, 2019; Koen et al., 2019, 2020), and importantly, also add to evidence suggesting that while the phenomenon is highly robust for scene stimuli, it is more elusive for other stimulus classes: faces in the present case, and objects in Koen et al. (2019). Additionally, analogous to the findings of Koen et al. (2019), the univariate metric of neural differentiation for scenes in the PPA demonstrated a positive, age-invariant, relationship with source memory performance.

Turning first to the behavioral findings, we observed no age differences either in study RT or in the vividness ratings assigned to the study items. Therefore, the age differences we identified in neural differentiation are unlikely to reflect the confounding effects of either of these variables. At test, younger adults outperformed their older counterparts in respect of both item and source memory performance, findings consistent with an extensive prior literature (for reviews, see Old

& Naveh-Benjamin, 2008; Koen & Yonelinas, 2014). Given these age differences in memory performance, we examined neural differentiation indices derived not only from all experimental items (as in prior studies) but also from only those study trials attracting correct source judgments. The results of the two analyses revealed that the findings of age-related neural dedifferentiation in the scene-selective ROIs were not confounded by differential neural activity associated with successful vs. unsuccessful memory encoding.

Age-related reductions in neural specificity have been linked to cognitive declines associated with healthy aging (Koen & Rugg, 2019). This putative link is motivated by the notion that age-related weakening of dopaminergic neuromodulation results in reduced neural signal-to-noise and hence reduced specificity of neural representations (Li et al., 2001; Li & Rieckmann, 2014; see also Abdulrahman et al., 2017). The proposal that age-related neural dedifferentiation plays a role in cognitive decline receives further support from findings that dedifferentiation is associated with lower memory performance (Yassa et al., 2011; Berron et al., 2018; Bowman et al., 2019; Koen et al., 2019) and lower fluid processing ability (Park et al., 2010; Koen et al., 2019). These findings suggest that the neural specificity of perceptual representations plays a role not only in subsequent memory performance but also broader aspects of neural efficiency and cognition. However, although increasing age is undoubtedly associated with reduced neural selectivity, the existing evidence suggests that the relationship between neural differentiation and cognitive performance is not moderated by age, that is, it is age-invariant (Koen & Rugg, 2019). The present findings of an age-invariant relationship between scene differentiation in the PPA and subsequent source memory performance add to this evidence. These findings serve as a conceptual replication of those reported by Koen et al., (2019), although in that experiment, PPA differentiation was related more strongly to item than to source memory performance. This disparity likely reflects the different experimental procedures: whereas the category exemplars in the present study served as the contextual features targeted in the source memory test, in Koen et al. (2019) the exemplars were the test items themselves.

For reasons that are presently unclear, we failed to replicate the finding (Koen et al., 2019) of a relationship between PPA differentiation and scores on a psychometric fluency factor. Prior studies of neural differentiation have reported a positive relationship between scores of

neuropsychological tests tapping fluid intelligence, but not other measures, such as crystallized intelligence (Koen et al., 2019; Park et al., 2010), or the psychometric factors of memory and processing speed (Koen et al., 2019). Although the lack of a significant relationship between differentiation and the fluency component in the present study runs counter to the findings discussed above, we note that the modest effect size for the relationship reported in the study of Koen et al. (2019) (r = 0.35) constrains the likelihood of replication in studies employing relatively small samples sizes, as was the case here.

As noted in the Introduction, evidence for age-related neural dedifferentiation in the visual domain appears to be most consistent for scenes and faces. Thus, the present findings for scenes in the PPA and RSC are fully consistent with prior findings, whereas the null effects we report for faces in FFA and OFA run counter to several prior results (Park et al., 2004; Voss et al., 2008; Park et al., 2012; but see Payer et al. 2006). There are several factors that, either jointly or in combination, might account for these disparate findings. One factor concerns the presentation format of the stimuli. Whereas the faces in the present study were rendered in color, as best we can determine, prior studies reporting age-related differentiation for faces all employed gray-scale images. A second factor concerns the processing demands placed on the participants: as we noted in the Introduction, whereas most prior studies reporting age effects on face specificity employed relatively passive viewing conditions (Park et al., 2004; Voss et al., 2008; Park et al., 2010, Zebrowitz et al., 2016; but see Goh et al., 2010, and Burianová et al., 2013), here we employed a task that required active engagement with the experimental stimuli (as did Payer et al., 2006). If, as has been suggested (see Introduction) older adults have a greater tendency to "zone out" during passive viewing, the resulting reduction in attention to the experimental stimuli may manifest as reduced neural selectivity (see Koen et al., 2019, for a similar account of inconsistent findings for objects). Additionally, whereas prior studies reporting age-related differentiation typically employed blocked experimental designs, here we employed an event-related design in which different category exemplars were presented in an unpredictable order. Lastly, we cannot rule out the possibility that younger and older adults adopted different cognitive strategies when encoding the word-face and word-scene study pairs. Although no age effects were observed for the vividness ratings of these scenarios, it is conceivable that while younger adults allocated attention relatively

evenly between the words and images, older adults may have focused less on the word – image integration and more on the image itself. Therefore, as neural selectivity of category-selective cortical regions has been reported to be modulated by selective attention (Baldauf & Desimone, 2014; Gazzaley et al., 2005, 2008), age-differences in neural differentiation for face stimuli may be blunted if older adults focus more on the elements of the facial features when completing the task. However, heightened attention to elements of the stimuli on the part of older adults is unlikely to explain the phenomenon of reduced neural selectivity observed in scene-selective ROIs.

While some combination of the above-mentioned factors might account for the absence of age-related neural dedifferentiation for faces in the present study, they offer no insight into why dedifferentiation effects for scenes are so robust. Relevant to this question, a recent "lifetime experience hypothesis" (Koen & Rugg, 2019) posits that neural differentiation might be moderated by prior experience that accrues over the lifespan. The hypothesis proposes that accumulating lifetime experience facilitates the assimilation of novel category exemplars into perceptual schemas (Gilboa and Marlatte, 2017). If scene processing becomes increasingly schema-dependent with age, age-related neural dedifferentiation in scene ROIs might reflect more efficient assimilation of scene information into relevant schema(s). As was noted by Koen et al. (2019), this proposal receives support from their finding that age-related neural dedifferentiation in the PPA took the form of an age-related reduction in neural responses to scenes (neural attenuation), as was also the case in the present study. By contrast, schemas for some other stimulus categories, such as canonical objects, high frequency words, and, possibly, faces, develop more rapidly and are largely fully formed by adolescence or early adulthood (Germine et al., 2011). By this view, therefore, the present findings of null age effects for face differentiation reflect the fact that young and older adults possess equally well-formed face schemas.

The mixed evidence for age differences in neural selectivity for different perceptual categories might also be explained by age differences in the perceptual processing of complex visual stimuli. For instance, age differences in neural differentiation may be more pronounced when viewing stimuli that comprise combinations of multiple, unpredictable features, such as scenes rather than faces. Notably, it has been reported that PPA activity is strongly modulated by scene complexity (Chai et al., 2010), whereby increasing complexity is associated with greater

activity in the region (see Aminoff et al., 2013, for review). If, as has been suggested (e.g. Boutet et al., 2019; Meng et al., 2019), older adults are less able to differentiate visual detail, then age differences in neural selectivity in the PPA might be anticipated. In contrast, the null effects of age in neural selectivity for exemplars of canonical objects, words, or human faces, might reflect their relatively low visual complexity, along with, perhaps, higher schema congruency (see above).

We note a number of limitations of the present study. First, measuring neural selectivity at the category level might not provide a sensitive enough measure to detect age differences in the fidelity of face (or object) representations, and it is possible that item-level measures would yield different findings (cf. Goh et al., 2010; St Laurent et al., 2014; Sommer et al., 2019; Trelle et al., 2019). Second, it is unclear to what extent the present (and previous) findings reflect age differences in the variability or the shape – as opposed to the gain (see Methods) - of stimulus-elicited hemodynamic responses (D'Esposito et al., 2003). Third, like all prior studies of age-related neural dedifferentiation, the present study employed a cross-sectional design. Hence, the reported age differences cannot unambiguously be attributed to the effects of aging as opposed to some correlated confounding factor such as a cohort effect (c.f. Rugg, 2016).

In conclusion, although increasing age is associated with reduced neural differentiation between different visual categories, the present study adds to the evidence that this is easier to demonstrate for visual scenes than for other visual categories. In addition, the age-invariant relationship identified here between scene-related neural differentiation and source memory performance adds to prior evidence that neural differentiation is predictive of individual differences in cognitive performance across much of the adult lifespan: lower neural differentiation is associated with lower cognitive performance irrespective of age. Thus, while the functional significance and mechanistic underpinnings of age-related neural dedifferentiation remain to be fully elucidated, individual differences in neural differentiation appear to reflect both age-dependent and age-invariant factors. Future research should examine the factors driving individual differences in neural differentiation irrespective of age. Additionally, longitudinal rather than cross-sectional designs using larger and more diverse samples are required to elucidate how neural differentiation is affected by aging and whether changes in neural differentiation predict cognitive change.

CHAPTER 3

EFFECTS OF AGE ON GOAL-DEPENDENT MODULATION OF

EPISODIC MEMORY RETRIEVAL

This chapter includes a manuscript which has been published in *Neurobiology of Aging* by me (Sabina Srokova) as the first author, along with co-authors Drs. P.F. Hill, R.L. Elward, & M.D. Rugg who provided substantial input via their comments and edits of the presented text.

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3.1   Introduction

Episodic memory decline is well recognized as a prominent feature of cognitive aging (Grady et al., 2012; Nilsson, 2003; Nyberg et al., 2012). While one established factor driving this decline is reduced efficacy of encoding operations (e.g. Craik & Rose, 2012; Friedman & Johnson, 2014; Old & Naveh-Benjamin, 2008), the contribution of age differences in retrieval processing is less clear. A recently identified aspect of retrieval processing, termed 'retrieval gating', concerns the ability to regulate the retrieval of features belonging to a single memory episode according to their relevance to behavioral goals (Elward & Rugg, 2015). Retrieval gating refers to the finding that goal-relevant mnemonic features of an episode can be selectively reinstated, while reinstatement of irrelevant information is attenuated (i.e. the task-irrelevant information is 'gated'). This process is yet to be examined from the perspective of cognitive aging, raising the possibility that age-related episodic memory decline may, in part, be explained by inefficient gating of goal-irrelevant features of an episode.

Successful episodic memory retrieval requires the establishment of high-fidelity representations of episodes relevant to the retrieval goal. It has been proposed that retrieval of such episodes depends on strategic processes that bias the processing of retrieval cues to align it with the retrieval goal (Jacoby et al., 2005; Rugg, 2004; Rugg & Wilding, 2000). As such, memory

search is optimized when cue processing can target goal-relevant episodes while avoiding retrieval of irrelevant information (memory 'filtering', in the terminology of Halamish et al. 2012). Indeed, recent findings point to the existence of mnemonic processes which work to attenuate the representation of goal-irrelevant associates of a retrieval cue in favor of relevant associates at the time of retrieval (Halamish et al., 2012; Wimber et al., 2015).

It has recently been demonstrated that, in addition to the processes discussed above that facilitate the retrieval and representation of goal-relevant episodes at the expense of irrelevant episodes, young adults appear also to be capable of retrieving a sub-set of the mnemonic features belonging to a *single* episode (Elward & Rugg, 2015; but see Kuhl et al., 2013 for conflicting findings). Elward & Rugg (2015) employed a paradigm akin to that of the present study in which participants incidentally encoded words superimposed over either scenes or a gray background. Each word-image pair was presented in one of three possible locations. At retrieval, participants underwent fMRI as they attempted to retrieve either the background or the location of studied test words. Goal-related modulation of episodic retrieval was investigated by examining task differences in the cortical reinstatement of scene information. Cortical reinstatement is a phenomenon characterized by the retrieval-related reactivation of neural patterns elicited during encoding (for reviews see Danker & Anderson, 2010; Rissman & Wagner, 2012; Rugg et al., 2015; Xue, 2018). In Elward and Rugg (2015), scene reinstatement effects were evident in parahippocampal and retrosplenial cortex - canonical scene-selective cortical regions (Aminoff et al. 2013; Bar 2004; Epstein & Baker, 2019) - when the retrieval task required a judgment about the nature of the backgrounds paired with the test words. Crucially, however, the effects were attenuated when scene information was irrelevant to the task, and instead, the task required a judgment about the test word's location at study. In light of prior research indicating that the strength of cortical reinstatement covaries with the amount and fidelity of recollected content (e.g. Thakral et al., 2015), these findings were interpreted as evidence that the retrieval of scene information was in some sense 'gated' when it was irrelevant to the retrieval goal.

Given the under-researched nature of retrieval gating and its underlying mechanisms, the term 'gating' as used here is not intended to imply a specific mechanism. Notably, we are agnostic as to whether gating is reflective of a biased memory search or a top-down control process which

operates post-retrieval to attenuate the representation of goal-irrelevant mnemonic features. That said, if it is assumed that gating does reflect an active control mechanism, the wealth of evidence demonstrating age deficits in top-down control motivates the hypothesis that older adults should have difficulty employing retrieval gating to regulate mnemonic content. For example, findings from prior behavioral studies examining age-differences in working memory (WM) suggest that the control processes that downregulate the representation of task-irrelevant information in WM are vulnerable to increasing age, consistent with the *inhibitory deficit hypothesis* of aging (Hasher & Zacks, 1988; Hasher et al., 1991; Lustig et al., 2001; Lustig et al., 2007, see also Campbell et al., 2020 and related articles in the same issue). However, despite the wealth of behavioral studies examining age deficits in WM, neuroimaging evidence for the inhibitory deficit hypothesis is relatively sparse. Nonetheless, extant findings suggest that older adults demonstrate reduced ability to strategically downregulate cortical activity in regions selectively responsive to specific classes of perceptual information (Chadick et al., 2014; Gazzaley et al., 2005, 2008; Weeks et al., 2020). For example, Chadick et al. (2014) reported that when participants were presented with overlapping images of a face and a scene in a delayed match to sample task, younger adults demonstrated attenuated activity in the parahippocampal cortex (relative to a 'no-task' baseline) when the scenes were task-irrelevant, and enhanced activity in the same region when they were task-relevant. In contrast, older adults did not demonstrate attenuated parahippocampal activity when the scenes were irrelevant, despite demonstrating enhancement to the same extent as young participants when the scenes were task-relevant.

In the present study, we examined whether, as might be anticipated on the basis of the foregoing brief review, retrieval gating becomes less efficient (i.e. weaker or absent) with increasing age. Younger and older adults undertook an incidental encoding task in which they elaboratively encoded words superimposed over scenes or scrambled backgrounds presented in one of three possible locations (cf. Elward and Rugg, 2015). Participants subsequently underwent fMRI as they completed two different retrieval tasks, requiring memory for either the background or the location of studied words. The location and background retrieval tasks required source memory judgments, such that for each test word participants were required to retrieve either its studied location or background context. One rationale for the employment of the source memory

procedure derives from well-established findings that performance on associative memory tests, including tests of source memory, is highly sensitive to increasing age (Koen & Yonelinas, 2014; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995). For the purposes of the present study, the motivation to employ a source memory task also arises from the fact that different mnemonic features can be selected by the experimenter to be diagnostic of the source judgement, allowing experimental manipulation of the mnemonic information that is relevant to the retrieval goal. We expected to replicate the findings of Elward & Rugg (2015) that younger adults demonstrate attenuated scene reinstatement effects when scene information is not behaviorally relevant to the task. However, we predicted that, relative to younger adults, older adults would be less able to modulate scene-related cortical reinstatement in accordance with the retrieval goal.

3.2   Materials and Methods

3.2.1   Participants

Twenty-five younger and 30 older adults were recruited from communities surrounding The University of Texas at Dallas and were compensated $30/hour. All participants were right-handed, had normal or corrected-to-normal vision, and were fluent English speakers before the age of five. None of the participants had a history of cardiovascular or neurological disease, substance abuse, or diabetes, and none were using medication affecting the central nervous system at the time of participation. Potential participants were excluded from participation if they demonstrated evidence of cognitive impairment based on their performance on a neuropsychological test battery (see *Neuropsychological Testing*).

Five younger and 6 older adults were excluded from the study and thus all subsequent fMRI analyses. Two younger adults and one older adult did not complete the scanning session due to claustrophobia or discomfort, and one younger adult was excluded due to technical difficulties during MRI scanning. Additionally, two younger and four older adults were excluded due to at-chance source memory performance in both the background and location tasks (see 2.4.2. Behavioral Data Analysis). Lastly, one older adult was excluded due to an incidental MRI finding. The final sample consisted of 20 younger adults (12 female, age range = 18 – 30 years) and 24 older adults (12 female, age range = 65 – 76 years).

3.2.2   Neuropsychological Testing

All participants completed a neuropsychological test battery on a separate day prior to participation in the fMRI session. The test battery consisted of the Mini-Mental State Examination (MMSE), the California Verbal Learning Test-II (CVLT; Delis et al., 2000), Wechsler Logical Memory (Tests 1 and 2; Wechsler, 2009), the Symbol Digit Modalities test (SDMT; Smith, 1982), the Trail Making (Test A and B; Reitan and Wolfson, 1985), the F-A-S subtest of the Neurosensory Center Comprehensive Evaluation for Aphasia (Spreen and Benton, 1977), the Wechsler Adult Intelligence Scale – Revised (Forward and Backward digit span subtests; Wechsler, 1981), Category Fluency test (Benton, 1968), Raven's Progressive Matrices (List 1; Raven et al., 2000), and a test of visual acuity. In addition, participants completed the Wechsler Test of Adult Reading (WTAR, Wechsler, 2001) or its revised version, the Wechsler Test of Premorbid Functioning (TOPF; Wechsler, 2011). Participants were excluded prior to the fMRI session if they performed > 1.5 SD below age norms on two or more non-memory tests, if they performed > 1.5 SD below at least one memory-based neuropsychological test, or if their MMSE score was < 27.

3.2.3   Experimental Procedure

3.2.3.1 Materials

All experimental stimuli were presented using Cogent 2000 software (www.vislab.ucl.ac.uk/cogent_2000.php) implemented in Matlab 2012b (www.mathworks.com). The study phase was completed outside the scanner using a laptop and a button box identical to that used in the scanned memory task. During the MRI session, stimuli were projected on a translucent screen situated at the rear end of the scanner bore and viewed through a mirror placed on the head coil. The critical experimental stimuli comprised 240 concrete nouns, 120 colored images of novel urban and rural scenes (60 each), and 60 scrambled backgrounds created by randomly shuffling the pixels of 60 of the scene images. An additional 110 scenes, 110 scrambled backgrounds, and 110 object images were employed in a functional localizer task which was completed after the memory test. The word list pool comprised high-frequency nouns selected from the Nelson et al. (2004) word norms. The words were fully randomized across the stimulus

lists such that, for a given stimulus list, all words from the pool were equally likely to be presented in each background and location contexts at study, and likewise they were equally likely to be tested in the location or background task. All images were scaled to 256 x 256 pixels. In addition to the critical stimuli, 33 nouns, 12 scenes, and 6 scrambled backgrounds were used either as practice stimuli or as filler trials at the beginning of a study or a test block. During the scanned test phase, the critical stimuli were randomly interspersed with 80 null trials, during which a black fixation cross was presented at the center of the display. Stimuli during the study and test phase were selected randomly to create 24 different stimulus sets, twenty of which were yoked between pairs of younger and older adults. Stimulus sets for the test phase were pseudo-randomized such that participants experienced no more than three consecutive new or old words studied against the same background or location, and no more than two consecutive null trials.

3.2.3.2 Study and Test Practice

Prior to completing the two experimental phases, participants completed study and test practice tasks on the same day as the experiment proper. The study practice was completed immediately prior to the study phase, and the test phase training was performed following the completion of the study phase and prior to entering the scanner for the experimental test phase. Both the study and test practice tasks were performed using a button box identical to the one used during the experiment to ensure that participants were comfortable with the mapping of their fingers to the different response options. For each practice task, participants first received written instructions which they then explained to the experimenter in their own words. The practice tasks were separated into untimed and timed trials. Study practice was divided into 5 untimed and 10 timed trials, and test practice comprised 6 untimed (3 trials per retrieval task) and 14 timed trials. During the untimed trials, the experimental items remained on the screen while the participant and experimenter discussed the trial and the rationale for the participant's selected response. Following the untimed trials, participants completed the timed trials (analogous to the experiment proper) to become familiar with the trial timing and to practice use of the button box to make timely responses. Participants were allowed to repeat the practice until they were comfortable that they

understood the task and the response mapping or until the experimenter was confident that the task was being performed adequately.

3.2.3.3 Study Phase

      At study, participants completed an incidental encoding task consisting of 180 trials divided across three study blocks of equal length, each taking 6 minutes 22 seconds to complete. Each block contained 60 words that were presented in one of three display locations (left, middle, right) and were superimposed over either a rural, an urban, or a scrambled background. Trials were equally divided such that a third of all words were presented over each background type and, independently, a third of the words were presented in each of the three locations. For example, across all study blocks, participants would study 60 words presented over an urban background, of which 20 would appear on the left side of the screen. A schematic of a study trial is presented in Figure 3.1-A. Each trial began with a black fixation cross presented for 200 ms in the square corresponding to the location in which the upcoming word-image pair was to be presented. The cross was replaced by the study word, followed 200 ms later by its background. The word and image pair remained together on the screen for 5500 ms, and participants were instructed to imagine a scenario in which the object denoted by the word is moving around or interacting with the background. Participants rated the vividness of this imagined scenario on a three-point scale by responding on the button box with the index, middle, and ring fingers (1 = not vivid, 2 = somewhat vivid, 3 = very vivid). The inter-trial-interval, during which only the three grey squares and response prompts remained on the screen, lasted 400 ms.

3.2.3.4 Test Phase

      Participants were trained on the memory test after completing the study task (hence, encoding was incidental). The test phase was completed inside the scanner approximately 30 minutes following the completion of the study task, and consisted of 240 critical trials (comprising 180 studied and 60 unstudied words) which were divided equally between 5 blocks of 'background' and 5 blocks of 'location' tests distributed across 5 scanning runs. Each scanning run lasted 8 minutes 15 seconds and contained a single location and a single background task

block. In each block, participants were presented with 24 critical test words (6 new, 18 old) intermixed with 8 null trials. The 18 old words were balanced such that a third of all old trials in a block comprised words which had been studied over one of the three types of background and, independently, one of the three locations at encoding. Figure 3.1-B illustrates a schematic of a single test trial and the response alternatives for the two retrieval tasks. Each test trial began with a red fixation cross presented for 500 ms in the middle of the screen, which was subsequently replaced by the test word for 2500 ms. At the word onset, the response prompt "Did you see?" appeared above the word, and cues "Yes – No" were presented underneath. Participants indicated whether they remembered seeing the word at study using the index and middle fingers of the right hand. For each word endorsed old (i.e. following a "Yes" response), participants were presented with a follow-up source memory prompt that was displayed for 3000 ms. For each word endorsed new (i.e. following a "No" response), a black fixation cross was displayed for 3000 ms until the end of the trial. The inter-trial-interval, during which the black fixation cross remained on the screen, lasted 1000 ms.

In the location task block, participants were required to recall the location of the studied word according to one of the following prompts presented above the word: "Was it on the LEFT?" or "Was it on the RIGHT?". In the background task block, participants recalled the background scene following either "Was it on an URBAN scene?" or "Was it on a RURAL scene?". Neither the central location nor the scrambled backgrounds were ever used as prompts for the two tasks. The response cues "Yes – No – Not Sure" were presented below the word, and participants made responses with their right hand using the index, middle, and ring fingers. The location and background task prompts were counterbalanced across participants such that, for a given participant, the prompts for the two tasks remained constant across all trials. Trials requiring a correct "Yes" source response are henceforth termed 'target' trials, whereas trials requiring a correct "No" response are termed 'non-target' trials. Thus, if a participant's location target type corresponded with trials studied on the right side on the screen, they would be presented with the prompt "Was it on the RIGHT?" on each location task trial. Similarly, for participants whose target background trials comprised words studied over the rural scenes, the prompt "Was it on a RURAL scene?" would be shown across all background task trials. Consequently, a third of all old trials in

a given retrieval task were target trials (requiring a "Yes" source response), and the other two thirds of old trials were nontarget trials (requiring a "No" source response). The mapping of the responses to fingers was counterbalanced across participants with the constraint that the "Not Sure" response was mapped onto the ring or index finger. If the "Not Sure" response was assigned to the ring finger, the "Yes" and "No" responses were assigned to the index and middle fingers, respectively. Otherwise, the "Yes" and "No" responses were assigned to the middle and ring fingers, respectively. The order of the response cues displayed on the screen was adjusted accordingly. Lastly, the ordering of the retrieval tasks was counterbalanced across participants, such that the first half of each scanning run corresponded with the either the location or background tasks. Participants were informed of the task they were about to complete by a reminder that was displayed prior to the onset of each task block.
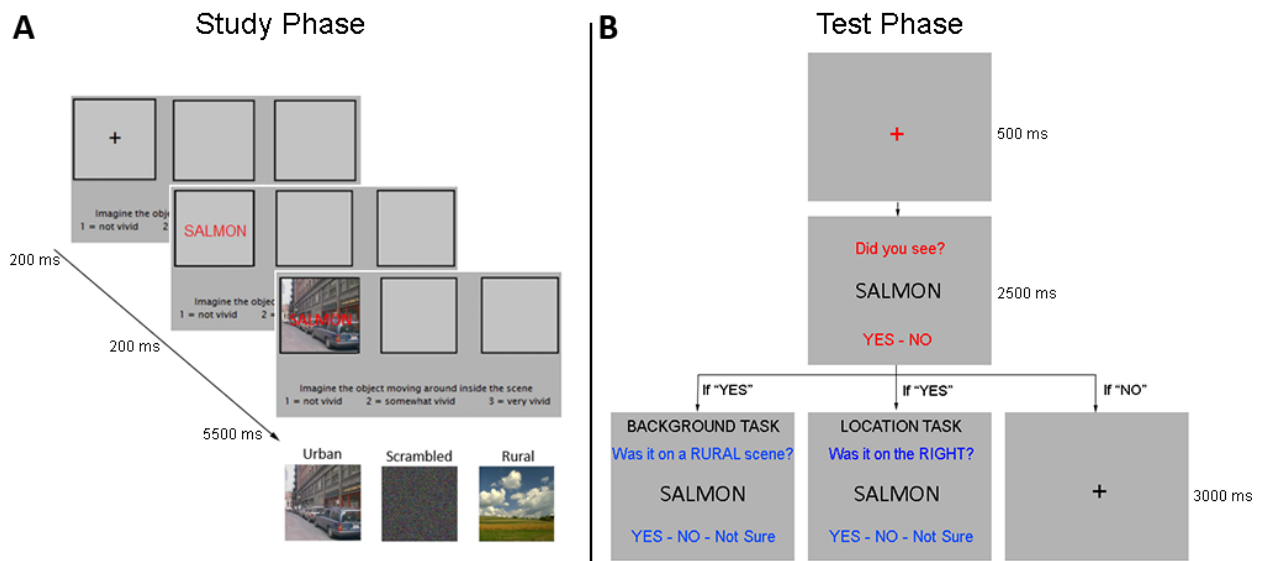
Figure 3.1. Task schematics for the Study (**A**) and Test Phases (**B**). The study phase was completed on a laptop while the memory test was completed inside an MRI scanner. The memory test consisted of two retrieval tasks: the background and the location task.

3.2.3.5 Functional Localizer

Following the completion of the test phase and the acquisition of a structural MRI scan, participants completed the functional localizer task. The task comprised 5 scanner runs. Each run lasted 2 minutes 51 seconds and consisted of 6 blocks of 11 trial-unique images that comprised

either scenes, scrambled backgrounds, or common objects. A single image of a face was interspersed randomly within each block. Participants were instructed to press a button whenever they saw the face image. Each image was presented for 750 ms and followed by a black fixation cross lasting for 250 ms. The blocks of images were separated by a 12 second interval during which a black fixation cross was continuously present in the middle of the display.

3.2.3.6 Experimental Design and Statistical Analysis

All statistical analyses and data visualization were performed using R software (R Core Team, 2020). Analyses of variance were performed with the package afex (Singmann et al., 2016) with the degrees of freedom and p-values corrected for nonsphericity with the Greenhouse and Geisser (1959) procedure. Correlations were performed with the cor.test function, linear regressions were performed with the lm function, and pairwise comparisons were performed with the function t.test, all in base R. All t-tests were two-tailed except for the one-sample t-tests that tested whether reinstatement and similarity indices were significantly greater than zero (i.e. to determine whether reinstatement effects were reliable). Effect sizes for the analyses of variance are reported as partial-η^2 and effect sizes for t-tests are reported as Cohen's d. Figures plotting fMRI data were created using the package ggplot2 (Wickham, 2016). All tests were considered significant at $p < 0.05$.

3.2.3.7 Behavioral Data Analysis

Item memory performance was evaluated by examining recognition memory performance in response to the "Did you see?" prompt. Item recognition (Pr) was computed as the difference between the proportion of correctly recognized old words (item hits) and the proportion of new trials which were incorrectly endorsed as old words (false alarms):

$$Pr = \frac{Item\ Hit}{Old\ Trials} - \frac{False\ Alarms}{New\ Trials}$$

Source memory performance (pSR; probability of source recollection) was evaluated in terms of correctly judging whether or not a word endorsed old had been studied in association with the

target background or location. pSR was estimated with a modified single high-threshold model (Snodgrass and Corwin, 1988; see also Gottlieb et al., 2010; Mattson et al., 2014) using the following formula:

$$pSR = \frac{pSource\ Correct - 0.5 * (1 - pDon't\ Know)}{1 - 0.5 * (1 - pDon't\ Know)}$$

Here, 'pSource Correct' and 'pDon't know' refer to the proportion of correctly recognized old trials which received an accurate source memory judgement or a 'Not Sure' response, respectively.

3.2.3.8 MRI Data Acquisition and Preprocessing

Functional and structural MRI data were acquired using a Philips Achieva 3T MRI scanner (Philips Medical Systems, Andover, MA) equipped with a 32-channel head coil. Functional images during the test phase were acquired with a T2*-weighted, blood-oxygen-level-dependent echoplanar imaging (EPI) sequence with a multiband factor of two (flip angle = 70°, field of view [FOV] = 200 x 240 mm, repetition time [TR] = 1.6 s, echo time [TE] = 30 ms). EPI volumes consisted of 44 slices at a voxel size of 2.5 x 2.5 x 2.5 mm with a 0.5 mm interslice gap. The slices were acquired in an interleaved order and oriented parallel to the anterior-posterior commissure line. The protocol for the functional localizer was identical to the test phase protocol except for the repetition time (TR = 1.5 s). Structural images were acquired with a T1-weighted MPRAGE sequence (FOV = 256 x 256 mm, 1 x 1 x 1 mm isotropic voxels, sagittal acquisition).

The MRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK) and custom Matlab code. The functional data were realigned to the mean EPI image and slice-time corrected using *sinc* interpolation with reference to the 12th acquired slice. The images were then normalized to a sample-specific template according to previously published procedures to ensure an unbiased contribution of each age group to the template (de Chastelaine et al. 2011, 2016). Prior to region-of-interest (ROI) definition, the time series of each localizer run were concatenated using the *spm_fmri_concatenate* function and smoothed with a 6 mm full-width half-maximum Gaussian

kernel. The reinstatement indices extracted from the test-phase data, as well as the test and localizer time series used in the pattern similarity analysis, were derived from unsmoothed data.

3.2.3.9 Region of Interest Selection

The data from the localizer task were analyzed in two stages prior to defining the ROIs. First, a separate 1st-level GLM was constructed for each participant by modeling 3 events of interest: scene blocks, object blocks, scrambled blocks. Given that the localizer task employed a blocked design comprising a mixture of scene, object, and scrambled blocks each lasting 12s, the blocks were modeled with a 12s duration boxcar regressor convolved with a canonical hemodynamic response function (HRF) with temporal and dispersion derivatives, onsetting concurrently with the presentation of the first stimulus in the block. Covariates of no interest comprised 6 regressors reflecting motion-related variance (rigid-body translation and rigid-body rotation) and the mean signal of each session run. Additionally, motion spikes with framewise translational displacement of > 1 mm or rotational displacement of $> 1°$ were modeled as additional covariates of no interest. The subject-level parameter estimates were carried over to a 2nd-level GLM that took the form of a 2 (age group: younger, older) x 3 (stimulus type: scene, object, scrambled) mixed effects ANOVA model. Age group was included in the ANOVA to ascertain that the age group-by-stimulus type interaction did not identify additional scene-selective clusters outside of those described below.

The ROIs were derived using the conjunction of scene > object and scene > scrambled contrasts at the 2nd-level, both height thresholded at $p < 0.0005$ (uncorrected), with a 50-voxel extent threshold. [Note that when the ROIs were defined using either stricter or more liberal thresholds ($p < 0.0001$ and $p < 0.01$ respectively) the results reported in the fMRI analyses below were unchanged]. The contrasts employed the simple effects of stimulus type to ensure that the ROIs were unbiased with respect to age group. This procedure identified scene-selective clusters in the parahippocampal place area (PPA) and retrosplenial cortex (RSC) bilaterally (Figure 3.2-A; peak MNI coordinates presented in Table 3.1). The left and right PPA were delimited by restricting the cluster with a combination of anatomical masks corresponding to the parahippocampal and fusiform gyri provided by the Neuromorphometrics atlas in SPM12. We created an RSC mask by

searching the Neurosynth database for the term "retrosplenial" (search in August 2019, search results FDR-corrected at p < 0.00001; Yarkoni et al., 2011). The resulting mask was used to restrict the outcome of the localizer contrast, thereby generating the left and right RSC ROIs (Figure 3.2-B).

Parahippocampal place area   Retrosplenial cortex
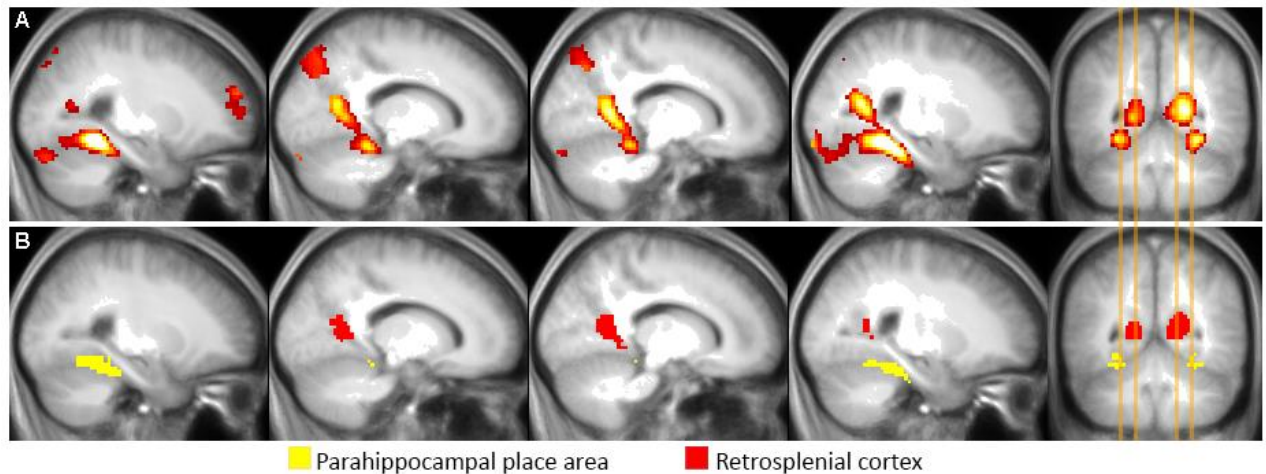
Figure 3.2. (**A**) Functional localizer data illustrating scene-selective clusters used to define the ROIs employed in the fMRI data analysis. The illustrated clusters, overlaid on the sample-specific T1 template, represent the conjunction of the scene > object and scene > scrambled background contrasts before masking (see main text). (**B**) Scene-selective PPA and RSC ROIs derived by masking the clusters in 3.2.A. (see main text).

Table 3.1. Cluster peak MNI coordinates and the number of voxels in of each ROI derived from the functional localizer. The peak MNI coordinates were obtained from the scene > object contrast which was inclusively masked with the scene > scrambled contrast.

	ROI Size	*Peak MNI Coordinates*		
	(voxels)	**X**	**Y**	**Z**
R. Parahippocampal place area	212	27	-47	-12.5
L. Parahippocampal place area	177	-28	-49.5	-10
R. Retrosplenial cortex	200	19.5	-57	10
L. Retrosplenial cortex	121	-18	-57	5

R = Right, L = Left

3.2.3.10 Univariate Reinstatement Index

The unsmoothed functional data from the test phase were concatenated and subjected to a 'least-squares-all' GLM analysis (Mumford et al., 2014; Rissman et al., 2004) to estimate the

BOLD response elicited on each test trial. Each trial was modeled as a separate event of interest with a delta function time-locked to stimulus onset and convolved with a canonical HRF. (The employment of the delta function follows the approach adopted by Elward and Rugg (2015) and is motivated by the presumed relatively short-lived nature of the processing of the retrieval cue. However, to ensure that the results reported below did not arise because of a failure to detect more sustained retrieval processing, we performed a secondary analysis in which the data were modeled with a 2.5s boxcar that tracked the duration of the 'did you see' prompt that onset concurrently with the test item. The results remained unchanged when the data were modeled in this fashion). Covariates of no interest consisted of the aforementioned 6 motion regressors reflecting translational and rotational displacement, and the regressors of session-specific means with the first run as the intercept.

'Reinstatement indices' based on the resulting single-trial β-weights in each scene-selective ROI, separately for the trials of the two retrieval tasks, were computed in a manner akin to a previously described 'differentiation index' (Koen et al., 2019; Srokova et al., 2020; Voss et al., 2008; Zebrowitz et al., 2016). The reinstatement index operationalizes retrieval-related reinstatement of scene information in terms of an effect size by computing the difference between the mean BOLD response associated with test words studied over scene backgrounds versus words studied over scrambled backgrounds, and then dividing the difference by pooled standard deviation:

$$Reinstatement\ Index = \frac{\mu_{scene} - \mu_{scrambled}}{\sqrt{\frac{\sigma_{scene}^2 + \sigma_{scrambled}^2}{2}}}$$

Reinstatement indices greater than zero reflect a greater mean BOLD response for words studied over scenes relative to words studied over scrambled backgrounds, and as such, are indicative of retrieval-related cortical reinstatement of scene information. Importantly, because of the scaling function, the reinstatement index is insensitive to individual differences in the gain of the HRF which mediates the relationship between neural activity and the resulting fMRI BOLD signal. Thus, the reinstatement index is unaffected by age-related differences in HRF gain (see, for example, Liu et al., 2013)

Following Elward and Rugg (2015), the test trials employed in the computation of the reinstatement index were those on which test words were correctly recognized as previously studied, irrespective of the accuracy of the subsequent source memory judgment. The inclusion of all correctly recognized trials allows for a fair comparison of the scene reinstatement effects in the two tasks (see Elward and Rugg, 2015). Trials on which test words had been paired with target scenes were however excluded from these fMRI analyses, such that the analyses were performed only for recognized test words associated with non-target backgrounds (i.e. non-target scenes and scrambled backgrounds). This approach was adopted to reduce the influence of any confound arising from the fact that scrambled trials in the background task were always non-targets (and hence should always have received a 'No' source response), whereas scene trials were a mixture of non-targets ('No' response) and targets ('Yes' response). Thus, we aimed to ensure that the analysis of scene reinstatement in the background task was not confounded by the differential responses to test words associated with scrambled as opposed to target scenes. To ensure that the contrast between scene reinstatement effects across the two tasks was between scenes belonging to same sub-category (rural or urban), analysis of scene reinstatement effects in the location task was also restricted to test words associated with non-target scenes. To the extent that item recognition performance was equivalent across the two retrieval tasks, this approach also balanced the number of background and location task trials contributing to the computation of the respective reinstatement indices.

3.2.3.11 Multivoxel Pattern Similarity Analysis

Pattern similarity analysis (PSA) was performed to complement the analyses of the univariate reinstatement index (e.g. Haxby et al. 2001; Kriegeskorte et al., 2008; cf. Koen et al., 2019; Srokova et al., 2020). Scene reinstatement was operationalized in terms of shared neural patterns between test trials and a scene-specific voxel-wise profile derived from the functional localizer. To this end, for each ROI, voxel-wise test-phase single-trial β-weights extracted from the least-squares-all GLM analysis described above were correlated with the voxel-wise β-weight profile derived from the scene > scrambled contrast conducted on the localizer data (although we note that the PSA results remain unchanged if the scene > scrambled + object contrast was

employed instead). Other than being performed on unsmoothed data, the localizer data were modeled as described previously, and the scene > scrambled profiles were derived for each participant from the first-level GLMs. The employment of scene > scrambled rather than scene > baseline profiles was motivated by the relatively brief baseline interval of 12s. This inter-block interval was too short to provide a stable baseline for the estimation of main effects, as the hemodynamic response to a preceding block would not have fully declined before the onset of the succeeding block. Accordingly, we elected to estimate across-voxel patterns of scene-related activity relative to the 'active' baseline provided by the blocks of scrambled images.

PSA was conducted on the same test trials as those employed for the analyses of reinstatement indices described in the previous section. Thus, only those trials containing correctly recognized test items associated with non-target backgrounds at study were included in these analyses. Scene-related cortical reinstatement was operationalized as the difference between the across-trial mean Fisher z-transformed correlation between the localizer contrast and non-target scene trials, and the mean Fisher z-transformed correlation between the localizer contrast and all scrambled trials (see Figure 3.3). Similarity scores were computed separately for the location and background tasks in each ROI. Similarity indices greater than zero are indicative of scene reinstatement at test. Importantly, as for the reinstatement index, the similarity index is insensitive to individual differences in HRF gain.
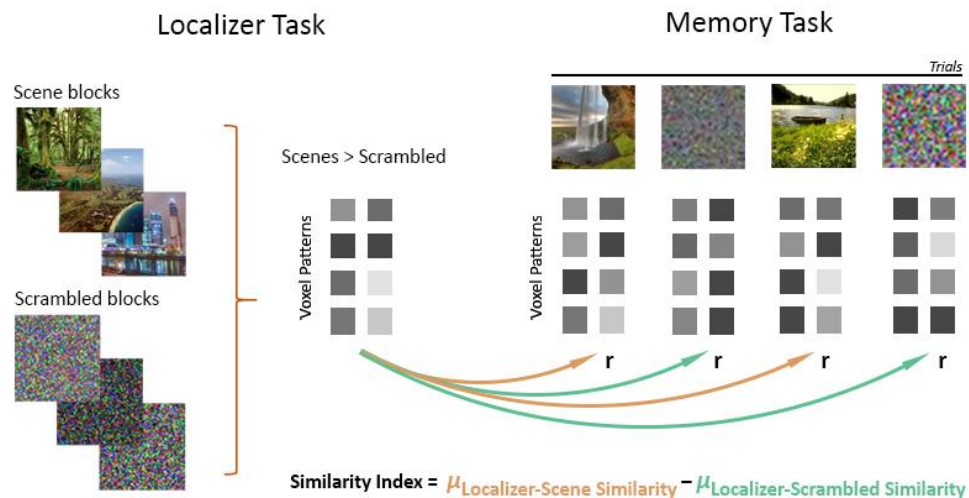
Figure 3.3. Schematic of the PSA. Similarity indices were computed separately for each task as the difference between the mean correlation between the localizer contrast and all non-target scene

trials (localizer-scene similarity) and the mean correlation between the localizer and all scrambled trials (localizer-scrambled similarity).

In light of the literature describing age differences in neural specificity ('age-related neural dedifferentiation', for review see Koen & Rugg, 2019), we performed a control analysis to ensure that the PSA results presented below were not driven by age differences in scene-selective activity identified by the functional localizer. To accomplish this, individual localizer blocks were modeled separately as 12s boxcars onsetting concurrently with the first stimulus of each block. A PSA was then performed on the resulting block-wise β-weights by computing a within – between similarity metric separately in each scene-selective ROI. The within similarity metric comprised the average Fisher z-transformed Pearson's correlation between a given scene block and all other scene blocks. The between similarity metric was the average Fisher z-transformed correlation between a given scene block and all scrambled blocks. A given block was never correlated with another block belonging to the same scanner run to avoid potential bias arising from carry-over effects (Mumford et al., 2014). The within – between similarity indices were then entered into a 2 (age group) by 4 (ROI) mixed ANOVA. This revealed a main effect of ROI ($F_{(2.41, 98.93)} = 45.244$, $p < 0.001$, partial-$\eta^2 = 0.525$), but neither the main effect of age nor the age-by-ROI interaction term reached significance ($F_{(1, 41)} = 1.648$, $p = 0.206$, partial-$\eta^2 = 0.039$, and $F_{(2.41, 98.93)} = 1.941$, $p = 0.140$, partial-$\eta^2 = 0.045$, respectively). These results indicate that scene-related neural specificity, as indexed by PSA, did not differ between younger and older adults in the localizer task. Thus, the localizer data provide an unbiased baseline for the examination of age differences in PSA metrics of scene reinstatement during the two retrieval tasks.

3.3   Results

3.3.1   Neuropsychological Test Results

Demographic data and performance on the neuropsychological test battery are reported in Table 3.2. Analysis of the test scores revealed that younger adults outperformed older adults on the Wechsler Logical Memory subtest I, achieved a greater overall number of recognition hits on CVLT, and demonstrated faster processing speed as reflected by their performance on Trails

Subtest A and the SDMT. Younger adults also demonstrated better performance relative to older adults on Raven's Progressive Matrices.

Table 3.2. Demographic data and performance on the neuropsychological test battery: Mean (SD) and age differences (significant age differences denoted by *).

	Younger Adults	*Older Adults*	*Age difference (p)*
N (male/female)	8/12	12/12	
Age	24.55 (3.64)	68.50 (3.19)	
Years of Education	15.95 (1.64)	17.25 (2.66)	0.054
MMSE	29.05 (0.89)	29.08 (0.88)	0.902
CVLT Short Delay - Free	11.90 (2.45)	10.29 (3.26)	0.069
CVLT Short Delay - Cued	12.95 (2.06)	11.63 (2.78)	0.077
CVLT Long Delay - Free	12.70 (2.16)	11.17 (3.13)	0.062
CVLT Long Delay - Cued	12.60 (2.37)	11.83 (2.57)	0.309
CVLT Recognition Hits	15.50 (0.69)	14.58 (1.38)	0.007 *
CVLT False Alarms	1.45 (1.64)	2.13 (2.35)	0.269
F-A-S	45.95 (11.01)	46.33 (10.68)	0.908
WMS Logical Memory I	31.55 (6.83)	27.79 (4.60)	0.044 *
WMS Logical Memory II	29.50 (5.42)	26.79 (4.63)	0.086
Digit-symbol Substitution Test	63.65 (10.73)	50.54 (7.59)	0.001 *
Trails A (s)	20.62 (7.50)	29.46 (10.23)	0.002 *
Trails B (s)	51.85 (32.71)	62.04 (20.29)	0.235
Digit Span[1]	18.70 (2.56)	18.38 (3.92)	0.743
Category Fluency Test	26.00 (6.68)	22.83 (4.07)	0.074
TOPF / WTAR[2]	109.55 (10.09)	113.58 (7.45)	0.147
Raven's Progressive Matrices I	10.85 (0.93)	9.63 (1.81)	0.007 *

[1] Digit span corresponds to the sum of forward and backward digit span.
[2] Presented as a standardized score computed from WTAR or TOPF raw scores

3.3.2 Behavioral Performance

Behavioral performance, including vividness ratings at study, study and test reaction times (RTs), and memory performance, is presented in Table 3.3. Vividness ratings and mean RTs at study were binned according the trials' background context (scrambled backgrounds, target scenes, non-target scenes). Vividness data from one older adult were not recorded due to a technical malfunction. The vividness ratings and RTs were submitted to a 2 (age group) x 3 (background context) mixed factorial ANOVA. In the case of rated vividness, the main effects of age group, background context, and the two-way interaction were all non-significant (age group: $F_{(1,41)}$ = 0.296, p = 0.589, partial-η^2 = 0.007; background context: $F_{(1.41, 57.72)}$ = 1.978, p = 0.159, partial-η^2

= 0.046; age-by-background interaction: $F_{(1.41, 57.72)} = 0.596$, $p = 0.498$, partial-$\eta^2 = 0.014$). Analysis of the study RTs revealed a significant main effect of age group ($F_{(1,41)} = 5.590$, $p = 0.023$, partial-$\eta^2 = 0.120$), reflective of faster RTs in the younger age group. The main effect of background context was also significant ($F_{(1.23, 50.29)} = 51.206$, $p < 0.001$, partial-$\eta^2 = 0.555$), reflecting faster RTs to scrambled trials relative to either scene type (scrambled vs. target scene: $t_{(42)} = 8.102$, $p < 0.001$, $d = 1.236$; scrambled vs. non-target scene: $t_{(42)} = 6.857$, $p < 0.001$, $d = 1.046$; target scene vs. non-target scene: $t_{(42)} = 0.676$, $p = 0.503$, $d = 0.103$). These background effects did not differ significantly between the age groups (two-way interaction: $F_{(1.23, 50.29)} = 3.041$, $p = 0.079$, partial-$\eta^2 = 0.069$).

Memory performance was analyzed with separate 2 (age group) x 2 (retrieval task) ANOVAs for item recognition (Pr) and source memory performance (pSR). With respect to Pr, the main effects of age group and retrieval task were both non-significant (age group: $F_{(1,42)} = 1.767$, $p = 0.191$, partial-$\eta^2 = 0.040$; retrieval task: $F_{(1,42)} = 0.056$, $p = 0.814$, partial-$\eta^2 = 0.001$), and the age group-by-task interaction also failed to reach significance ($F_{(1,42)} = 1.321$, $p = 0.257$, partial-$\eta^2 = 0.030$). The ANOVA of pSR revealed a significant main effect of age group ($F_{(1,42)} = 5.458$, $p = 0.024$, partial-$\eta^2 = 0.115$), a main effect of retrieval task ($F_{(1,42)} = 63.417$, $p < 0.001$, partial-$\eta^2 = 0.602$), but no age group-by-task interaction ($F_{(1,42)} = 0.291$, $p = 0.593$, partial-$\eta^2 = 0.007$). The main effect of task was driven by superior accuracy in the background relative to the location task across both age groups. Additionally, older adults' source accuracy was lower than that of their younger counterparts across both tasks.

To examine the effects of background context on memory performance (analogous to the analysis of the study data), we examined the proportions of correctly recognized items that went on to receive a correct source memory judgement (pSource correct) in test trials binned according to their background context at study (scrambled backgrounds, target scenes, non-target scenes). Effects of study context were examined with a 2 (age group) x 2 (retrieval task) x 3 (background context) mixed factorial ANOVA. This revealed a significant main effect of task ($F_{(1, 42)} = 66.992$, $p < 0.001$, partial-$\eta^2 = 0.615$), but no main effect of age group ($F_{(1, 42)} = 3.239$, $p = 0.079$, partial-$\eta^2 = 0.072$) or background context ($F_{(1.81, 75.87)} = 0.693$, $p = 0.489$, partial-$\eta^2 = 0.016$). Additionally, the ANOVA revealed a significant task-by-background context interaction ($F_{(1.84, 77.16)} = 10.061$, p

< 0.001, partial-η^2 = 0.193), along with non-significant interactions between background context and age group ($F_{(1.81, 75.87)}$ = 0.162, p = 0.830, partial-η^2 = 0.004), age group-by-task ($F_{(1, 42)}$ = 0.056, p = 0.814, partial-η^2 = 0.001) and a non-significant three-way interaction ($F_{(1.84, 77.16)}$ = 0.199, p = 0.802, partial-η^2 = 0.005).

The significant task-by-background context interaction was examined with additional 2 (age group) x 3 (background context) ANOVAs performed separately for the location and background tasks. In the location task, the ANOVA identified a main effect of background context ($F_{(1.95, 81.79)}$ = 3.983, p = 0.023, partial-η^2 = 0.087), while the main effect of age group and the two-way interaction were not significant ($F_{(1, 42)}$ = 2.861, p = 0.098, partial-η^2 = 0.064; $F_{(1.95, 81.79)}$ = 0.483, p = 0.614, partial-η^2 = 0.011, respectively). The main effect of background context was driven by better location memory for words studied over scrambled backgrounds relative to either non-target ($t_{(43)}$ = 2.869, p = 0.006, d = 0.433) or target scenes ($t_{(43)}$ = 2.192, p = 0.034, d = 0.330). The corresponding ANOVA for the background task also identified a main effect of background context ($F_{(1.74, 72.98)}$ = 5.534, p = 0.008, partial-η^2 = 0.116). The main effect of age group and the two-way interaction were again not significant ($F_{(1, 42)}$ = 1.749, p = 0.193, partial-η^2 = 0.040; $F_{(1.74, 72.98)}$ = 0.044, p = 0.939, partial-η^2 = 0.001, respectively). In this case, the main effect of context was driven by lower source memory for words studied in association with scrambled backgrounds relative to non-target ($t_{(43)}$ = 3.465, p = 0.001, d = 0.522) or target scenes ($t_{(43)}$ = 2.210 , p = 0.032, d = 0.333).

Two 2 (age group) x 2 (retrieval task) x 3 (background context) mixed ANOVAs were also employed to evaluate RTs for the item and source memory judgements. The ANOVA examining item recognition RTs identified a main effect of age group ($F_{(1, 42)}$ = 23.729, p < 0.001, partial-η^2 = 0.361); the remaining main effects and the interactions were not significant (ps > 0.080). Thus, while older adults were slower overall in making their recognition judgements, neither background context nor retrieval task moderated RTs in either age group. The ANOVA for source memory RTs again revealed a main effect of age group ($F_{(1, 42)}$ = 25.512, p < 0.001, partial-η^2 = 0.378), but in this case the effect was modified by an age group-by-task interaction ($F_{(1, 42)}$ = 5.517, p = 0.024, partial-η^2 = 0.116). The main effects of background context and task, and the remaining two- and three-way interactions were not significant (ps > 0.165). These results indicated that, akin to item

recognition, older adults were slower overall to make source memory judgements relative to younger adults. Additionally, the age group-by-task interaction for source RTs indicated that age differences in source RTs were sensitive to retrieval task. Follow-up comparisons demonstrated that the interaction was driven by faster source judgements in the location relative to the background task in younger adults ($p = 0.027$), whereas the task effect was not significant in the older adults ($p = 0.173$). As was the case for item recognition, the source memory RTs were insensitive to the nature of the associated background context.

Table 3.3. Mean (SD) memory performance and RT at test.

	Younger Adults		*Older Adults*	
Study Phase				
Vividness Ratings				
Scrambled background	2.32 (0.41)		2.19 (0.56)	
Target scene	2.39 (0.31)		2.37 (0.40)	
Non-target scene	2.34 (0.38)		2.32 (0.43)	
Study RTs (ms)				
Scrambled background	2704.08 (745.65)		3012.18 (580.91)	
Target scene	3077.41 (734.65)		3661.12 (616.52)	
Non-target scene	3101.65 (712.29)		3603.46 (685.27)	
Test Phase	*Location*	*Background*	*Location*	*Background*
Item Hit Rate	0.81 (0.12)	0.80 (0.14)	0.72 (0.12)	0.71 (0.10)
False Alarm Rate	0.15 (0.15)	0.16 (0.12)	0.14 (0.09)	0.12 (0.08)
Item Recognition (Pr)	0.66 (0.21)	0.64 (0.18)	0.58 (0.15)	0.59 (0.15)
Source Memory (pSR)	0.23 (0.16)	0.49 (0.19)	0.16 (0.13)	0.38 (0.19)
Proportion Source Correct				
Scrambled background	0.52 (0.17)	0.63 (0.21)	0.47 (0.18)	0.56 (0.25)
Target scene	0.48 (0.15)	0.70 (0.17)	0.41 (0.15)	0.65 (0.16)
Non-target scene	0.49 (0.17)	0.73 (0.17)	0.39 (0.15)	0.66 (0.19)
Proportion Don't Know				
Scrambled background	0.31 (0.18)	0.25 (0.18)	0.33 (0.22)	0.18 (0.18)
Target scene	0.28 (0.18)	0.15 (0.12)	0.33 (0.19)	0.14 (0.13)
Non-target scene	0.27 (0.17)	0.16 (0.15)	0.33 (0.22)	0.14 (0.16)
Test RT (ms)				
Item responses	1298.09 (113.22)	1300.49 (109.53)	1506.76 (149.81)	1479.31 (155.34)

Source responses	995.97 (224.98)	1055.38 (232.62)	1439.47 (310.48)	1383.78 (271.35)

Item recognition memory computed as the difference between hit and false alarm rates
Source memory computed using the single high-threshold model described in Behavioral Data Analysis

3.3.3 Univariate Reinstatement Index

The fMRI reinstatement indices were subjected to a 2 (age group) x 2 (retrieval task) x 2 (hemisphere) x 2 (ROI) mixed effects ANOVA, the results of which are reported in Table 3.4. As is evident from the table, none of the main effects reached significance, and likewise, the age group-by-ROI, age group-by-hemisphere, task-by-hemisphere, and ROI-by-task interactions were also non-significant. However, the ANOVA revealed significant interactions between the factors of ROI and hemisphere (of little interest in the current context), and age group and task. The significant age group-by-task interaction indicated that younger and older adults demonstrated differential scene reinstatement effects according to the retrieval task (see Figure 3.4). Since the factors of hemisphere and ROI did not interact either with age group or retrieval task, reinstatement indices were averaged across these factors to simplify the follow-up analyses.

Table 3.4. Results for the 2 (age group) x 2 (retrieval task) x 2 (hemisphere) x 2 (ROI) mixed ANOVA of the univariate reinstatement index. Significant effect denoted by *.

	df	*F*	*partial-η^2*	*p-value*
Age group	1, 42	0.405	0.010	0.528
Task	1, 42	1.542	0.035	0.221
Hemisphere	1, 42	3.901	0.085	0.055
ROI	1, 42	1.284	0.030	0.263
Age group x Task	1, 42	10.496	0.200	0.002 *
Age group x Hemisphere	1, 42	0.719	0.017	0.401
Age group x ROI	1, 42	1.691	0.039	0.201
Task x Hemisphere	1, 42	0.395	0.009	0.533
Task x ROI	1, 42	0.314	0.007	0.578
Hemisphere x ROI	1, 42	8.832	0.174	0.005 *
Age group x Task x Hemisphere	1, 42	0.064	0.002	0.802
Age group x Task x ROI	1, 42	0.180	0.004	0.673
Age group x Hemisphere x ROI	1, 42	1.411	0.032	0.242
Task x Hemisphere x ROI	1, 42	0.476	0.011	0.494
Age group x Task x Hemisphere x ROI	1, 42	0.389	0.009	0.536

In light of the results of the foregoing ANOVA we went on to examine scene reinstatement (collapsed across ROIs and hemispheres) as a function of task separately in younger and older adults (Figure 3.4-A). In the younger adult group, reinstatement indices were significantly lower in the location relative to the background task ($t_{(19)}$ = 2.973, p = 0.008, d = 0.665). In the older adult group, however, scene reinstatement did not significantly differ as a function of retrieval task ($t_{(23)}$ = 1.508, p = 0.145, d = 0.308), suggesting that reinstatement was not modulated according to the retrieval goal. Although the main effect of ROI and its interactions with task or age group were not significant, additional panels in Figure 3.4-B present the reinstatement indices in the two tasks plotted separately for the PPA and RSC for illustrative purposes (allowing us to directly compare our findings with those of Elward & Rugg (2015), who reported significant retrieval gating in younger adults in the PPA but not the RSC). In the younger adults, task differences were significant in both PPA and RSC (PPA: $t_{(19)}$ = 2.669, p = 0.015, d = 0.597; RSC: $t_{(19)}$ = 2.509, p = 0.021, d = 0.561), whereas no task effects were identified in older adults in either of the ROIs (PPA: $t_{(23)}$ = 0.831, p = 0.414, d = 0.170; RSC: $t_{(23)}$ = 1.710, p = 0.101, d = 0.349). We evaluated whether reinstatement effects differed reliably from zero as a function of age group and retrieval task with one-sample t-tests (one-tailed). Reliable effects were evident in all cases (Younger Adults: Location task: $t_{(19)}$ = 1.979, p = 0.031, d = 0.443, Background task: $t_{(19)}$ = 6.233, p < 0.001, d = 1.394; Older Adults: Location task: $t_{(23)}$ = 4.661, p < 0.001, d = 0.951, Background task: $t_{(23)}$ = 1.967, p = 0.031, d = 0.402).
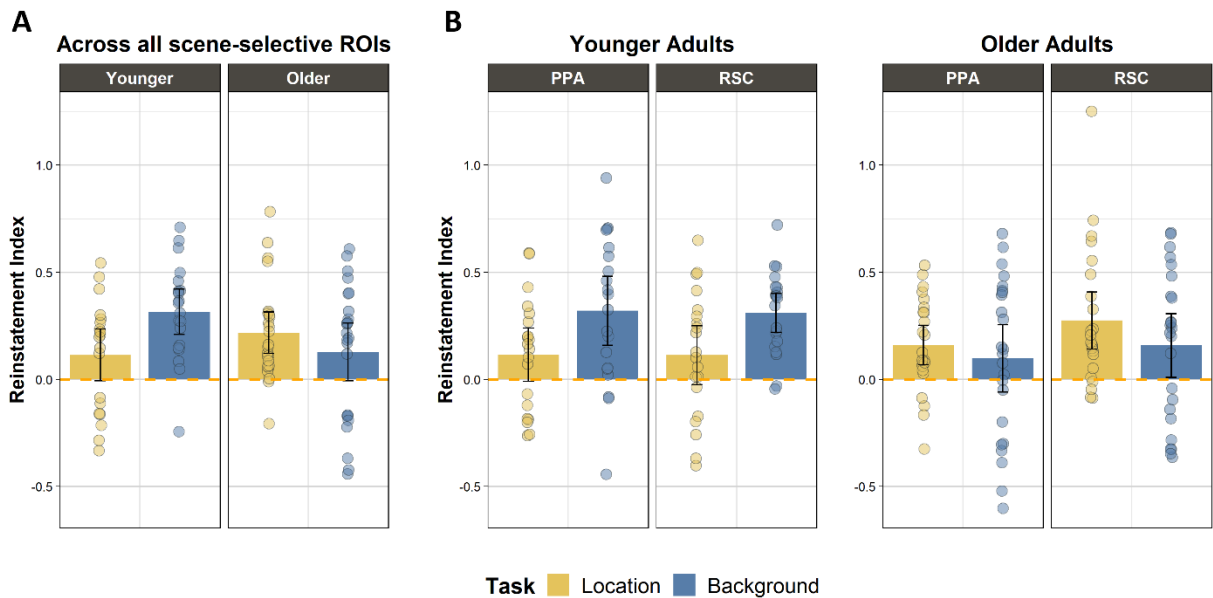
Figure 3.4. Reinstatement indices computed separately for the background and location tasks. (**A**) Reinstatement indices in the two tasks collapsed across ROIs. (**B**) Although the main effect of ROI and its interaction with task or age group were not significant, we further plot the reinstatement indices in the two tasks plotted separately for PPA and RSC for illustrative purposes. Error bars represent 95% confidence intervals.

3.3.4 Pattern Similarity Analysis

Similarity indices (see PSA Methods) were subjected to a 2 (age group) x 2 (retrieval task) x 2 (hemisphere) x 2 (ROI) mixed effects ANOVA analogous to that employed for the reinstatement indices. As is indicated in Table 3.5, none of the four factors gave rise to a significant main effect. Of the interaction effects, only the 2-way interaction between age group and task, and the 3-way interaction between age group, task and ROI reached significance. The age group-by-task interaction parallels the findings for the reinstatement index, in that similarity indices were differentially moderated by retrieval task according to age group (Figure 3.5-A). Additionally, the significant 3-way interaction between age group, task and ROI indicates that age-dependent task differences differed between the PPA and RSC ROIs.

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Table 3.5. Results for the 2 (age group) x 2 (retrieval task) x 2 (hemisphere) x 2 (ROI) mixed ANOVA of the similarity indices derived from the localizer-test Pattern similarity analysis. Significant effect denoted by *.

	df	F	partial-η^2	p-value
Age group	1, 41	1.176	0.028	0.285
Task	1, 41	1.712	0.040	0.198
Hemisphere	1, 41	0.885	0.021	0.352
ROI	1, 41	2.679	0.061	0.109
Age group x Task	1, 41	6.034	0.128	0.018 *
Age group x Hemisphere	1, 41	0.323	0.008	0.573
Age group x ROI	1, 41	0.553	0.013	0.461
Task x Hemisphere	1, 41	3.844	0.086	0.057
Task x ROI	1, 41	0.268	0.006	0.608
Hemisphere x ROI	1, 41	0.775	0.019	0.384
Age group x Task x Hemisphere	1, 41	0.127	0.003	0.723
Age group x Task x ROI	1, 41	8.218	0.167	0.007 *
Age group x Hemisphere x ROI	1, 41	1.169	0.028	0.286
Task x Hemisphere x ROI	1, 41	0.243	0.006	0.625
Age group x Task x Hemisphere x ROI	1, 41	1.114	0.026	0.297

Note: One younger adult did not contribute localizer data, and hence was not included in the PSA.

To follow-up the significant 3-way interaction between age group, ROI, and task, additional 2 (ROI) x 2 (retrieval task) ANOVAs were performed separately for the younger and older age groups (Figure 3.5-B). In the younger adults, the ANOVA identified a significant main effect of retrieval task ($F_{(1, 18)} = 5.674$, p = 0.028, partial-η^2 = 0.240), while neither the main effect of ROI ($F_{(1, 18)} = 0.368$, p = 0.552, partial-η^2 = 0.020) nor the interaction between task and ROI were significant ($F_{(1, 18)} = 2.117$, p = 0.163, partial-η^2 = 0.105). The similarity indices for this group significantly exceeded zero in the background task in both RSC ($t_{(18)} = 3.616$, p < 0.001, d = 0.830) and the PPA ($t_{(18)} = 3.466$, p = 0.001, d = 0.795), but did not differ reliably from zero in the location task (PPA: $t_{(18)} = 1.488$, p = 0.077, d = 0.341; RSC: $t_{(18)} = 0.664$, p = 0.257, d = 0.152). Thus, the PSA findings for the younger adults complement the results of the reinstatement index and are consistent with the proposal that younger adults gated scene reinstatement during the location task.

In the older adults, the main effects of retrieval task and ROI were not significant (Task: $F_{(1, 23)} = 0.822$, p = 0.374, partial-η^2 = 0.035; ROI: $F_{(1, 23)} = 3.134$, p = 0.090, partial-η^2 = 0.120). However, the ANOVA revealed a significant interaction between task and ROI ($F_{(1, 23)} = 7.461$, p = 0.012, partial-η^2 = 0.245). To unpack this interaction, we performed additional pair-wise

contrasts to examine task effects separately in the PPA and RSC. In neither ROI was there a significant difference between the tasks (PPA: $t_{(23)} = 0.605$, $p = 0.551$, $d = 0.123$; RSC: $t_{(23)} = 1.844$, $p = 0.078$, $d = 0.376$). Above-zero similarity indices were identified in the RSC during the location task ($t_{(23)} = 3.460$, $p = 0.001$, $d = 0.706$), whereas the similarity indices in the PPA during the location task, and in both ROIs during the background task, did not differ significantly from zero ($ps > 0.093$). These findings suggest that although PSA was sensitive to scene reinstatement in older adults, this was confined to the RSC during the location task.
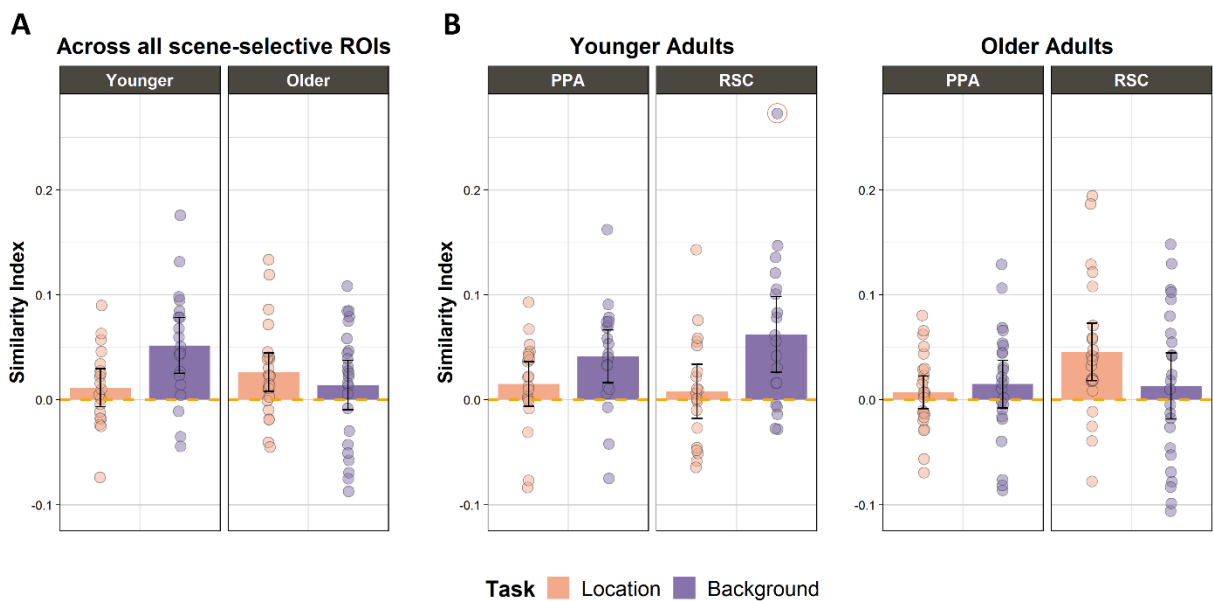
Figure 3.5. Similarity indices derived from PSA between localizer and memory test. **(A)** Similarity index for younger and older adults collapsed across the two ROIs, reflective of the significant age group-by-task interaction. **(B)** Similarity index plotted separately for PPA and RSC. Removing the highlighted outlier does not change the outcome of the age group-by-task interaction, nor the main effect of task in the younger cohort. Error bars represent 95% confidence intervals.

3.3.5   Relationship Between Scene Reinstatement and Memory Performance

In light of prior research indicating that the strength of cortical reinstatement covaries with the amount and fidelity of retrieved content (e.g. Gordon et al., 2014; Hill et al., 2021; Johnson et al., 2009; Thakral et al., 2015; Trelle et al., 2020), exploratory multiple regression analyses were

conducted to examine the relationship between scene reinstatement effects and memory performance. Separate regression models were employed to predict item recognition and source memory performance. Because the item memory scores (Pr) for the two tasks were highly correlated ($r = 0.844$, $p < 0.001$), and did not significantly differ (see 3.2 Behavioral performance results), we averaged the scores to generate a single estimate of item memory for each participant. In the case of source memory performance, regression analyses were conducted for the pSR metrics derived from the respective background and location tasks. The initial regression models employed age group, reinstatement index (separately for each ROI and task), and the age group-by-reinstatement interaction terms as predictors of memory performance. The interaction terms were included in the models to examine whether any relationship between reinstatement and memory was moderated by age group. If the interaction term did not approach significance, the regression model was re-run after dropping the term. Otherwise, the regression was followed-up by zero-order correlations between the reinstatement index and memory performance in younger and older adults separately. Given the explicitly exploratory nature of these analyses, we assessed the significance of these correlations by correcting for family-wise error at the level of each of the memory metrics, i.e., treating the analyses of item and source memory performance as two families. Thus, the family-wise corrected significance level was $p < 0.00625$ (0.05/8). The results reported below tested for relationships between the univariate reinstatement indices and memory performance. When we repeated the analyses using similarity indices derived from the PSA as predictors, we were unable to identify any significant relationships with memory performance.

3.3.5.1 Relationship with Item Recognition

The interaction term in the regression model predicting Pr from PPA reinstatement in the background task was significant ($\beta = 0.806$, $p < 0.001$), indicating that the strength of the relationship between PPA reinstatement and item memory performance differed between younger and older adults (Figure 3.6-A). Simple correlations computed for each age group revealed that, in younger adults, there was a positive relationship between PPA reinstatement and Pr ($r = 0.791$, $p < 0.001$, $p_{(corrected)} < 0.001$), whereas this relationship was absent in older adults ($r = -0.111$, $p = 0.607$; difference between correlations: $Z = 3.634$, $p < 0.001$). The remaining 3 regression models

(employing reinstatement indices from RSC in the location and background tasks, and in the PPA in the location task) failed to identify a significant age group-by-reinstatement term (ps > 0.089), and nor did reinstatement predict Pr when the interaction term was dropped from the models (ps > 0.464).

3.3.5.2 Relationship with Source Memory

We next performed regression analyses to examine the relationship between reinstatement and pSR in the background task. Neither the PPA nor the RSC reinstatement indices interacted with age group (β = 0.412, p = 0.065, β = 0.125, p = 0.720, respectively), and nor did RSC reinstatement predict pSR when the interaction term was omitted (p = 0.345). Because the interaction between age group and PPA reinstatement approached significance (p = 0.065), we went on to examine the relationship between PPA reinstatement and pSR in the background task separately for younger and older adults (Figure 3.6-B). There was a significant positive correlation in the younger (r = 0.610, p = 0.004, $p_{(corrected)}$ = 0.034) but not in the older sample (r = 0.087, p = 0.687), although the difference between the correlations did not quite reach significance (Z = 1.906, p = 0.057).

The regression models predicting location pSR from the reinstatement indices in the PPA and RSC derived from the location task failed to identify any significant interaction terms (ps > 0.576), and the reinstatement indices did not predict location memory when the terms were omitted (ps > 0.469).
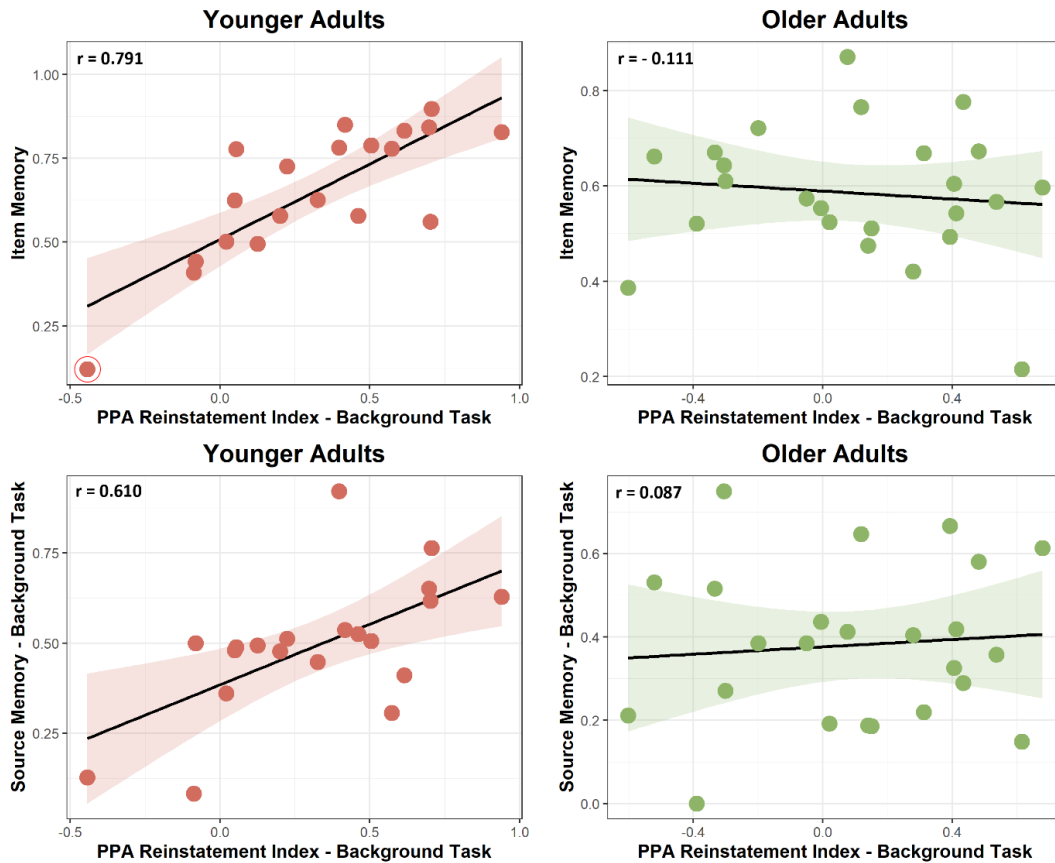
Figure 3.6. (A) Scatterplots illustrating zero-order correlations between overall item memory and PPA reinstatement indices derived from trials of the background task. Eliminating the highlighted outlier from the younger adult scatterplot does not change the results ($r = 0.698$, $p < 0.001$, $p_{(corrected)} = 0.007$). **(B)** Zero-order correlations between PPA reinstatement of the background task and source memory for backgrounds.

3.4   Discussion

The present study examined potential age differences in a recently identified aspect of retrieval processing termed 'retrieval gating' - the ability to regulate the contents of episodic memory retrieval to align them with a retrieval goal. Here, we assessed gating by examining retrieval-related cortical reinstatement of scene information according to whether the information was relevant or irrelevant to the retrieval task. Reinstatement was operationalized with both univariate and multivariate approaches, which converged to suggest that younger, but not older adults, engaged goal-dependent retrieval gating. Additionally, in younger participants only,

univariate scene reinstatement indices in the PPA demonstrated strong positive correlations with both scene and item memory. Below, we discuss the significance of these findings for the understanding of the impact of age on controlled episodic retrieval.

Turning first to behavioral performance at encoding, we observed no age or background context differences in vividness ratings. Younger adults were however faster to make their vividness responses, and both age groups were faster to make vividness responses to items which were studied over scrambled relative to either of the two scene backgrounds. Under the assumption that the two age groups employed similar criteria when rating the vividness of their imagined scenarios, the null effect of age on vividness ratings suggests that differential reinstatement effects in younger and older adults across the two tasks are unlikely to have been confounded by differences in vividness of the imagined scenarios at encoding. With regards to performance at retrieval, item recognition did not differ as a function of age or retrieval task. By contrast, source memory performance was lower in older relative to younger adults. These findings are consistent with numerous prior reports indicating that item memory is less impacted by age than is performance on associative and source memory tests, that is, tests that depend heavily on recollection of episodic information (Koen & Yonelinas, 2014; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995).

Relative to either scene type, test words studied over scrambled backgrounds were associated with better memory for location, but worse memory for the background. These findings are consistent with those reported by Elward & Rugg (2015), who suggested that the lower location memory performance for words studied over scenes was driven by interference from the relatively rich scene information, which could have operated either at encoding or retrieval. According to the first of these possibilities, encoding a word-scene pair is more cognitively demanding than encoding a word presented in association with a scrambled background. The consequent freeing of attentional resources during scrambled trials thus benefited the incidental encoding of the word's location. This account receives support from the finding that study RTs were shorter for word-scrambled image pairs than for word-scene pairs. Elward and Rugg (2015) also suggested that location memory for words studied over scenes may have suffered because task-irrelevant scene information was insufficiently gated at retrieval and hence interfered with the ability to

retrieve or attend to other features of the study episode. The present data arguably speak against this possibility: although older adults demonstrated little evidence for retrieval gating during the location task (discussed below), the effects of age on source memory performance did not reliably differ between the two retrieval tasks. Under the 'retrieval interference' account outlined above, older adults should however have been disadvantaged to a greater extent in the location than the background task.

Both younger and older adults demonstrated reliable scene-related cortical reinstatement effects, adding to the already large literature documenting that encoding-related cortical activity is reinstated at retrieval (for reviews see Danker & Anderson, 2010; Rissman & Wagner, 2012; Rugg et al., 2015; Xue, 2018). The present findings in our younger cohort replicate those of Elward & Rugg (2015). Employing an exclusively univariate approach, those researchers reported that younger adults were capable of exerting control over retrieved content, attenuating reinstatement of scene information in the PPA (but not RSC) when it was not task-relevant. The present study replicates the findings observed in the PPA and extends them to the RSC. Additionally, we expand on these findings by demonstrating that the phenomenon of retrieval gating in younger adults extends to multi-voxel indices of reinstatement. The present results join those of Elward and Rugg (2015) in conflicting with the findings reported by Kuhl et al. (2013). Using MVPA classifiers to quantify cortical reinstatement (cf. Johnson et al., 2009), these researchers reported that neither scene nor face reinstatement effects differed according to retrieval goal (which was either to retrieve the face/scene associate of the test word or to retrieve the associate's study location). The divergence between the results of Kuhl et al. (2013) and the present findings are likely explained by an important procedural difference. At encoding, Kuhl et al. (2013) had their participants view a word presented above two horizontally separated squares, one of which contained an image of a face or a scene. The retrieval phase comprised location and 'background' tasks similar to those employed in the present study. Crucially, though, in the location task participants were required to retrieve the location not of the cued word, but of the image that the word had been paired with. Consequently, participants would likely have been motivated to retrieve the image both when prompted to recall its category (face/scene) or its location.

As already noted, unlike younger adults, older adults did not modulate scene reinstatement according to retrieval goal, and hence showed no evidence of retrieval gating (indeed, if anything, there was a non-significant trend towards stronger scene reinstatement in the location task). Thus, the present study provides novel evidence that older adults reinstate features of an episode regardless of whether the information is relevant to the retrieval goal. It is important to note, however, that the mechanisms that underlie retrieval gating remain unclear. Thus, the present findings are compatible with multiple possible accounts, three of which we outline below.

One possible account of age deficits in retrieval gating is based on evidence that the ability to inhibit task-irrelevant or distracting information declines in older age (e.g. Campbell et al., 2020; Hasher & Zacks, 1988; Hasher et al., 1991; Lustig et al., 2001; see Lustig et al., 2007 for a review of studies examining inhibitory deficits during working memory maintenance). The wealth of behavioral studies motivated a series of fMRI studies that employed working memory paradigms to demonstrate that older adults show less 'down-regulation' of cortical activity in regions responsive to task-irrelevant stimuli (Chadick et al., 2014; Gazzaley et al., 2005, 2008; Weeks et al., 2020). From this perspective, therefore, the seeming absence of retrieval gating in older adults might reflect an age-related decline in the frontally-mediated control processes that have been proposed to downregulate the representation of intrusive and task-irrelevant information in other experimental settings (e.g. Zanto & Gazzaley, 2019). This proposal is consistent with a broader literature linking age-related decline in executive control to reduced structural and functional integrity of the prefrontal cortex (Buckner, 2004; Dennis & Cabeza, 2008; Tromp et al., 2015).

A second account of the present findings stems from the long-standing proposal that episodic memory retrieval depends on strategic processes that optimize memory search by targeting goal-relevant information at the expense of irrelevant content (Rugg & Wilding, 2000; Rugg, 2004; Jacoby et al., 2005; see Introduction). These findings raise the possibility that retrieval gating reflects the outcome of a similar 'biased search' process (albeit, *within* rather than across episodic memory representations, see Introduction). Thus, the present absence of gating effects in older adults might reflect a failure to bias their memory search towards goal relevant mnemonic features. Like the prior 'inhibitory' account, this account also implies a failure on the part of older adults to engage goal-directed control processes.

A final account of the present findings proposes that the absence of gating in older adults is not indicative of an impairment, but rather the adoption of a specific retrieval strategy in an effort to optimize performance on a retrieval task on which task-relevant information was relatively inaccessible. From this perspective, when performing the location task, older adults attempted to retrieve both task-relevant and putatively task-irrelevant information to enhance performance. By this argument, the finding that older adults strongly reinstated scene information during the location task does not signify an inability to gate retrieved content. For example, older adults might have retrieved the scene information to take advantage of the fact that both the item and its background shared the same location. Thus, the absence of retrieval gating in these participants might be reflective of a compensatory mechanism rather than an age-related deficit.

As already noted, the present evidence does not permit an adjudication between the three accounts outlined above, which will depend on the outcome of future research.

We performed a set of exploratory analyses to examine the relationship between cortical reinstatement and memory performance. These analyses were motivated by prior research demonstrating that the strength of reinstatement covaries with the amount of retrieved information (e.g. Gordon et al., 2014; Hill et al., 2021; Johnson et al., 2009; Thakral et al., 2015; Trelle et al., 2020). In the younger group, PPA reinstatement effects in the background task were positively correlated with source memory performance in that task, and with item memory across both retrieval tasks. The reasons for the absence of a relationship between reinstatement and memory performance in the older group are currently unclear. We note, however, that prior studies reporting age differences in the ability to adopt specific retrieval orientations (Duverne et al., 2009; Jacoby et al., 2005; Morcom & Rugg, 2004) raise the possibility that the absent relationship between reinstatement and memory performance in our older adults reflects the employment of different or more variable retrieval strategies during the background task. For example, some older adults might have attempted to retrieve scene information by generating candidate images of scene exemplars when presented with test words that had been paired with a scrambled background. Scene-related activity might also have been elevated on test trials where participants falsely remembered that a word had been studied over a scene rather than a scrambled background (cf. Kurkela & Dennis, 2016). In support of this possibility, we note that in the background task older

adults were more likely to endorse a word as having been studied with a target scene when the word had actually been studied with a scrambled background rather than with a non-target scene (probability of incorrect source response [pSource incorrect] of 0.25 vs. 0.18 respectively; $t_{(23)} = 2.277$, $p = 0.032$). This difference was not evident in the younger adult group (pSource incorrect for scrambled = 0.12; pSource incorrect for non-target scene = 0.11; $t_{(19)} = 0.639$, $p = 0.530$). Because scrambled trials are the baseline against which reinstatement was assessed, scene-related activity elicited by test words that had not in fact been studied with a scene could have led both to an under-estimation of scene reinstatement effects and a breakdown in the relationship between reinstatement and memory.

As noted above, on the assumption that activity in the PPA scaled with success in retrieving scene information, it is unclear why a relationship between scene reinstatement and memory performance was evident not only for source memory, but for item memory also. One possibility is that younger adults employed scene context as an additional cue when determining whether a word was previously studied. According to dual-process models, recognition memory is supported by the functionally distinct processes of recollection and familiarity (for reviews see Yonelinas, 2002; Yonelinas et al., 2010) and it is highly likely that, in the present experiment, item memory was supported by both processes. Thus, since the strength of scene reinstatement scales with the likelihood of successful scene recollection, scene reinstatement likely also acted as a proxy for the probability of successful recollection more generally, and hence for the contribution of recollection to item memory.

An alternative explanation for the relationship between item recognition and scene reinstatement stems from prior reports that study events comprising items superimposed over a background image (item-context presentation), rather than presented adjacent to it (item-item presentation), are more likely to be encoded as an integrated memory representation (e.g. Dennis et al., 2019; Memel & Ryan, 2017). Relatedly, it has been proposed that parahippocampal cortex plays a critical role in item-context binding, such that the memory representations supported by this region can facilitate memory for individual items even when memory for context is not explicitly cued (Hayes et al., 2007, 2010). Nonetheless, it is worth noting that no relationship between scene reinstatement and memory performance was evident in the location task, consistent

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with the proposal that, at least in younger adults, scene reinstatement during location trials was downregulated and played little or no role in supporting either item or source memory performance on the task.

The foregoing arguments do not shed any light on why correlations between scene reinstatement and memory performance were evident for the PPA but not for the RSC. In accounting for this dissociation, we first note that, to our knowledge, it is currently unclear whether scene (or any other) information represented in the RSC is available for the conscious control of behavior. Additionally, or alternatively, the absence of reliable correlations in the RSC might be a consequence of the relatively low fidelity with which scene information appears to be represented in this region; notably, it has been reported that the RSC supports gist-based, 'schematic' representations of scenes and spatial contexts, in contrast to the PPA, which supports more fine-grained, detailed representations (Aminoff et al., 2013; Bar, 2004; see also Epstein, 2008; Epstein & Baker, 2019). We conjecture that, in the present case, the scene representations supported by the RSC were too undifferentiated to permit a determination of whether a reinstated scene should be classified as rural or urban. Examination of this proposal would be a fruitful avenue for future research.

One important limitation of the present study arises from the cross-sectional nature of the design. Consequently, the findings cannot be unambiguously attributed to the effects of aging rather than to a confounding variable such as a cohort effect (Rugg 2017). We also note the possibility that the correlations identified in the younger adults between PPA scene reinstatement and memory performance - which arguably are unexpectedly high given the inherently noisy nature of neural and behavioral measures – are likely an overestimation of the true effect size (Button et al., 2013). Thus, especially in light of our modest sample size, these values should be treated with circumspection until a replication study has been reported (Wilson et al., 2020). We note however that the present results represent a replication of the retrieval gating effect reported in younger adults by Elward and Rugg (2015), alleviating concerns that the findings in the present younger group reflect a Type I error. Of course, we cannot rule out the possibility that our relatively modest sample size precluded the detection of a small but nonetheless reliable gating effect in our older adult group. Of importance, though, the robust age group-by-task interaction effects that

were identified here strongly suggest that any such effects in older adults would be significantly smaller than those evident in younger individuals.

The present study does however overcome some of the constraints which commonly apply to studies examining age differences in episodic memory retrieval. Firstly, age differences in retrieval gating cannot be attributed to simple age differences in the strength of cortical reinstatement (Bowman et al., 2019; Folville et al., 2020; Hill et al., 2021; St-Laurent & Buchsbaum, 2019), as both the univariate and multivariate approaches failed to identify a moderating effect of age group on the two metrics of reinstatement (see Thakral et al., 2017; Wang et al., 2016 for similar findings). Secondly, as noted in the methods, the reinstatement index and PSA metrics employed here to quantify reinstatement effects are insensitive to individual differences in HRF gain; hence, the present results are free from the confounding influence of systematic age differences in this variable (e.g. Lu et al., 2011), although it remains unclear to what extent the findings might have reflected age differences in the variability or the shape of the hemodynamic response (D'Esposito et al., 2003).

The present study provides novel evidence that younger, but not older adults, control the contents of recollection in alignment with behavioral goals. As discussed above, the absence of retrieval gating effects in the older adult group might be reflective of an age-related vulnerability in the ability to prioritize relevant over irrelevant information during episodic memory retrieval. This possibility is compatible with other recent evidence suggesting that, relative to younger adults, older individuals are more likely to 'clutter' their memories with irrelevant information (Amer et al., 2020). However, the present findings are also consistent with the possibility that older adults retrieve seemingly task-irrelevant episodic content as a strategy to maximize the likelihood of successful memory performance. Future research should aim to gain insight into how age-related differences in retrieval gating relate to other processes known to be sensitive to increasing age, such as age deficits in inhibitory control. Moreover, given that it remains unclear whether the absence of retrieval gating in older adults reflects an *incapacity* to gate as opposed to a preference for a different retrieval strategy, future studies should examine whether older adults can be incentivized to engage retrieval gating (cf. Duverne et al., 2009).

CHAPTER 4

THE RETRIEVAL-RELATED ANTERIOR SHIFT IS MODERATED BY AGE

AND CORRELATES WITH MEMORY PERFORMANCE

This chapter includes a manuscript which has been published in *The Journal of Neuroscience* by me (Sabina Srokova) as the first author, along with co-authors Drs. P.F. Hill & M.D. Rugg who provided substantial input via their comments and edits of the presented text.

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4.1   Introduction

Cognitive aging is associated with a disproportionate decline in memory for contextual details of previously experienced episodes. Relative to younger adults, older adults tend to retrieve memories with less specificity and fewer details (Levine et al., 2002; Addis et al., 2008), while memory for semantic information and general knowledge remains relatively preserved (Nilsson, 2003; Nyberg et al., 2012). Recent findings suggest that even when a memory of an event is successfully retrieved, the precision and specificity of the retrieved content is reduced with increasing age (Nilakantan et al., 2018; Korkki et al., 2020). These findings are consistent with the notion that older adults rely on relatively abstract or 'gist-like' memories and experience a reduction in episodic detail (Koustaal & Schacter, 1997; Dennis et al., 2007; 2008, Gallo et al., 2019).

Episodic memory retrieval is associated with the 'reactivation' of patterns of cortical activity elicited when the episode was experienced, a phenomenon termed cortical reinstatement (for reviews see Danker and Anderson, 2010; Rissman and Wagner, 2012; Rugg et al., 2015; Xue, 2018). The strength and specificity of cortical reinstatement have been reported to be reduced in older age (Bowman et al., 2019; St-Laurent & Buchsbaum, 2019; Folville et al., 2020; Hill et al., 2021, but see Wang et al., 2016; Thakral et al., 2017). The strength of cortical reinstatement has also been reported to predict the likelihood of successful retrieval, leading to the proposal that

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cortical reinstatement indexes the amount of retrieved episodic content (e.g., Johnson et al., 2009; Trelle et al., 2020; Hill et al., 2021). Thus, age-related reductions in the strength of cortical reinstatement may reflect older adults' tendency to retrieve less detailed episodic information than their younger counterparts.

Whereas cortical reinstatement is a well-established phenomenon, recent research demonstrates that there are systematic differences in the localization of content-selective cortical activity observed at encoding and retrieval, thus challenging the notion that the neural populations active at encoding are merely reactivated at retrieval. Mental imagery and retrieval of perceptual stimuli (e.g., scene images) have been reported to be associated with neural activation that peaks slightly anterior to the regions maximally recruited during direct perception of the stimuli (for review, see Favilla et al., 2020). This retrieval-related bias towards more anterior neural recruitment has been termed the 'anterior shift' (e.g., Rugg & Thompson-Schill, 2013; Bainbridge et al., 2021). The functional significance of the shift is largely unknown, although it has been suggested that it reflects a 'transformation' of a mnemonic representation such that different attributes of an event (such as perceptual details) are differentially emphasized at encoding and retrieval (Favilla et al., 2020). Given that the posterior-anterior axis of occipito-temporal cortex has been held to be hierarchically organized, forming a gradient of increasing abstraction, the anterior shift may reflect a shift towards abstracted representations that emphasize conceptual attributes of a stimulus event at the expense of 'lower-level' perceptual and sensory features (e.g., Peelen & Caramazza, 2012; Martin et al., 2018).

Here, younger and older adults underwent fMRI as they viewed concrete words paired with images of faces and scenes. Participants remained in the scanner to complete a retrieval task during which they were presented with old or novel words under the requirement to retrieve the image associated with each word judged to be old. We addressed two key questions. First, we examined whether the anterior shift is moderated by age. In light of evidence suggesting that older adults tend to retrieve more gist-like (abstracted) memories than younger individuals, the aforementioned 'abstraction' account of the anterior shift leads to the prediction that it will be exaggerated in older relative to young adults. Second, we asked whether the anterior shift is a moderator of individual differences in memory performance. According to the abstraction account, to the extent that a

memory test depends on the retrieval of detailed perceptual information, a negative relationship between the magnitude of the shift and memory performance is predicted.

4.2   Materials and Methods

Outcomes of analyses of data from the present experiment have been described in two prior reports (Srokova et al., 2020; Hill et al., 2021). Descriptions of the experimental design, procedure, and the outcomes of the behavioral analyses were reported previously and are summarized here for the convenience of the reader. The analyses of the retrieval-related 'anterior shift' described below have not been reported previously.

All experimental procedures were approved by the Institutional Review Boards of The University of Texas at Dallas and The University of Texas Southwestern Medical Center. Each participant gave informed consent prior to their participation in the study.

4.2.1   Participants

Twenty-seven younger and 33 older adult participants were recruited from the University of Texas at Dallas and surrounding metropolitan Dallas communities. All participants were compensated $30/hour and were reimbursed up to $20 for travel. Participants were right-handed, had normal or corrected-to-normal vision, and were fluent English speakers before the age of five. None of the participants had a history of neurological or cardiovascular disease, diabetes, substance abuse, or current or recent use of prescription medication affecting the central nervous system. Potential MRI-eligible participants were excluded if they did not meet pre-determined performance criteria on our neuropsychological test battery (see below).

Three younger and nine older adults were excluded from subsequent analyses. Two participants voluntarily withdrew from the study and one participant was excluded due to technical difficulties during MRI scanning. Additionally, the behavioral performance of two participants resulted in critical memory bins having too few trials, and six participants were excluded due to at- or near-chance source memory performance (probability of source recollection, pSR, < 0.1). Lastly, one participant was excluded due to an incidental MRI finding. The final sample consisted

of 24 younger adults (15 females; age range = 18-28 years, M (SD) = 22.4 (3.2) years) and 24 older adults (14 females; age range = 65-75 years, M (SD) = 70.1 (3.4) years).

4.2.2 Neuropsychological Testing

All participants completed a neuropsychological test battery which was administered on a separate day prior to participation in the fMRI session. The battery consisted of the following tests: Mini-Mental State Examination (MMSE), the California Verbal Learning Test II (CVLT: Delis et al., 2000), Wechsler Logical Memory Tests 1 and 2 (Wechsler, 2009), the Symbol Digit Modalities test (SDMT; Smith, 1982), the Trail Making Tests A and B (Reitan & Wolfson, 1985), the F-A-S subtest of the Neurosensory Center Comprehensive Evaluation for Aphasia (Spreen & Benton, 1977), the Forward and Backward digit span subtests of the revised Wechsler Adult Intelligence Scale (Wechsler, 1981), Category fluency test (Benton, 1968). Raven's Progressive Matrices List I (Raven et al., 2000), and the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). Potential participants were not accepted into the study for any of the following reasons: if their MMSE score was below 27, if they scored more than 1.5 standard deviations below age- and education-adjusted norms on one or more long-term memory test or on at least two non-memory tests, or if their estimated full-scale IQ was less than 100. These criteria were employed to minimize the likelihood of including older participants with mild cognitive impairment or early dementia.

4.2.3 Experimental Procedure

4.2.3.1 Materials

Experimental stimuli were presented using Cogent 2000 (www.vislab.ucl.ac.uk/cogent_2000.php) implemented in Matlab (www.mathworks.com). The study and test phases were completed inside the scanner, and stimuli were projected onto a translucent screen placed at the rear end of the scanner bore and viewed through a mirror fixed onto the head coil. The critical experimental stimuli comprised 288 concrete nouns, 96 colored images of faces (48 male, 48 female) and 96 colored images of scenes (48 urban, 48 rural). An additional 68 words and 40 images were used as practice stimuli or as filler trials during the experiment proper. The critical stimuli were used to create 24 stimulus lists which were assigned

to yoked pairs of younger and older participants. Each study list consisted of 192 randomly selected word-image pairs interspersed with 96 null trials (white fixation cross) and divided into 4 study blocks. Consequently, a single study block comprised 48 critical word-image trials (divided equally between male and female faces, and urban and rural scenes) and 24 null trials. The test list comprised 192 old (studied) trials, 96 new trials, and 96 null trials, evenly distributed into 4 test blocks. The orderings of the items in the study and test lists were pseudorandomized while ensuring that participants experienced no more than three consecutive critical trials of the same image category, no more than three new trials, and no more than two null trials.

4.2.3.2 Study and Test Phase

Participants received instructions and completed practice study and test tasks prior to entering the scanner. Participants then underwent fMRI as they completed two study-test cycles. Each cycle consisted of two study runs (approx. 8 minutes each) followed by two test runs (approx. 10 minutes each). A schematic of the study and test tasks is illustrated in Figure 4.1. Each study trial began with a red fixation cross presented for 500 ms. The fixation cross was followed by the presentation of the word-image pair, which remained on the screen for 2000ms. When presented with an image of a face, participants were to imagine the person in the image interacting with the object. During scene trials, participants imagined the object interacting or moving around within the scene. Participants rated the vividness of the imagined scenario on a 3-point scale ("not vivid", "somewhat vivid", "very vivid") using a scanner-compatible button box and the index, middle, and ring fingers of the right hand, respectively. The presentation of the word-image pair was followed by a white fixation cross that lasted for an additional 2000 ms. Participants were allowed to make their vividness response from the onset of the word-image pair until the termination of the white fixation cross, thus providing a 4000 ms response window.

Each test trial began with a red fixation cross for 500 ms, which was immediately replaced by the test item for a duration of 2000 ms. Response prompts appeared underneath the item at its onset. Participants were instructed first to indicate whether they remembered seeing the word at study by making an "Old" or "New" response. For each word endorsed "Old", participants went on to make a source memory judgment, indicating whether the word had been studied with a face

or a scene. A third "Don't Know" option was included to discourage participants from guessing. As with the study phase, the test item was replaced with a white fixation cross for 2000 ms, and participants were allowed to make their memory judgments throughout the full 4000 ms response window. Responses were made using a scanner-compatible button box. Old / New responses were made with the index and middle fingers of the right hand with the ordering of the fingers counterbalanced across participants. The Face / Scene / Don't Know responses were made with the index, middle, and ring fingers of the right hand and were also counterbalanced across participants while ensuring that the Don't Know response was never assigned to the middle finger.
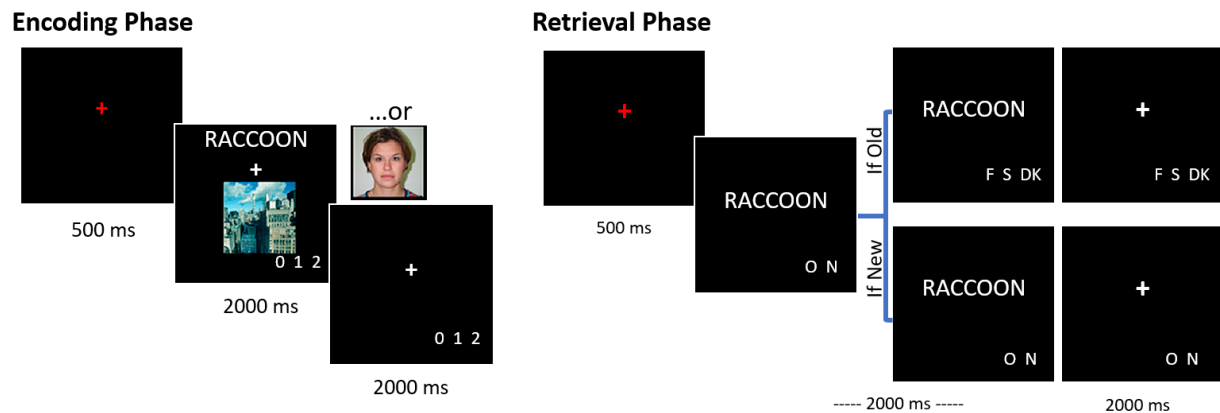
Figure 4.1. Schematic of the encoding and retrieval tasks. At encoding, participants were presented with words paired with an image of a face or a scene. At retrieval, they were presented with a test word and required to indicate whether they remembered seeing the word during the encoding phase, and if so, whether it had been paired with an image of a face or a scene.

4.2.3.3 MRI Data Acquisition and Preprocessing

Functional and structural MRI data were acquired using a Philips Achieva 3T MRI scanner (Philips Medical System, Andover, MA, US) equipped with a 32-channel head coil. Anatomical scans were acquired with a T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) pulse sequence (field of view [FOV] = 256 x 256 mm, voxel size = 1 x 1 x 1 mm, 160 slices, sagittal acquisition). Functional data was obtained with a T2*-weighted echo-planar-imaging (EPI) sequence (FOV = 240 x 240 mm, TR = 2 s, TE = 30 ms, flip angle = 70°). EPI volumes consisted of 34 axial slices acquired in an ascending order parallel to the anterior-

posterior commissure, with an interslice gap of 1 mm. The voxel size of the EPI volumes was 3 mm isotropic.

The MRI data were preprocessed using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK) and custom Matlab code (MathWorks). The functional data were realigned to the mean EPI image and slice-time corrected using *sinc* interpolation with reference to the 17th slice. Following realignment, images were reoriented and normalized to MNI space using a sample-specific EPI template according to previously published procedures (de Chastelaine et al., 2011, 2016). This approach ensures an unbiased contribution of each age group to the normalization template, minimizing age biases in the extent of the warping required to normalize each participant's images (Buckner et al., 2004). Note that it is essential to characterize the anterior shift in a standardized space (in the present case, defined by MNI coordinates) when contrasting group differences in the magnitude of the shift and assessing its relationship with behavior. Lastly, the functional images were smoothed with an 8 mm full-width at half-maximum Gaussian kernel. The time series of the study and test runs were concatenated using the *spm_fmri_concatenate* function prior to the implementation of the first-level general linear model (GLM; see below).

4.2.3.4 Whole-brain Univariate Analysis

The functional data were analyzed with a two-stage univariate GLM approach. At the first stage, separate GLMs were implemented for the study and test data of each participant. The study trials were binned into two events of interest (face and scene trials) and the neural activity elicited by the trials was modeled with a boxcar function extending over the 2s period during which the word-image pair remained on the screen. The boxcar regressors were convolved with two canonical hemodynamic response functions (HRFs): SPM's canonical HRF and an orthogonalized delayed HRF. The delayed HRF was created by shifting the canonical HRF by one TR (2s) later and using the Gram-Schmidt procedure to orthogonalize it with the canonical HRF (Andrade et al., 1999). The delayed HRF did not produce any findings in addition to those described below and thus is not discussed further. In addition to the events of interest described above, the GLM for the study phase also modeled the following trials as covariates of no interest: filler trials, trials with

missing or multiple responses, trials receiving a response before 500 ms or after 4500 ms following stimulus onset, and the 30-second rest period. Additional covariates of no interest comprised 6 motion regressors reflecting rigid-body translation and rotation, spike covariates regressing out volumes with transient displacement > 1 mm or $> 1°$ in any direction, and the mean signal of each scanner run. The parameter estimates from the first level GLM were carried over to a 2 (age group: younger, older) x 2 (study trial: face, scene) mixed factorial ANOVA which was height-thresholded at $p < 0.001$ uncorrected, retaining only those clusters which survived FWE correction at $p < 0.05$.

The test phase trials were binned into five events of interest: face trials associated with a correct source memory judgement (face source correct), scene trials associated with a correct source memory judgement (scene source correct), recognized old items which received an incorrect source memory judgement or a Don't know response (source incorrect + DK), studied items attracting an incorrect 'new' response (item miss), and new items attracting a correct 'new' response (correct rejection). Events of interest were modeled with a delta function time-locked to stimulus onset (the choice of a delta function was motivated by the presumed short-lived nature of the processing of the retrieval cue) and convolved with the canonical and orthogonalized delayed HRFs. As with the encoding data, the delayed HRF did not identify any additional clusters of interest. Covariates of no interest comprised filler trials, false alarms, trials with missing or multiple responses, trials attracting a response before 500 ms and after 4500 ms following stimulus onset, the 30 second rest periods, six motion regressors reflecting translational and rotational displacement, motion spike covariates, and the mean signal for each run. The second level GLM took the form of a 2 (age group: younger, older) x 5 (test trial: face source correct, scene source correct, source incorrect + DK, item miss, correct rejection) mixed factorial ANOVA. Analogous to the GLM of the study data, the ANOVA was height-thresholded at $p < 0.001$ uncorrected and clusters were retained if they exceeded the FWE corrected threshold of $p < 0.05$.

4.2.3.5 Anterior Shift in Scene- and Face-selectivity Between Study and Test

The primary aim of the analyses described below centered on examining age differences and the functional significance of the retrieval-related anterior shift. Here, the term 'anterior shift'

refs to a statistically significant difference in the localization of neural activity observed at encoding and retrieval, such that the retrieval of the memory of a perceptual stimulus (e.g., an image of a scene in the context of the present study) is associated with a peak response in category-selective cortex that is anterior to the peak response elicited when the image was experienced directly. The present analyses were restricted to scene- and face-selective cortical regions where significant clusters could be identified across both age groups (i.e. clusters surviving the FWE corrected threshold of $p < 0.05$) in both the encoding and retrieval phases (see 3.2, Whole-Brain Results). The resulting scene-selective ROIs were localized to the parahippocampal place area (PPA), medial place area (MPA; sometimes referred as retrosplenial cortex), and occipital place area (OPA). Among face-selective clusters, only the precuneus (PCU) could be identified at both encoding and retrieval. When examining the coordinates of peak scene- and face-selective responses within these regions at the individual subject level, the analyses were restricted to anatomical masks which corresponded to the cortical regions encompassing the clusters described above. Each anatomical mask was defined by reference to SPM's Neuromorphometrics atlas with the exception of the MPA, which was not well captured by the labels provided by Neuromorphometrics and was instead defined by reference to the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA; Joliot et al., 2015). The PPA was delimited by the parahippocampal and fusiform gyrus labels. The OPA mask was created using the atlas labels for the inferior and middle occipital gyri and the PCU mask comprised the precuneus and posterior cingulate labels. The MPA was defined using the following AICHA labels: precuneus (AICHA indices: 265, 267, 269 for the left hemisphere; 266, 268, 270 for the right hemisphere), parieto-occipital (left hemisphere: 283, 285, 289, 291; right hemisphere: 284, 286, 290, 292), and posterior cingulate (left hemisphere: 253, 255; right hemisphere: 254, 256). The AICHA atlas was resampled to 3mm isotropic voxels to match the resolution of the functional data prior to ROI definition. More details about each mask are given in Table 4.1.

Using the outcome of each participant's 1st level GLMs, we computed *scenes > faces* and *faces > scenes* contrasts from the encoding data, and *scene source correct > face source correct* and *face source correct > scene source correct* contrasts from the retrieval data. The contrasts at retrieval were limited to source correct trials to ensure that any age effects in the anterior shift were

not confounded by differential mixing of trials associated with successful and unsuccessful source recollection. Next, we performed anatomically constrained univariate searchlight analyses on spherical ROIs (i.e. searchlights) of 5 mm radius that were iteratively centered around each voxel falling within a given anatomical mask. The voxels comprising each searchlight were restricted to those that fell within the relevant mask to ensure that we did not intrude on adjacent cortical regions. This approach resulted in truncated spheres at the mask edges, and any searchlights that contained fewer than 6 voxels were eliminated from the analysis. The final numbers of searchlights included in these analyses and their sizes are given in Table 4.1. Note that the anatomical masks comprised voxels common to all subjects and both task phases. As a result, any task and age differences in the localization of category selectivity could not have arisen due to age or task differences in the number of the searchlights employed within each ROI. We also conducted a secondary analysis in which searchlights were allowed to extend over the mask edges into adjacent gray matter (as defined by SPM's Tissue Probability Mask). This analysis yielded results that were essentially identical to those described below.

For each participant, mean across-voxel parameter estimates corresponding to the scene- and face-selective encoding and retrieval contrasts were extracted from each searchlight. We employed scene > faces (encoding) and scene source correct > face source correct (retrieval) contrasts when examining selectivity within the PPA, MPA and OPA. The face-selective face > scene and face source correct > scene source correct contrasts were used in the case of the face-selective PCU. To localize peaks manifesting maximal scene or face selectivity in each region, for each participant we ranked the searchlights in terms of their mean category-selective responses and selected the top 5%. This was done separately for the encoding and retrieval contrasts. The MNI coordinates of the centers of these spheres were then averaged across each plane to compute the coordinates of their centroid, and this defined the locus of peak selectivity. This approach resulted in two centroids for each participant and ROI, one defining the location of peak category selectivity at encoding and the other at retrieval. Encoding-retrieval shifts were defined as the distance (in mm) between the two centroids along the posterior – anterior plane (i.e. the difference between the respective Y coordinates). Thus, negative values would indicate a retrieval-related posterior shift (such that the peak category selectivity at retrieval is located posterior to the

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encoding peak) and positive values indicate an anterior shift (such that the retrieval peak is localized anterior to the encoding peak). A schematic describing the analysis approach is illustrated in Figure 4.2. The searchlight approach to estimating peak selectivity was motivated by the aim of avoiding the pitfalls associated with approaches such as identifying a single 'peak voxel'. Notably, the size of the effect estimated from a peak voxel overestimates the 'true' effect size by the virtue of the summation of signal with positively biased noise (Kriegeskorte et al., 2010), inflating measurement error in the localization of peak selectivity. The 'multiple searchlight' metric described above provides a spatially smoothed estimate of the locus of a peak effect that minimizes the impact of measurement error caused by positive bias.

To ensure the results we report below were not dependent on the choice of searchlight parameters (i.e., searchlight radius and proportion of top ranked searchlights), we conducted additional analyses employing searchlights of 3 mm, 5 mm and 8 mm radius while selecting the top 1%, 5% or 10% of searchlights to build the centroids. The effect of age group (see 3.3. *Retrieval-related Anterior Shift* below) remained stable regardless of parameter choice. A reliable relationship across participants between the size of the shift and memory performance in the PPA (see *3.4 Relationship with Memory Performance* below) was however evident only for the 5 mm and 8 mm searchlights. We note that since we eliminated searchlights containing fewer than 6 voxels, and a full 3 mm searchlight contained only 7 voxels, approximately 60% of the 3mm searchlights in the PPA were lost because they extended outside the boundary of the anatomical mask (by contrast, only 5% were lost in the case of the 5 mm radius searchlight). We attribute the failure to find a reliable relationship between the PPA anterior shift and memory performance when employing the 3mm searchlights to this data loss and the attendant increase in measurement noise.
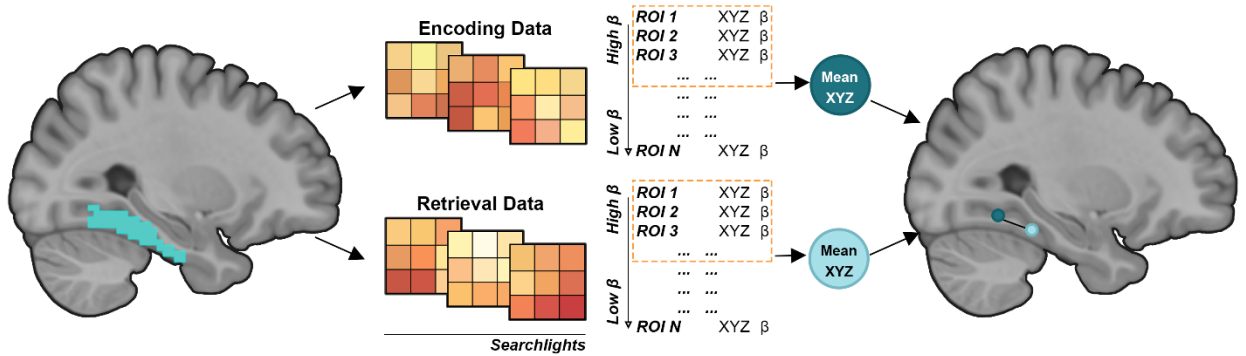
Figure 4.2. Schematic illustration of the encoding-retrieval displacement analysis pipeline. Searchlights were iteratively centered around every voxel inside a given anatomical mask. We selected the top 5% most category-selective spheres, separately for the encoding and retrieval data. The MNI coordinates of the searchlight centers were averaged to compute the center of mass (centroids) of category selectivity. The retrieval-related anterior shift was defined as the distance (in mm) between the encoding and retrieval centroids along the posterior-anterior plane. See main text for details.

Table 4.1. Size of the anatomical regions of interest, the number of searchlights from which parameter estimates were extracted, and the mean (SD) size of the searchlights.

	Mask size (in voxels)	*Number of searchlights*	*Mean (SD) searchlight size (in voxels)*
Scene ROIs			
Left PPA	410	388	11.56 (3.14)
Right PPA	404	381	11.73 (3.26)
Left MPA	633	625	14.28 (3.75)
Right MPA	688	669	14.51 (3.67)
Left OPA	645	636	13.37 (3.55)
Right OPA	561	550	13.12 (3.47)
Face ROIs			
Left PCU	913	902	13.79 (3.37)
Right PCU	816	806	13.333.26)

4.2.3.6 Experimental Design and Statistical Analyses

Statistical analyses were performed using R software (R Core Team, 2020). Statistical tests were considered significant at $p < 0.05$ unless otherwise stated (e.g., see exploratory analyses in 3.4. *Relationship with Memory Performance*, where we correct for family-wise error). ANOVAs were performed using the afex package (Singmann et al., 2016) and degrees of freedom were corrected for nonsphericity using the Greenhouse-Geisser procedure (Greenhouse and Geisser, 1959). All t-tests were performed using the t.test function and regression analyses were performed

using the lm function, both in base R. Partial correlations were conducted using pcor.test in the ppcor package (Kim, 2015).

4.3   Results

4.3.1   Behavioral Results

Behavioral performance and neuropsychological test performance have been reported previously (Srokova et al., 2020; Hill et al., 2021) and are only briefly summarized below. With regards to neuropsychological test performance, younger adults outperformed older adults on the CVLT Short Delay – Free recall, CVLT recognition – False alarms, WMS Logical Memory I and II, SDMT, Trails A and B, and Raven's matrices. On the experimental task, item recognition (Pr) was operationalized as the difference between hit rate (the proportion of items correctly endorsed 'old') and the false alarm rate (the proportion of new items incorrectly endorsed 'old'). ANOVA revealed a main effect of age ($F_{(1,46)} = 10.112$, $p = 0.003$, partial-$\eta^2 = 0.180$), reflective of higher Pr in younger (M [SD] = 0.68 [0.17]) relative to older adults (M [SD] = 0.54 [0.13]). The ANOVA also identified a main effect of image category ($F_{(1,46)} = 5.443$, $p = 0.024$, partial-$\eta^2 = 0.106$), reflective of higher Pr for words studied with faces (M [SD] = 0.63 [0.16]) relative to scenes (M [SD] = 0.60 [0.15]). The interaction between age group and image category was not significant ($F_{(1,46)} = 0.766$, $p = 0.386$, partial-$\eta^2 = 0.016$). Source memory performance (pSR) was operationalized by a single high-threshold model (Snodgrass and Corwin, 1988; see also Gottlieb et al., 2010; Mattson et al., 2014) using the formula: pSR = [pSource correct - 0.5 *(1 – pDon't Know)] / [1 - 0.5 * (1 – pDon't Know)], where 'pSource Correct' and 'pDon't know' refer to the proportion of correctly recognized old trials receiving an accurate source memory judgement or a 'Don't Know' response, respectively. An independent samples t-test revealed that pSR was significantly lower in older (M [SD] = 0.51 [0.16]) than in younger adults (M [SD] = 0.68 [0.18]; $t_{(45.51)} = -3.440$, $p = 0.001$).

4.3.2   Whole-Brain Results

Figure 4.3-A illustrates the *Scene > Face* and *Face > Scene* contrasts at encoding, and Figure 4.3-B depicts the *Scene source correct > Face source correct* and *Face source correct >*

Scene source correct contrasts at retrieval. These results have been reported previously (Hill et al., 2021) and are re-reported here because of their relevance to the present analyses and ROI definition (we note however that Hill et al., 2021 focused on face and scene recollection contrasts [*face/scene source correct > source incorrect + DK],* the outcomes of which are highly similar to those reported here). At encoding, scene-selective clusters were identified along the parahippocampal and fusiform gyri, extending into the retrosplenial and medial occipital cortices. Face-selective clusters were identified in the precuneus/posterior cingulate cortex, medial prefrontal cortex, and along the medial temporal lobe bilaterally extending into the amygdala and anterior hippocampus. Face-selective clusters were also evident in middle temporal gyri and the right fusiform cortex. At retrieval, scene-selective clusters were evident in bilateral parahippocampal cortex, retrosplenial cortex, and the left middle occipital cortex along with a cluster in the right orbitofrontal cortex extending into the subgenual anterior cingulate cortex. The sole face-selective cluster at retrieval was observed in the precuneus, extending into the posterior cingulate cortex.
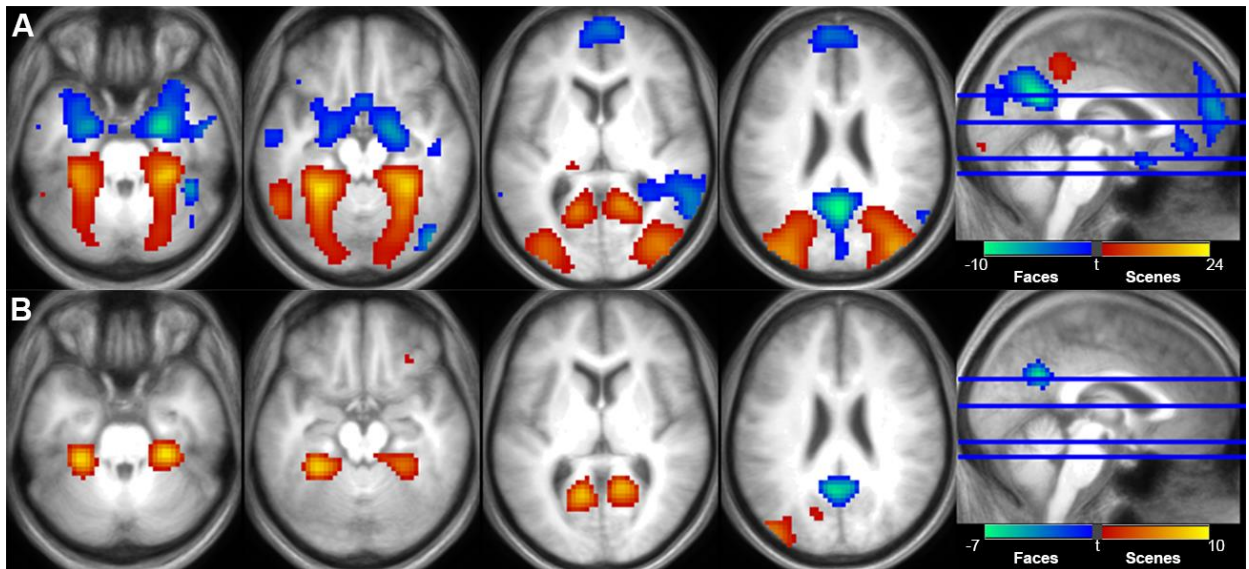
Figure 4.3. Univariate scene-selective (red) and face-selective (blue) effects at encoding **(A)** and retrieval **(B)**, collapsed across age groups. Clusters are overlaid on the across-participant mean T1 image. In both cases, clusters are displayed at p < 0.001 after FWE cluster size correction (p < 0.05).

4.3.3 Retrieval-related Anterior Shift

First, we aimed to establish which ROIs, if any, exhibited a retrieval-related anterior shift. To this end, we examined whether the coordinates of retrieval centroids were systematically displaced relative to the encoding centroids. To achieve this, for each participant we measured the distance along the Y plane in MNI space between encoding and retrieval centroids. We then tested whether these distances were significantly different from zero, using a one sample t-test. As noted previously (see 2.6.2. *Anterior shift in scene- and face-selectivity between study and test*), distance measures greater than zero indicate that the retrieval centroid is shifted anteriorly to the encoding centroid, whereas negative values indicate a posterior shift. Figure 4.4 depicts the encoding and retrieval centroids and their corresponding distances for each individual participant. As is evident from Table 4.2, in younger adults there was a reliable anterior shift in bilateral PPA and OPA, while the shift was not significantly different from zero in either the MPA (for scenes) or the PCU (for faces). By contrast, older adults exhibited a reliable anterior shift in all ROIs except for the left MPA, where it approached significance. Given the consistent trend in all ROIs towards a retrieval-related anterior shift, in the interest of clarity we refer to this simply as the 'anterior shift' in the analyses described below.

Table 4.2. Mean (SD) of retrieval-related anterior shift (in mm) and the outcomes of one-sample t-tests against zero.

	Younger Adults	*Older Adults*
Left PPA	7.29 (5.79)	11.09 (8.83)
	t = 6.169, p < 0.001	t = 6.159, p < 0.001
Right PPA	9.03 (6.40)	13.82 (10.05)
	t = 6.906, p < 0.001	t = 6.741, p < 0.001
Left MPA	1.24 (6.69)	3.45 (8.21)
	t = 0.907, p = 0.374	t = 2.059, p = 0.051
Right MPA	2.25 (5.51)	3.70 (6.51)
	t = 2.005, p = 0.057	t = 2.784, p = 0.011
Left OPA	3.01 (4.21)	4.34 (3.59)
	t = 3.503, p = 0.002	t = 5.927, p < 0.001
Right OPA	2.83 (5.55)	5.65 (4.90)
	t = 2.504, p = 0.020	t = 5.651, p < 0.001
Left PCU	0.99 (5.83)	5.83 (8.85)
	t = 0.833, p = 0.413	t = 3.229, p = 0.004
Right PCU	1.71 (7.31)	5.33 (11.88)
	t = 1.146, p = 0.264	t = 2.197, p = 0.038

For all t-tests: df = 23
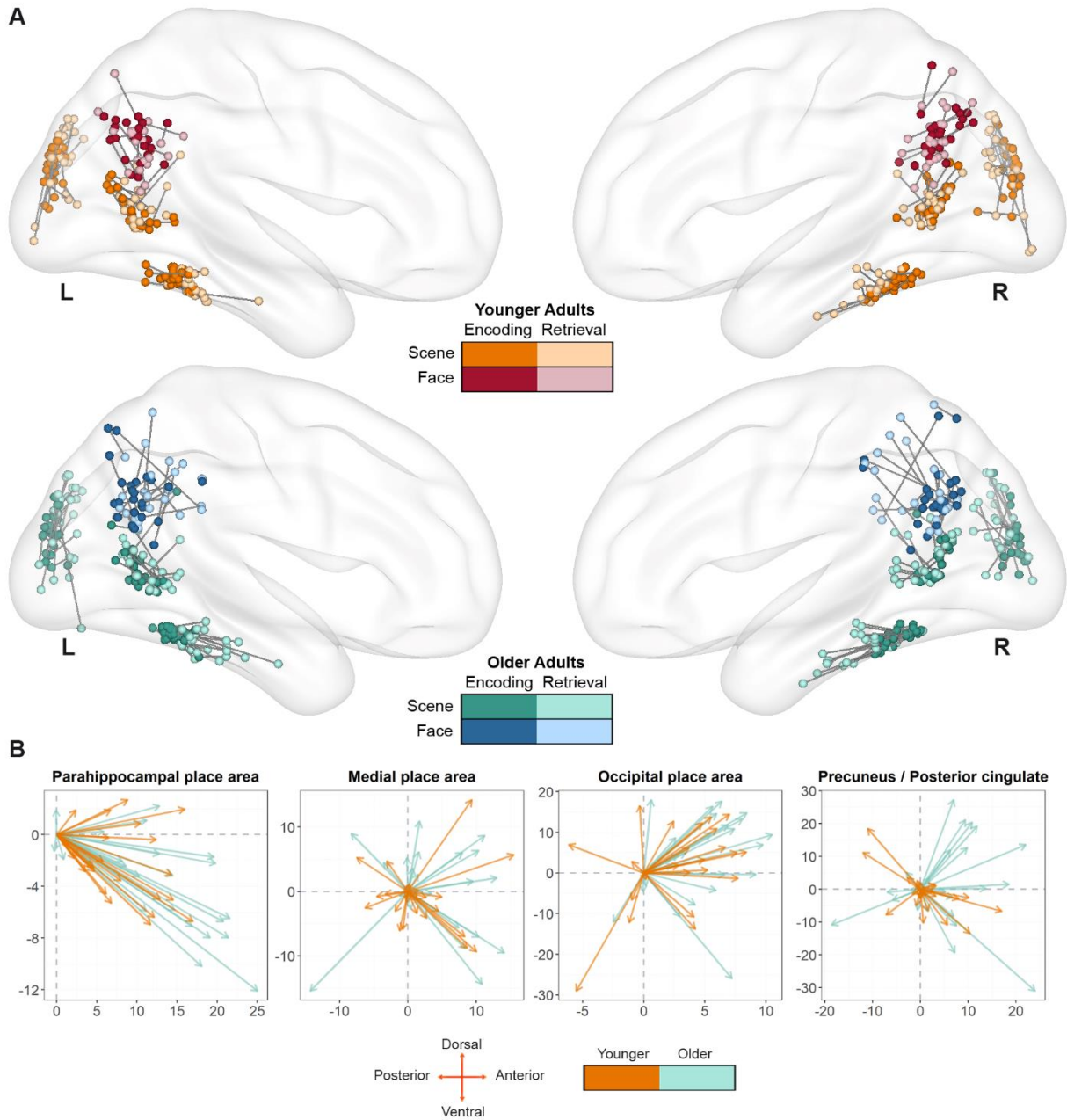
Figure 4.4. (A) Encoding and Retrieval centroids for each subject plotted on a medial view of the brain surface template provided by BrainNet (Xia et al., 2013). Each subject's centroid pair is linked with a line. **(B)** Retrieval-related shift (in mm) of the retrieval centroid (arrow) relative to the encoding centroid (origin) for each subject, collapsing across the two hemispheres.

The shift metrics were entered into a 2 (Age group) x 4 (ROI) x 2 (Hemisphere) mixed effects ANOVA. This revealed significant main effects of ROI ($F_{(2.25, 103.65)} = 14.672$, $p < 0.001$, partial-$\eta^2 = 0.242$), and age group ($F_{(1,46)} = 12.897$, $p = 0.001$, partial-$\eta^2 = 0.219$). The main effect of hemisphere was not significant, ($F_{(1,46)} = 2.855$, $p = 0.098$, partial-$\eta^2 = 0.058$), and neither were any of the two- or three-way interactions ($p > 0.456$). The main effect of age group is indicative of a greater anterior shift in the older relative to younger adults and the absence of an ROI x age group interaction indicates that this age difference did not differ according to ROI (see Figure. 4.5-A). The main effect of ROI reflected the fact the anterior shift was greater in the PPA than in the remaining ROIs. However, when assessed across all participants, the shift was robust in every ROI (PPA: $t_{(47)} = 10.826$, $p < 0.001$; OPA: $t_{(47)} = 7.221$, $p < 0.001$; MPA: $t_{(47)} = 2.943$, $p = 0.005$; PCU: $t_{(47)} = 2.914$, $p = 0.005$) Since no hemisphere effects in the magnitude of the shift were identified (see Bainbridge et al., 2019 and Steel et al., 2020 for closely similar findings), subsequent analyses were performed averaging across the hemispheres.

4.3.4   Relationship Between Anterior Shift and Memory Performance

We performed a series of multiple regression analyses to examine whether the retrieval-related anterior shift covaried across participants with their memory performance. Separate regression models were constructed to predict Pr (collapsed across image category) and pSR, using age group, the anterior shift in each ROI, and their interaction as predictors. The interaction term was included in the models to examine whether any relationships between the anterior shift and memory performance were moderated by age group. If the term was not significant, the regression analysis was followed-up by computing the partial correlation between the anterior shift and memory, controlling for age group. Considering that these analyses were exploratory in nature, we assessed the significance of any findings after Bonferroni correction for family-wise error (8 tests; corrected significance level: $p < 0.00625$). For completeness, effects that achieved significance before correction are also reported; these findings should however be interpreted with caution and are not discussed further.

The interaction term in the regression model predicting Pr from the predictors of age group and the anterior shift in the face-selective PCU was significant before ($p = 0.033$) but not following

correction ($p_{(corrected)} = 0.264$). The interaction terms in the remaining regression models were not significant ($p > 0.052$ before correction). Thus, there was little evidence to suggest that age group moderated any potential relationships between the anterior shift and memory performance. Therefore, as noted previously, we went on to examine partial correlations between anterior shift metrics and memory performance, controlling for the influence of age group.

The only partial correlation to survive correction was that between the PPA anterior shift and pSR ($r_{partial} = -0.421$, $p = 0.003$, $p_{(corrected)} = 0.024$). This result (see Figure 4.5-B) reflected the fact that, regardless of age group, a greater PPA anterior shift was associated with relatively lower source memory performance. The correlation remained significant when either encoding- or retrieval-related selectivity (see below) was included as an additional covariate ($r_{partial} = -0.409$, $p = 0.005$ and $r_{partial} = -0.476$, $p < 0.001$ respectively). Additionally, the MPA anterior shift exhibited a sizeable negative correlation with Pr ($r_{partial} = -0.377$, $p = 0.009$), but this narrowly failed to survive correction ($p_{(corrected)} = 0.072$). A positive correlation between pSR and the shift in the PCU ($r_{partial} = 0.316$, $p = 0.031$) also failed to survive correction ($p_{(corrected)} = 0.248$). No other significant correlations were identified ($p > 0.120$, $p_{(corrected)} = 0.960$). In summary, after correcting for family-wise error, a single correlation met our criterion for statistical significance: an age-invariant correlation between the PPA anterior shift and pSR.
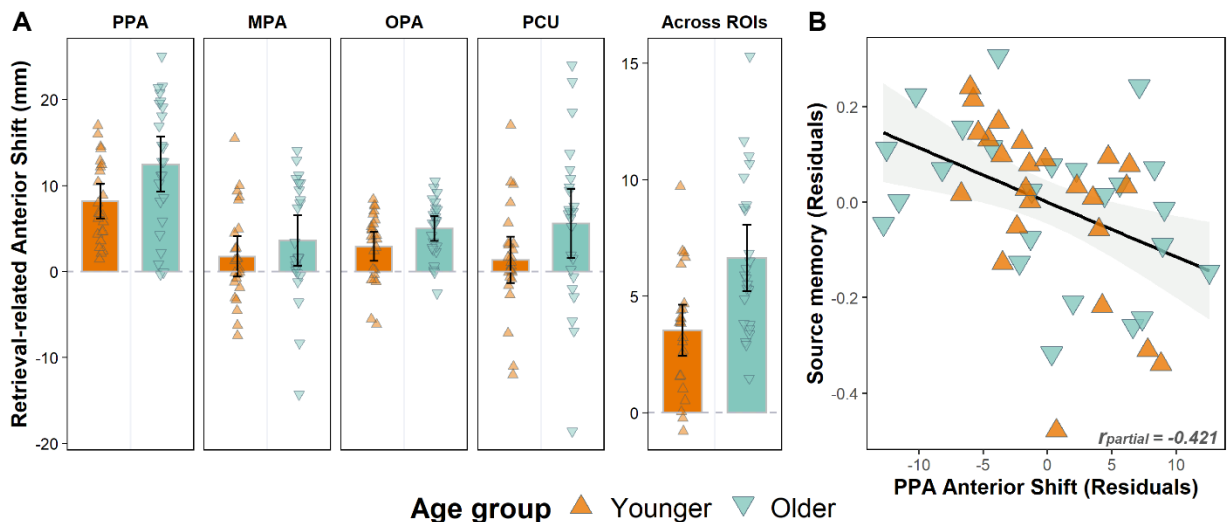
Figure 4.5. (A) The anterior shift plotted separately for younger and older adults in each ROI. The distance values are plotted after collapsing across hemispheres, and an additional panel is provided

illustrating the distances after collapsing across all ROIs to illustrate the main effect of age. Error bars signify 95% confidence intervals. (**B**) Age-invariant relationship between retrieval-related anterior shift in the PPA and source memory performance.

4.3.5   Age Differences in the Localization of Peak Encoding and Retrieval Selectivity

Group differences in the anterior shift might have arisen due to differences in the localization of the peaks of either encoding or retrieval selectivity (or a combination of the two effects). To examine whether younger and older adults differed in respect of the localization of encoding or retrieval peaks, we entered the Y coordinates of the centroids that were employed to compute the anterior shift metrics into a 2 (age) x 2 (phase; encoding vs. retrieval) x 4 (ROI) ANOVA. The ANOVA revealed a main effect of phase ($F_{(1,46)} = 138.763$, $p < 0.001$, partial-$\eta^2 = 0.751$) reflective of more anterior coordinates at retrieval relative to encoding, a main effect of age ($F_{(1,46)} = 7.973$, $p = 0.007$, partial-$\eta^2 = 0.148$) indicative of more anterior coordinates for older relative to younger adults and, of necessity, a main effect of ROI ($F_{(1,46)} = 994.765$, $p < 0.001$, partial-$\eta^2 = 0.956$). The ANOVA also identified a significant phase x age interaction ($F_{(1,46)} = 12.897$, $p < 0.001$, partial-$\eta^2 = 0.219$) and a significant phase x ROI interaction ($F_{(3,103.65)} = 14.672$, $p < 0.001$, partial-$\eta^2 = 0.242$). Neither the ROI x age nor the three-way interaction were significant ($F_{(3,103.65)} = 1.554$, $p = 0.211$, partial-$\eta^2 = 0.033$ and $F_{(3,103.65)} = 0.534$, $p = 0.6091$, partial-$\eta^2 = 0.011$, respectively).

The phase x ROI interaction reflected the fact that, as is already reported above, the anterior shift was significantly greater in the PPA than the remaining ROIs. The phase x age interaction was followed-up by examining the age differences in average Y coordinates for study and test. Age differences were non-significant for the study phase coordinates (across ROIs: $t_{(45.38)} = 0.312$, $p = 0.756$; min $p = 0.181$ for individual ROIs). There was however a robust age effect at test, driven by relatively more anterior coordinates in older than younger adults (across ROIs: $t_{(37.43)} = 3.702$, $p < 0.001$). Thus, the age effect in the anterior shift was driven by age differences in the localization of peak selectivity at retrieval rather than at encoding. These findings are illustrated in Figure 4.6-A.

4.3.6 Age differences in neural selectivity and the relationship with anterior shift and memory

Next we examined whether there were age differences in peak neural selectivity identified in the searchlights used to construct the centroids, and whether the degree of selectivity was associated with age differences in the anterior shift and memory performance (Figure 4.6-B). This analysis was motivated by prior findings that neural selectivity is reduced in older age (e.g., at encoding see Srokova et al., 2020; and at retrieval see Hill et al., 2021), raising the posibility that age differences in anterior shift may arise due to age differences in neural selectivity. We extracted the average parameter estimates for scene- and face-selective contrasts within the searchlights used to construct the encoding and retrieval centroids. We entered these into a 2 (age) x 2 (phase) x 4 (ROI) ANOVA. The ANOVA gave rise to a significant main effect of phase, reflecting larger parameter estimates at retrieval ($F_{(1,46)} = 6.088$, $p = 0.017$, partial-$\eta^2 = 0.117$), a main effect of age, reflecting greater selectivity in younger adults ($F_{(1,46)} = 18.724$, $p < 0.001$, partial-$\eta2 = 0.289$), and a main effect of ROI ($F_{(3,87.55)} = 9.633$, $p < 0.001$, partial-$\eta^2 = 0.173$). The ROI x age and the phase x age interactions were not significant ($F_{(1,46)} = 0.411$, $p = 0.654$, partial-$\eta^2 = 0.009$ and ($F_{(3,87.55)} = 2.398$, $p = 0.128$, partial-$\eta^2 = 0.050$, respectively). The phase x ROI and the phase x ROI x age interactions were both significant ($F_{(3,87.55)} = 25.132$, $p < 0.001$, partial-$\eta^2 = 0.353$ and ($F_{(3,87.55)} = 3.771$, $p = 0.026$, partial-$\eta^2 = 0.076$, respectively).

In light of these findings, we went on to perform a series of independent samples t-tests to examine age differences in selectivity at encoding and retrieval. At encoding, selectivity was lower in older relative to younger adults in the scene-selective PPA ($t_{(41.16)} = 5.459$, $p < 0.001$), MPA ($t_{(41.70)} = 3.230$, $p = 0.002$) and OPA ($t_{(44.31)} = 5.683$, $p < 0.001$), but not in the face-selective PCU ($t_{(40.49)} = 0.954$, $p = 0.346$). At retrieval, there were no age differences in any of the scene-selective ROIs: (PPA ($t_{(38.10)} = 0.967$, $p = 0.339$), MPA ($t_{(45.28)} = 1.423$, $p = 0.162$) and OPA ($t_{(46.00)} = 0.815$, $p = 0.162$). There was, however, a significant age difference in the PCU, indicating greater selectivity in younger adults ($t_{(33.10)} = 2.181$, $p = 0.036$).

To examine whether neural selectivity was related to the anterior shift, we correlated (controlling for age group) the anterior shift metric for a given ROI with its selectivity metric at

either encoding or retrieval. In none of the ROIs did neural selectivity correlate with the magnitude of the shift ($ps > 0.170$).

Lastly, we also perfomed correlation analyses to examine whether either the encoding or retrieval selectivity metrics covaried with memory performance. In neither case was the partial correlation (controlling for age group) significant ($r_{partial} = 0.187$, $p = 0.207$, $r_{partial} = 0.258$, $p = 0.079$).
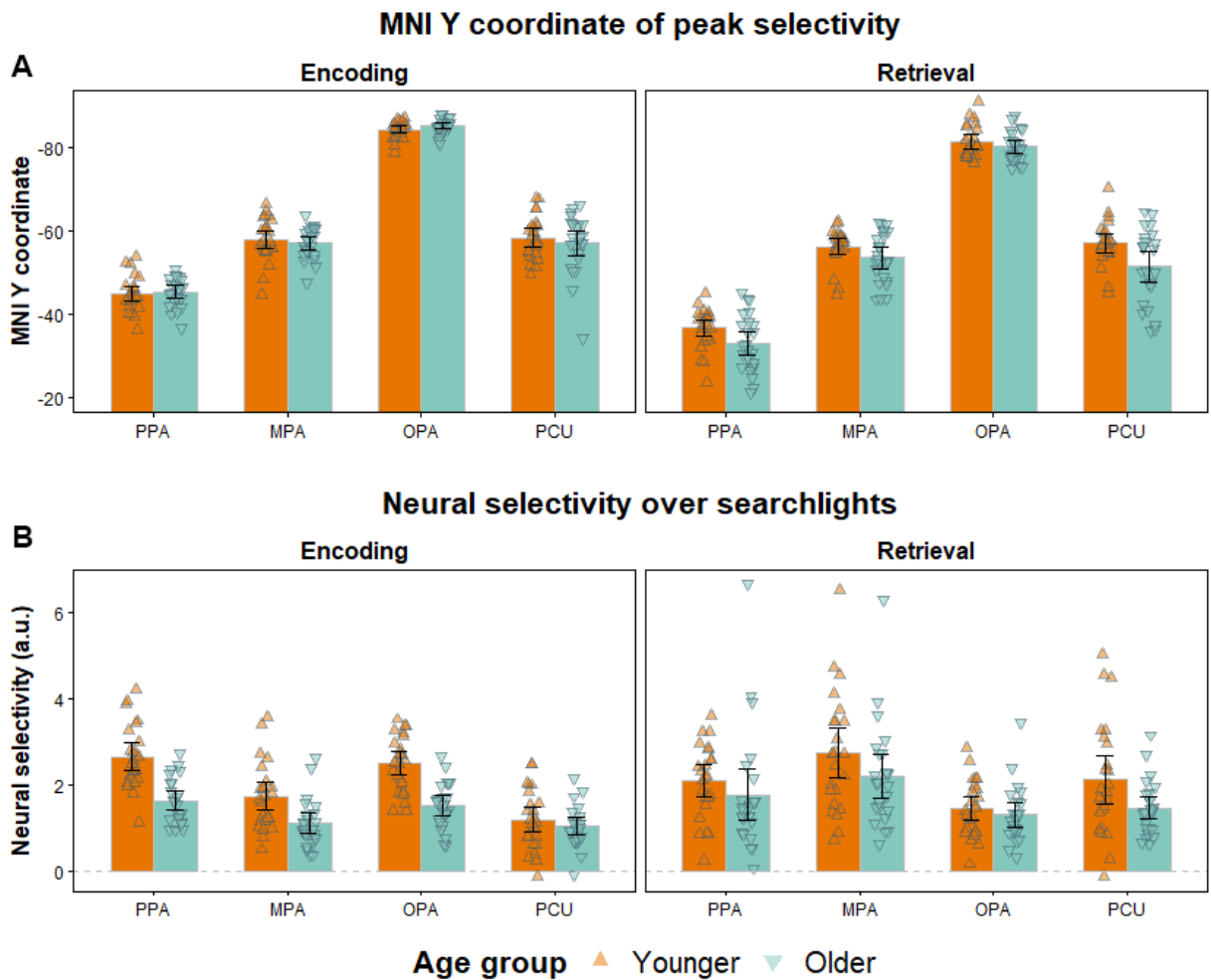
Figure 4.6. (A) Localization of peak selectivity at encoding and retrieval in younger and older adults. The figure depicts the Y coordinate in MNI space of the encoding and retrieval centroids. **(B)** Average neural selectivity over the searchlights which were used to define the encoding and retrieval centroids. In both panels, error bars signify 95% confidence intervals.

4.4   Discussion

In the present study, we examined age effects on the retrieval-related anterior shift and its relationship with memory performance. In both young and older adults, we identified robust evidence for an anterior shift in two scene-selective cortical regions (PPA & OPA). In addition, in older adults only, the shift was reliable for scenes in the MPA and for faces in the PCU. Of importance, independently of ROI, the anterior shift was robustly larger in the older group. Moreover, the magnitude of the shift in the scene-selective PPA demonstrated an age-invariant, negative correlation with source memory performance. In sum, consistent with the predictions outlined in the Introduction, the retrieval-related anterior shift covaried positively with increasing age and negatively with memory performance.

The earliest findings suggestive of systematic differences in the loci of cortical activity associated with perception versus memory were reported in studies contrasting color perception and color imagery (e.g., Chao & Martin, 1999; Simmons et al., 2007). Extending these findings, more recent research has reported that regions recruited during scene retrieval and scene imagery are localized anteriorly to the regions recruited during scene perception (e.g., Chrastil 2018; Silson et al., 2019; Bainbridge et al., 2021; Steel et al., 2021). These findings are consistent with the proposal that scene-selective cortical regions can be sub-divided into two networks (Baldassano et al., 2016). The 'posterior scene network' is held to include retinotopically organized regions responsible for processing visual input, while the 'anterior network', which includes the hippocampus as one of its constituents, supports scene representations retrieved from memory as well as spatial navigation and other memory-guided behaviors (e.g., visual exploration). This subdivision is held to be honored within the PPA, which has been partitioned into posterior (perceptual) and anterior (mnemonic) sub-divisions (Baldassano et al., 2016). However, our findings, which demonstrate that the size of the anterior shift is sensitive to age and memory performance, challenge the view that regions such as the PPA can be dichotomized into functionally distinct posterior and anterior sub-regions. Furthermore, findings of analogous shifts in other scene-selective cortical regions such as the OPA (see Figure 4.5-A), and for other perceptual categories (Lee et al. 2012), add further weight to the proposal that the anterior shift

reflects more than a segregation between two functional networks (see also the discussion of the present findings for faces below).

In a recent review, Favila and colleagues (2020) proposed that mnemonic representations undergo a 'transformation', with perceived and retrieved representations differing in terms of their quality, content and amount of information. This transformation reflects a differential weighting of episodic attributes, such that a retrieved representation is biased towards the representation of 'high-level' conceptual information at the expense of lower-level perceptual detail. The differential emphasis on higher- versus lower-level features is reflected in the localization of concurrent cortical activity. Notably, it has been conjectured that cortical regions extending along the posterior-anterior axis are hierarchically organized, such that more posterior regions support the processing of relatively low level stimulus properties, while more anterior regions support higher-level semantic or conceptual processing (e.g. Simmons et al., 2007, Peelen & Caramazza, 2012). This proposal implies the existence of a processing gradient along which modality-specific perceptual properties are increasingly 'abstracted away' at the expense of higher-level conceptual features (see Introduction). This 'abstraction account' leads to the prediction that the magnitude of the anterior shift will vary depending on whether a retrieval test requires retrieval primarily of conceptual information as opposed to high-fidelity, modality-specific detail (Simmons et al., 2007).

To date, reports of the anterior shift have been confined to young adults. The data from the present study extend these findings by demonstrating that the shift is exaggerated in older adults. As noted above, the abstraction account of the shift implies that it reflects a representational 'transformation' that de-emphasizes perceptual detail. This account allows for a simple explanation of the present effects of age on the anterior shift, given the extensive evidence that retrieved episodic information contains less detail, and is more 'gist-based' in older than younger adults (Koustaal & Schacter, 1997; Dennis et al., 2007; 2008, Gallo et al., 2019). That is, whereas memory for the gist of an event is relatively spared in older adults, the retention of more fine-grained, individuating features of an episode appears to be especially susceptible to increasing age (Nilakantan et al., 2018; Korkki et al., 2020). We propose that the neural expression of this age

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difference in retrieved episodic content accounts for the exaggerated anterior shifts evident in our older sample in the present study.

Of importance, we identified a reliable anterior shift not only in scene selective cortical regions, but in the face selective PCU also, albeit in older adults only. Our failure to identify an anterior shift for faces in the PCU in younger adults is consistent with prior findings that face stimuli do not elicit a retrieval-related anterior shift in this population (Steel et al., 2021). There are two possible explanations for why we find an anterior shift in the PCU for faces in older but not younger adults. First, it could be that this effect is specific to older adults; that is, for unknown reasons, younger adults did not retrieve face representations that were abstracted away from the original stimulus event. Alternatively, the seeming absence of a PCU effect in the younger adults might merely be a consequence of the fact that the shift in this region is smaller than that in other regions (compare, for example, the magnitude of the shift in the PPA vs. the PCU in the older participants illustrated in Figure 4.5-A). By this argument, a shift might be detectable in the PCU of young adults given sufficient spatial resolution and statistical power.

Whereas the notion of a cortical posterior-anterior gradient from perception to memory is well supported, the question whether the magnitude of the retrieval-related anterior shift impacts memory performance has been largely unexplored (but see Davis et al., 2021). Here, we sought for relationships between the anterior shift and memory performance on the assumption that memory for the details of an event is more likely to be accurate when there is strong overlap (indexed by a relatively small anterior shift) between experienced and retrieved event representations (see Introduction). Consistent with this prediction, we identified a negative, age-invariant correlation between the PPA anterior shift and source memory performance. That is, regardless of age group, a greater anterior shift was associated with poorer memory for the study pairs. This finding supports the proposal that the localization of retrieval-related neural activity has implications for the content of retrieval, and it is also consistent with the notion that more anterior regions of the PPA support mnemonic representations containing relatively sparse perceptual detail (Bainbridge et al., 2021; Steel et al., 2021). Nonetheless, as alluded to earlier, the finding that the shift (at least, in the PPA) both correlates with memory performance and is

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enhanced in older adults suggests an intriguing mechanism that might partially account for age-related memory decline.

It is currently unclear why a relationship between the magnitude of the anterior shift and memory performance was only evident in the PPA. One possibility is that the anatomy of the parahippocampal and fusiform gyri (i.e., their length and orientation along the posterior-anterior axis) is well suited to detecting functionally significant variance in the shift across participants. By this argument, similar relationships might emerge for other ROIs in more highly-powered, higher resolution studies. Another possibility is that that the PPA supports one or more functions that are especially important for successful episodic memory encoding and retrieval. One such function, for example, is the processing of mnemonically-relevant contextual information in concert with the hippocampus (Aminoff et al., 2013). By this account, the scene-related anterior shift in the PPA is a reflection of the role of this region in supporting the encoding and retrieval of contextual information more generally. From this perspective, we think that it is unlikely to be a coincidence that memory performance is also predicted by metrics of scene selectivity derived from the PPA, with no evidence for such a relationship in other category-selective cortical regions (see Koen et al., 2019; Srokova et al., 2020).

In conclusion, the present study revealed robust age differences in the retrieval-related anterior shift in both scene-and face-selective cortical regions. We also demonstrate that the shift is (negatively) associated with source memory performance, supporting the notion that low- and high-level stimulus information is represented in different cortical regions at multiple levels of abstraction along the posterior-anterior axis. Future research should examine whether the age effects observed here extend to other stimulus categories (such as objects) or other sensory modalities (e.g. auditory stimuli). In sum, the findings reported here shed light on the functional significance of the anterior shift in relation to memory accuracy and potentially provide an increased understanding of the factors contributing to age-related memory decline.

CHAPTER 5

EXAMINING THE EFFECTS OF AGE ON NEURAL DIFFERENTIATION

AT THE LEVEL OF INDIVIDUAL STIMULUS EXEMPLARS

This chapter is being prepared for submission to a scientific journal by me (Sabina Srokova) as the first author, along with co-authors A.N.Z. Aktas, J.D., Koen, and M.D. Rugg who provided substantial input via their contributions to conceptualization, data collection and edits of the presented text.

5.1   Introduction

As reviewed more fully in Chapter 1, increasing age is associated with a progressive decline in many cognitive abilities, including the ability to recollect previously experienced events, i.e., episodic memory (Nilsson, 2003; Nyberg et al., 2012). Cognitive aging has a detrimental effect on every-day activities and detracts from the quality of life even in the absence of pathology. For that reason, understanding the factors that contribute to age-related cognitive decline is a pressing concern. One potential factor which has been a subject of substantial interest in the recent years is the phenomenon of age-related neural dedifferentiation (for reviews see Koen & Rugg, 2019; Koen et al., 2020). As discussed in Chapters 1 and 2, neural dedifferentiation is characterized by reductions in the neural selectivity and fidelity of neural representations with increasing age.

The evidence for neural dedifferentiation at the level of stimulus 'categories' is rooted in studies which operationalized neural dedifferentiation as a reduction in the selectivity of fMRI BOLD responses elicited by different categories of visual stimuli (see Chapter 2). The first study to report evidence for age-related neural dedifferentiation at the level of stimulus categories was that of Park et al (2004). In this study, older relative to younger adults demonstrated reduced fMRI BOLD responses to images of houses, faces, objects, and pseudowords. Research over the past 20 years has largely corroborated this evidence by demonstrating category-level age-related neural dedifferentiation for scenes (Voss et al., 2008; Carp et al. 2011; Zheng et al., 2018; Koen et al., 2019; Srokova et al., 2020) and faces (Park et al., 2004, 2012; Voss et al., 2008; but see: Payer, et

al., 2016; Srokova et al. 2020), but with null effects in object- and word-selective cortical regions (Chee et al., 2006; Voss et al., 2008; Zheng et al., 2018; Koen et al., 2019; for discussion, see Srokova et al., 2020; Chapter 2).

A computational model of cognitive aging proposed by Li and colleagues (Li et al., 2001; Li and Rieckmann, 2014; see Chapter 1) posits that age-related neural dedifferentiation, and by extension the behavioral effects of cognitive aging, arise from a decline in the integrity of ascending neuromodulatory systems, especially the dopaminergic system. The reduction in dopamine availability is assumed to lead to the increase in neural noise, which in turn reduces the signal-to-noise ratio of neuronal firing. Although this model has motivated researchers to investigate neural dedifferentiation for stimulus categories, the model also implies that cognitive aging should be associated with a reduction in the fidelity of neuronal representations for individual stimulus exemplars (Koen & Rugg, 2019; Koen et al., 2020). However, evidence for neural dedifferentiation at the categorical level does not directly testify to the existence of neural dedifferentiation at the item level.

Several studies have examined age-related neural dedifferentiation for individual exemplars, yielding mixed findings. In one study, Goh and colleagues (2010) examined item-level neural dedifferentiation by taking advantage of the well documented phenomenon of 'repetition suppression', a reduction in the neural response elicited by the repeated presentation of a stimulus exemplar (Barron et al., 2016). With this approach, neural differentiation can be operationalized by comparing the repetition suppression effects for identical stimuli versus perceptually similar stimuli. The underlying rationale is that reduced fidelity of neural representations (i.e., neural dedifferentiation) should lead to neuronal activation which is non-specific to the presented item. The subsequent presentation of a similar foil then re-engages these neurons, leading to an overlap in neural representations, and thus enhancing the repetition suppression effects for perceptually similar lure exemplars. Accordingly, Goh and colleagues reported null effects of age for repetitions of identical faces in the face-selective fusiform face area, but enhanced repetition suppression effects for similar (morphed) faces in older relative to younger adults. This approach has also been employed in studies examining age differences in pattern separation processes supported by the hippocampus and the entorhinal cortex, reporting reduced pattern separation (greater repetition

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effects to perceptual lures) in older adults (Yassa et al., 2010; 2011; Reagh et al., 2016; Stark & Stark, 2017). However, these latter studies did not control for the possibility of reduced fidelity of neural representations in the cortical regions upstream of the hippocampus (Murray et al., 2017). Given the evidence for age differences in the fidelity of neural representations in extrastriate visual cortex, it is possible that the decline in hippocampal pattern separation is confounded by the attenuated fidelity of neural representations outside of the hippocampus.

Given the scarcity and conflicting nature of prior evidence, the present study aimed to fill an important gap in the literature by examining age differences in item-level neural selectivity. Here, younger and older adults underwent fMRI while they viewed images of scenes and objects. The individual exemplars were either: i) followed by an exact repetition of the item, ii) followed by the presentation of a visually similar exemplar, or iii) went on to be tested in an out-of-scanner memory test. Item-level dedifferentiation was operationalized by contrasting age differences in fMRI BOLD repetition suppression effects for identical repeats versus visually similar exemplars. The experiment had two primary aims: First, we predicted that repetition suppression would be equivalent in younger and older adults for identical exemplars while repetition suppression effects for perceptually similar items would be enhanced in the older group. Second, as discussed above and in Chapter 2, prior research suggests that category-level age-related neural dedifferentiation is not ubiquitous for all stimulus categories. Therefore, the second aim of the study was to examine whether any effects of age on item-level dedifferentiation are moderated by stimulus category.

5.2   Materials and Methods

5.2.1   Participants

Twenty-five young and 25 older adults participated in the study. One young and one older adult were excluded from the analyses due to incidental MR findings, resulting in a final sample of 24 young and 24 older adults. Participants were recruited from the University of Texas at Dallas and from the surrounding Dallas metropolitan area and were compensated for their time at a rate of \$30/hour and up to \$30 for travel. Demographic information and neuropsychological test performance for the final sample are reported in Table 5.1. Participants were right-handed, had normal or corrected-to-normal vision, and were fluent English speakers before the age of five.

None of the participants had a history of neurological of psychiatric disease, substance abuse, diabetes, or current or recent use of prescription medication affecting the central nervous system. All participants undertook a neuropsychological test battery prior to the MRI session, and a set of inclusion and exclusion criteria were employed to minimize the likelihood of including older participants with mild cognitive impairment or early dementia. All participants provided written informed consent before participation in accordance with the requirements of the Institutional Review Board of the University of Texas at Dallas.

5.2.2 Neuropsychological Testing

Participants completed our laboratory's standard neuropsychological test battery on a separate day prior to the MRI session. The assessment battery consists of the Mini-Mental State Examination, the California Verbal Learning Test II (CVLT; Delis et al., 2000), Wechsler Logical Memory Tests 1 and 2 (Wechsler, 2009), the Symbol Digit Modalities test (SDMT; Smith, 1982), the Trail Making Tests A and B (Reitan and Wolfson, 1985), the F-A-S subtest of the Neurosensory Center Comprehensive Evaluation for Aphasia (Spreen and Benton, 1977), the Forward and Backward digit span subtests of the revised Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1981), Category fluency test (Benton, 1968), Raven's Progressive Matrices List I (Raven et al., 2000), and the Test of premorbid functioning (TOPF; Wechsler, 2011). Participants were excluded prior to the fMRI session if they performed more than 1.5 SD below age norms on two or more non-memory tests, if they performed more than 1.5 SD below the age norm on at least one memory-based neuropsychological test, or if their MMSE score was less than 26. The neuropsychological test scores were missing for one participant (younger adult male).

5.2.3 Experimental Procedure

5.2.3.1 Materials

Experimental stimuli were presented using PsychoPy v2021.1.3 (Pierce et al., 2019). The study phase was completed inside the MRI scanner. Experimental stimuli were projected onto a translucent screen (41 cm x 25 cm; 1920 x 1080 pixels resolution) placed at the rear end of the scanner bore and viewed via a mirror mounted on the head coil (viewing distance of approx. 105

cm). The critical experimental stimuli were presented on a gray background and consisted of images of objects and scenes which were resized to fit in a frame subtending 256 x 256 pixels (visual angle: 3° x 3.2°). During the study phase, participants viewed a total of 160 scene trials and 160 object trials. For a given image category, out of the 160 trials, 24 of the stimuli ('first presentation' trials) were re-presented ('exact repeats') while another 24 stimuli were 'repeated' as perceptually similar lures ('lures'). An additional 72 stimuli were presented once only, and these items were used as test items in the subsequent memory task. Thirty-six of to-be-tested items were presented at test as identical targets, and 36 were tested as perceptually similar lures (see below). Lastly, 126 null trials, comprising a white fixation cross presented at the center of the display, were randomly interspersed among the critical trials of the study phase.

The post-scan memory test was completed on a Dell laptop with a 17-inch display and a resolution of 1920 x 1080 pixels. During the test phase, participants viewed a total of 108 images of scenes and 108 images of objects. Out of the 108 trials belonging to a given category, 36 were repetitions of images that the participant had viewed during the study phase ('target old'), 36 trials were images that were perceptually similar to previously viewed study images ('lure old'), and 36 trials were presentations of new images.

The stimulus pool described above was used to create 24 stimulus lists which were assigned to yoked pairs of younger and older adults. The study lists were divided into 9 blocks (scanner runs) while the test lists consisted of 2 blocks. For all stimulus lists, the stimuli were pseudorandomized such that participants viewed no more than 3 consecutive trials of the same visual category or trial type, and no more than 2 consecutive null trials. To ensure that the neural similarity between the first presentation trial and its corresponding lure or exact repeat was not driven by the within-session autocorrelation between trials (Mumford et al., 2014), lures and exact repeat trials were always presented in the next consecutive scanner run while ensuring that the lag between first presentations and either exact or lure repetitions conformed to a rectangular distribution of 18 to 42 trials (mean = 30). Thus, the first study list did not contain any repetition or lure trials, and the last run never contained a first presentation trial. An additional 24 filler trials were randomly interspersed within the first and last blocks to ensure that item types remained balanced.

5.2.3.2 Study and Test Phase

A schematic of the study and test tasks, and examples of the experimental stimuli, are illustrated in Figure 5.1. Participants received instructions for the study phase and completed a short practice run prior to entering the scanner. The study phase consisted of a total of 9 scanner runs lasting 4 minutes and 38 seconds each. Each study trial began with a red fixation cross presented in the middle of the screen for 500 ms, followed by the image for 2 seconds, and then a white fixation cross for an additional 2 seconds. Participants had a total of 4 seconds following the onset of the image to indicate whether the presented scene or object would be considered 'indoor' or 'outdoor'. The indoor and outdoor judgements were mapped to the right and middle finger of the right hand with finger assignment counterbalanced across participants. Responses were made using a scanner compatible button box.

The instructions and a practice run for the test phase were administered immediately following the MRI session outside of the MR scanner. The test phase consisted of 2 blocks lasting approximately 8 minutes each. Like the study phase, each test phase trial began with a red fixation cross lasting 500 ms, followed by the test image for 2 seconds, and then a white fixation cross for an additional 2 seconds, thus providing a 4 second response window. Participants were instructed to indicate whether the test image was either the same as one they had viewed at study ('old'), similar to an image they had viewed at study ('similar'), or a completely new exemplar. The three response alternatives were mapped onto the index, middle, and ring fingers of the right hand with finger assignment counterbalanced across participants.
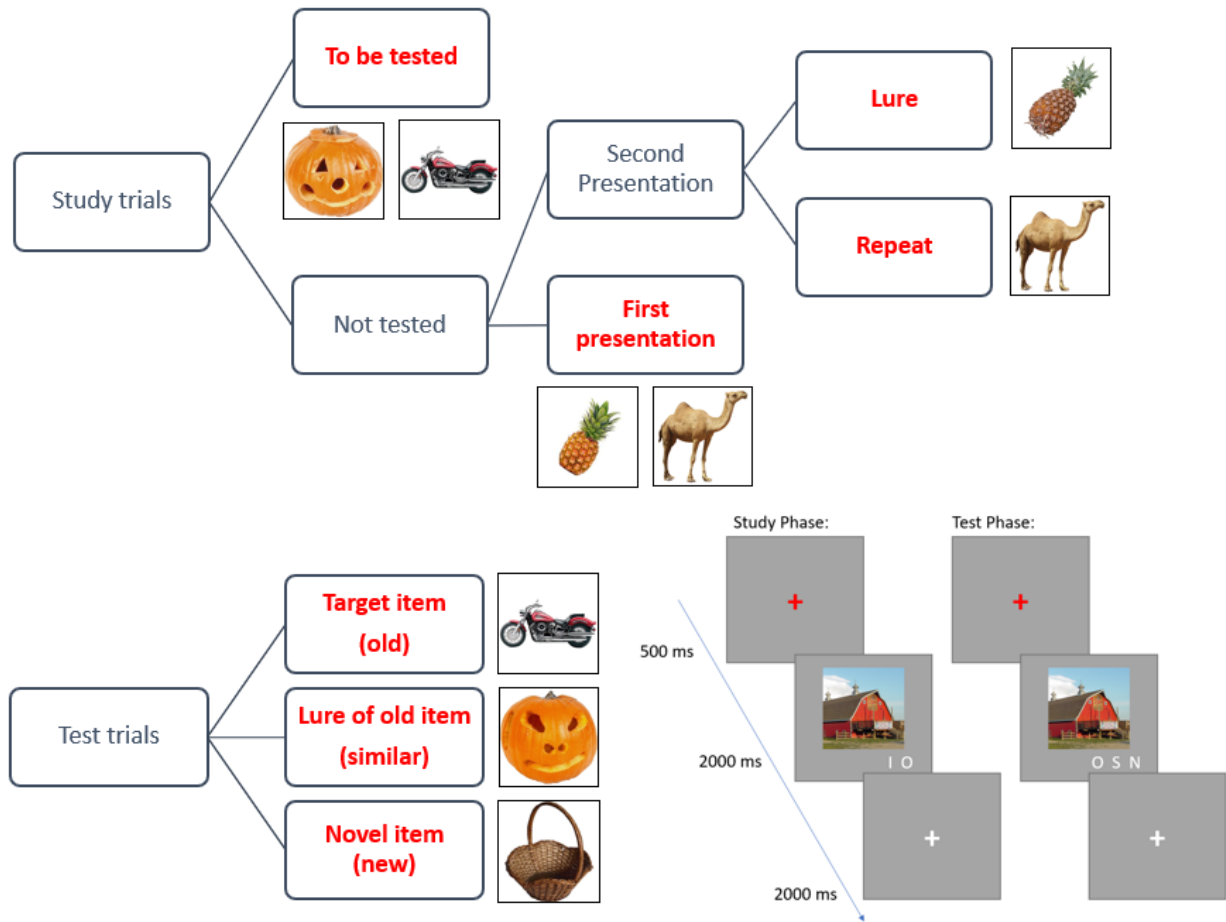
Figure 5.1. A schematic illustrating the trial types in the study and test phases along with an illustration of an example trial from the study and test phase. Study trials could be categorized into 5 trial types: to-be-tested trials, first presentation trials for images which are to be subsequently repeated, first presentation trials which are followed by a presentation of a perceptually similar lure, and second presentation trials (either identical repeats or perceptual lures of the first presentation). At test, trials were binned into three trial types: target items (previously studied exemplars), lure of old items (similar to a studied exemplar), or new items. At study, participants made indoor/outdoor judgements, and at test they made old/similar/new judgements.

5.2.3.3 Online Similarity Rating Task

As discussed above (see Introduction), one of the aims of the present study was to determine whether metrics of item-level neural differentiation for scene and object exemplars are differentially impacted by age. To ensure that any potential effects of category did not arise merely because of categorical differences in perceived visual similarity between items and their lures, we collected similarity ratings between perceptually similar images from 210 online participants. The

similarity rating task was presented using PsychoJS hosted on Pavlovia.org. Participants were recruited through Prolific.co, compensated $15/h, and provided informed consent in accordance with the requirements of the Institutional Review Board at the University of Texas at Dallas.

We collected ratings on a total of 86 scene and 86 object perceptually similar triplets which were presented in pairs such that, given a triplet 'ABC', the similar images were presented in three trials 'AB', 'BC', 'AC' randomly interspersed within the stimulus list. The stimulus list included an additional 68 perceptually dissimilar image pairs which served as 'catch trials' to ensure that participants were paying attention to the stimuli. Therefore, the entire stimulus list included a total of 516 lure pairs and 68 catch pairs. Given the length of the stimulus list, we chose to split the stimulus set into two lists of 258 lure and 34 catch pairs while still maintaining that all similar image pairs that belonged to a single triplet were presented in a single list. Each participant was presented with one list, such that each image pair was assessed by a total of 105 raters. Prior to the similarity judgment task, participants completed an instruction phase and a small number of practice trials to familiarize themselves with the procedures and the rating scale. Each critical trial began with a 500 ms red fixation cross followed by a 5-second presentation of the image pair and a continuous rating scale below. Participants used a computer mouse to place the response marker anywhere on the scale. For the purposes of the analysis of similarity ratings, this rating scale was coded to range from 0 to 10. Participants had 5 seconds in which to use a computer mouse to position the similarity marker anywhere on the rating line. The task lasted approximately 30 minutes with a 30 second break provided halfway through the task.

Figure 5.2 illustrates each participant's average similarity rating for object and scene image pairs as well as object and scene catch trials. The similarity ratings for catch trials were robustly lower relative to lure trials, indicating that participants complied with the task instructions. Across all trials, object lure pairs were on average rated as more similar than scene lure pairs ($t_{(206)} = 8.567$, $p < 0.001$). To ensure that scene and object lures employed in the fMRI experiment were matched in perceptual similarity, we followed these steps: Firstly, to decide which two images out of a given triplet would go on to be used in the fMRI experiment, we sorted the lure pairs associated with each triplet as 'most similar pair', 'middle pair', and 'least similar pair', according to their across-participant ratings. This allowed us to compare three groups of object and scene pairs

according to their mean similarities. We selected all pairs from the 'most similar' scene group, and all 'middle pairs' from the object group, resulting in a total of 86 scene and 86 object pairs. Next, we iteratively selected 60 scene and 60 object pairs until the average across-participant similarity ratings for scenes and objects were equal. The outcome of the matching procedure is illustrated in Figure 5.2-C. The average across-participant ratings to the final 60 lure pairs was 6.744 for both objects and scenes. The resultant 60 scene and 60 object lure pairs were employed in the experiment as described in the procedures above.
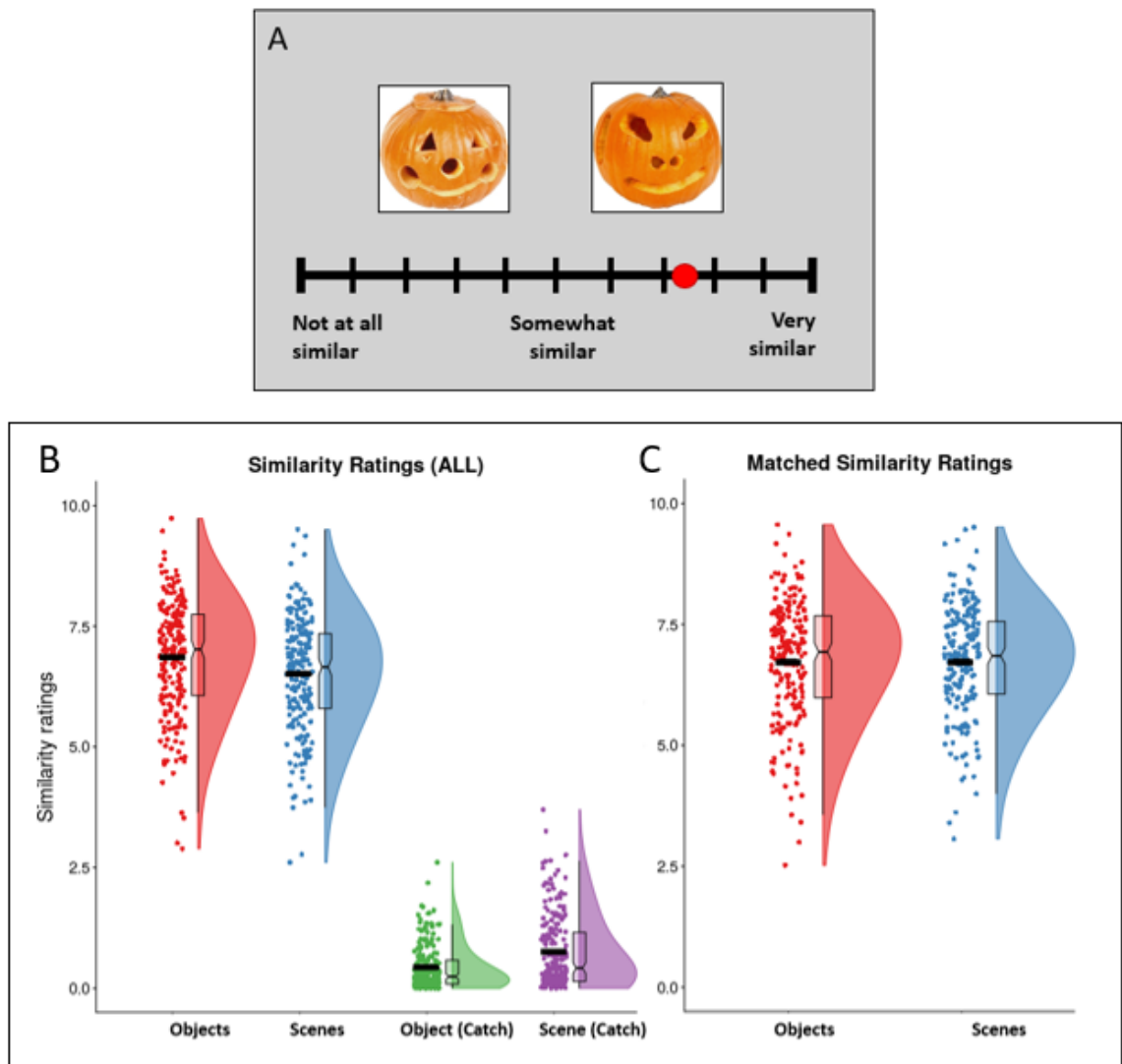
Figure 5.2. (A) An illustration of a single trial in the online similarity rating task. **(B)** The raw similarity rating scores for object and scene lures, demonstrating lower similarity ratings for scenes

relative to objects. The similarity ratings of the catch trials demonstrate that participants complied with the task instructions. **(C)** The similarity ratings of object and scenes after matching stimuli in their ratings. The dots in **(B)** and **(C)** represent the average rating for a given participant.

5.2.3.4 MRI Data Acquisition and Preprocessing

fMRI and structural data were acquired using a Siemens Prisma 3T scanner at the Sammons Imaging Center at the University of Texas at Dallas. The data were acquired with a 32-channel head coil. A whole-brain anatomical scan was acquired with a T1-weighted 3D MPRAGE pulse sequence (FOV = 256×256 mm, voxel size = $1 \times 1 \times 1$ mm, 176 slices, sagittal acquisition). A hippocampal high-resolution T2-weighted scan was acquired perpendicular to the hippocampal axis (FOV = 215 x 20 x 215 mm, voxel = 0.42 x 2 x 0.42, 20 slices). Functional data were acquired with a T2*-weighted blood-oxygen-level-dependent echoplanar imaging (EPI) sequence with a multiband factor of 3 (flip angle = 70°, FOV = 220×220 mm, voxel size = 2 x 2 x 2 mm, TR = 1.52 ms, TE = 30 ms, 66 slices). Lastly, a dual echo fieldmap sequence which matched the 3D characteristics of the EPI sequence was acquired at TEs 4.92 ms and 7.38 ms immediately after the last run of the study phase. This sequence results in two magnitude images (one per echo), and a pre-subtracted phase image (the difference of the phases acquired at each echo).

The MRI data were preprocessed using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology) and custom MATLAB code (The MathWorks). The functional data were preprocessed in 6 steps. Firstly, we employed the FieldMap toolbox in SPM to calculate voxel displacement field maps necessary for the fieldmap correction. These maps were calculated using the magnitude and phase difference images acquired in the aforementioned dual-echo fieldmap sequence. Second, the SPM's realign & unwarp procedure was applied which operates in two steps: spatial realignment of the time series registered to the mean EPI image and a dynamic correction of the deformation field using the voxel displacement maps. Thirdly, the functional images were reoriented along the anterior and posterior commissures, then spatially normalized to SPM's EPI template, and renormalized to a sample-specific EPI template according to procedures standardly employed in our laboratory (see de Chastelaine et al., 2016). Lastly, the functional data were smoothed with a 5 mm FWHM Gaussian kernel.

5.2.3.5 Whole-brain Univariate Analysis

The fMRI data were analyzed with a two-stage univariate GLM approach. At the first stage, a GLM of the study data was implemented on a subject-wise basis. The study trials were binned into 10 events of interest (5 trial types separately for scenes and objects): 1. Trials which went on to be later tested, 2. First presentation of identical repeat trials, 3. First presentation of similar lure trials, 4. Second presentation of identical repeats, 5. Second presentation of similar lure trials. Neural activity elicited by the events of interest was modeled with a boxcar function extending over the 2s period during which the image remained on the screen. The boxcar functions were convolved with a canonical hemodynamic response function (HRF) to estimate the predicted BOLD responses. Additional regressors in the design matrix were trials of no interest (filler trials and trials with missing responses), 6 motion regressors reflecting rigid-body translation and rotation, spike covariates regressing out volumes with displacement greater than 1mm or 1° in any direction, and the mean signal of each run. Prior to model estimation, the fMRI time series from each scanner run was concatenated into a single session using the *spm_fmri_concatenate* function. The parameter estimates from these first level GLMs were entered into a second-level mixed factorial ANOVA with factors of age group (2) and events of interest (10). The pre-experimentally determined voxel-wise significance threshold for whole-brain analyses was $p < 0.001$, which was combined with a cluster-wise FWE correction ($p < 0.05$) of $k > 74$.

5.2.3.6 Region of Interest Analysis

We defined four *a priori* regions of interest (ROIs) which are illustrated in Figure 5.3 (see Table 5.1 for details of their sizes). To ensure the ROIs were derived independently of the data, we employed an unpublished localizer dataset (22 participants; 14 younger and 8 older adults; see Koen et al., 2019). In this localizer task, participants viewed images of scenes, objects, and faces, and rated each image for its perceived pleasantness on a 4-point scale. The scene-selective parahippocampal place area (PPA) was defined using a scene > object + face contrast, whereas the object-selective lateral occipital complex (LOC) was derived from the object > scene + face contrast, in both cases height-thresholded at $p < 0.001$. For both ROIs, the clusters derived from the aforementioned contrasts were inclusively masked with anatomical labels derived from the

Neuromorphometrics atlas provided in SPM12. The PPA was masked using the fusiform and parahippocampal gyri, and the LOC was masked with the middle and inferior occipital gyri. The anterior (head) and posterior (body and tail) hippocampal ROIs (aHPC, pHPC, respectively) were obtained by manually tracing the hippocampus on an average T1 structural scan acquired from a large previously published dataset (de Chastelaine et al., 2012).

Table 5.1. Size (in voxels) of a-priori defined regions of interest.

	Left Hemisphere	*Right Hemisphere*
Parahippocampal place area	380	378
Lateral occipital complex	356	469
Anterior hippocampus	95	98
Posterior hippocampus	119	93
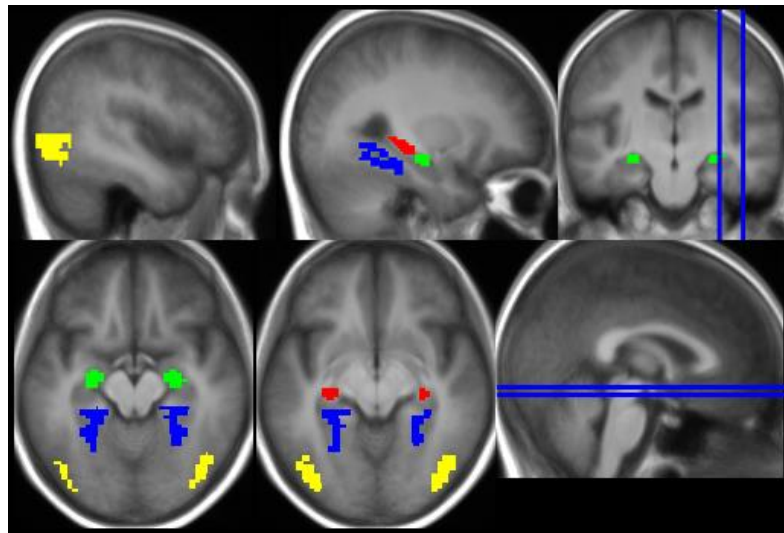
Figure 5.3. Regions of interest plotted on a sample specific T1 template. aHPC (green), pHPC (red), PPA (blue), LOC (yellow).

5.2.3.7 Behavioral Data Analysis

Item recognition performance was assessed separately for object and scene stimuli by computing the difference in the proportion of target trials correctly endorsed 'old' (item hits) and the proportion of new trials incorrectly endorsed 'old' (false alarms). The 'lure discrimination index' (LDI; Stark et al., 2013), held to reflect the ability to discriminate perceptually similar items,

was computed as the difference between the proportion of lure trials correctly endorsed 'lure', and the proportion of new trials incorrectly endorsed as a 'lure' (Stark et al., 2013).

5.3 Results

5.3.1 Behavioral and Neuropsychological Results

Both younger and older adults completed the neuropsychological test battery described above (see *5.2.2. Neuropsychological Test Battery*). As can be seen from Table 5.2, younger adults performed better than older adults on the Short Delay – Free Recall portion of the CVLT and the Raven's progressive matrices. Younger adults also exhibited fewer false alarms, were faster on the SDMT and Trails A, performed better on the category fluency test, and had better visual acuity than older adults. In contrast, older adults overperformed relative to their younger counterparts on the TOPF.

Table 5.2. The outcome of the neuropsychological test battery in younger and older adults.

	Younger Adults	Older Adults	p-value
Age	21.54 (3.60)	68.50 (3.73)	
Sex (male/female)	13/11	13/11	
Years of Education	15.04 (1.63)	17.21 (2.04)	
MMSE	28.70 (1.22)	29.12 (0.83)	0.171
CVLT Short Delay - Free	12.74 (2.49)	10.64 (3.00)	**0.011**
CVLT Short Delay - Cued	12.48 (2.50)	12.16 (2.41)	0.656
CVLT Long Delay - Free	12.70 (2.63)	11.40 (2.83)	0.107
CVLT Long Delay - Cued	12.82 (2.50)	12.60 (2.47)	0.754
CVLT Recognition Hits	15.12 (0.95)	15.16 (1.14)	0.850
CVLT False Alarms	1.04 (1.52)	2.36 (2.66)	**0.040**
F-A-S	42.91 (11.79)	43.36 (11.19)	0.897
WMS Logical Memory I	28.43 (28.43)	29.60 (6.56)	0.538
WMS Logical Memory II	26.09 (6.35)	27.00 (7.21)	0.643
Symbol-digit Substitution Test	59.96 (10.81)	50.64 (8.23)	**0.002**
Trails A (s)	22.29 (6.98)	29.15 (14.04)	**0.037**
Trails B (s)	46.51 (15.91)	56.67 (19.32)	0.052
Digit Span	18.52 (4.92)	17.52 (4.49)	0.466
Category Fluency Test	24.17 (5.33)	20.64 (3.57)	**0.012**
TOPF	49.70 (10.40)	56.16 (9.09)	**0.027**
Raven's Progressive Matrices I	10.91 (1.31)	9.56 (2.10)	**0.010**
Visual Acuity	-0.04 (0.09)	0.13 (0.15)	**< 0.001**

Moving on to memory performance, trial proportions binned according to category, trial type, and endorsement are reported in Table 5.3. The estimates of item memory performance (hits – false alarms) were entered into a 2 (age) x 2 (category) mixed effects ANOVA which revealed a significant effect of category ($F_{(1, 45)} = 73.027$, $p < 0.001$, partial-$\eta^2 = 0.619$), reflective of better item memory for object relative to scene trials, which was accompanied by a null effect of age ($F_{(1, 45)} = 0.852$, $p = 0.361$, partial-$\eta^2 = 0.019$). The age-by-category interaction was not significant ($F_{(1, 45)} = 2.482$, $p = 0.122$, partial-$\eta^2 = 0.052$). A 2 (age) x 2 (category) ANOVA was also employed in case of the LDIs, which revealed a significant effect of category ($F_{(1, 45)} = 31.123$, $p < 0.001$, partial-$\eta^2 = 0.409$), reflective of greater discrimination indices for objects relative to scenes, as well as a significant effect of age group ($F_{(1, 45)} = 12.787$, $p = 0.001$, partial-$\eta^2 = 0.221$). The age effect reflected better lure discrimination performance in younger than older adults. The two way interaction between age group and category was not significant ($F_{(1, 45)} = 0.168$, $p = 0.684$, partial-$\eta^2 = 0.004$). A summary of the item memory and LDI data is presented in Figure 5.4.

Table 5.3. Memory performance in younger and older adults. The data reflect the proportion of trials (separately for image category and trial type) endorsed as targets, lures, or novel.

		Younger Adults			*Older Adults*	
Image category	**Trial type**	**Endorsed as**	**Proportion Mean (SD)**	**Trial type**	**Endorsed as**	**Proportion**
Scenes	Target	Target	0.47 (0.18)	Target	Target	0.53 (0.22)
		Lure	0.25 (0.11)		Lure	0.33 (0.13)
		New	0.27 (0.11)		New	0.14 (0.14)
	Lure	Target	0.17 (0.08)	Lure	Target	0.25 (0.11)
		Lure	0.47 (0.14)		Lure	0.51 (0.14)
		New	0.36 (0.14)		New	0.23 (0.15)
	New	Target	0.04 (0.06)	New	Target	0.08 (0.10)
		Lure	0.20 (0.13)		Lure	0.40 (0.17)
		New	0.76 (0.15)		New	0.51 (0.21)
Objects	Target	Target	0.64 (0.23)	Target	Target	0.75 (0.15)
		Lure	0.24 (0.16)		Lure	0.13 (0.10)
		New	0.12 (0.10)		New	0.12 (0.10)
	Lure	Target	0.26 (0.14)	Lure	Target	0.47 (0.14)
		Lure	0.52 (0.14)		Lure	0.33 (0.12)
		New	0.21 (0.15)		New	0.19 (0.14)
	New	Target	0.04 (0.05)	New	Target	0.05 (0.13)
		Lure	0.15 (0.11)		Lure	0.11 (0.11)
		New	0.81 (0.16)		New	0.84 (0.18)
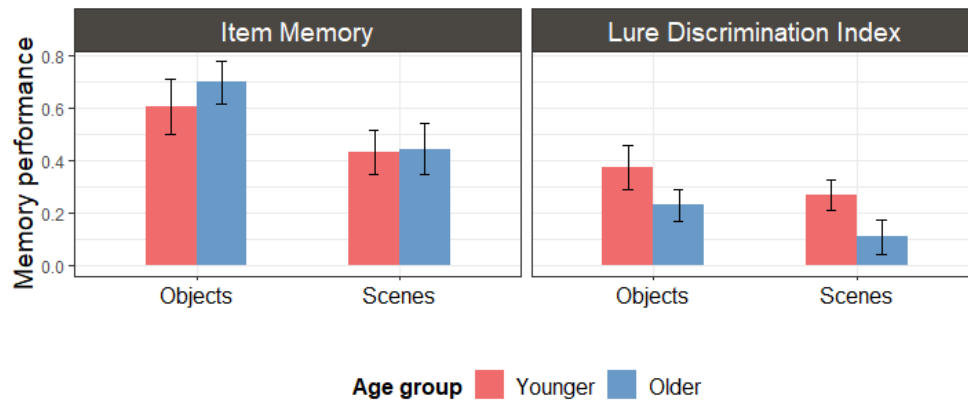
Figure 5.4. Item memory and lure discriminability in younger and older adults, plotted separately for object and scene trials. Error bars reflect the 95% confidence interval.

5.3.2. Region-of-Interest Analysis: Neural Differentiation at the Category Level

Firstly, we examined whether the mass-univariate metric of neural selectivity differed with age group in the scene-selective PPA and the object-selective LOC (c.f., Koen et al., 2019). To achieve this, we computed the difference between the fMRI BOLD activity elicited by the trials of the ROI's preferred image category minus the non-preferred image category (in both cases averaging across the to-be-tested items and all first presentation trials). With this approach, PPA selectivity was computed for each subject as the difference between neural activity elicited by scene trials minus object trials, whereas selectivity in the LOC was operationalized as object trials minus scene trials. The selectivity metric was then entered into a 2 (age group) x 2 (ROI) mixed factorial ANOVA which revealed that the effects of age group, ROI, and the 2-way interaction were all non-significant (age group: $F_{(1, 46)} = 1.816$, $p = 0.184$, partial-$\eta^2 = 0.038$; ROI: $F_{(1, 46)} = 0.458$, $p = 0.502$, partial-$\eta^2 = 0.010$; age group x ROI: $F_{(1, 46)} = 0.349$, $p = 0.558$, partial-$\eta^2 = 0.008$; Figure 5.5). Although the interaction was not significant, we performed two pairwise comparisons motivated by the findings of Koen et al. (2019). The independent samples t-tests demonstrated that selectivity in neither the PPA or in the LOC exhibited age differences (PPA: $t_{(45.23)} = 1.571$, $p = 0.123$; LOC: $t_{(45.63)} = 0.386$, $p = 0.701$). These findings suggest that, using the present ROIs, neural selectivity for scenes or objects at the category-level was not moderated by age group.

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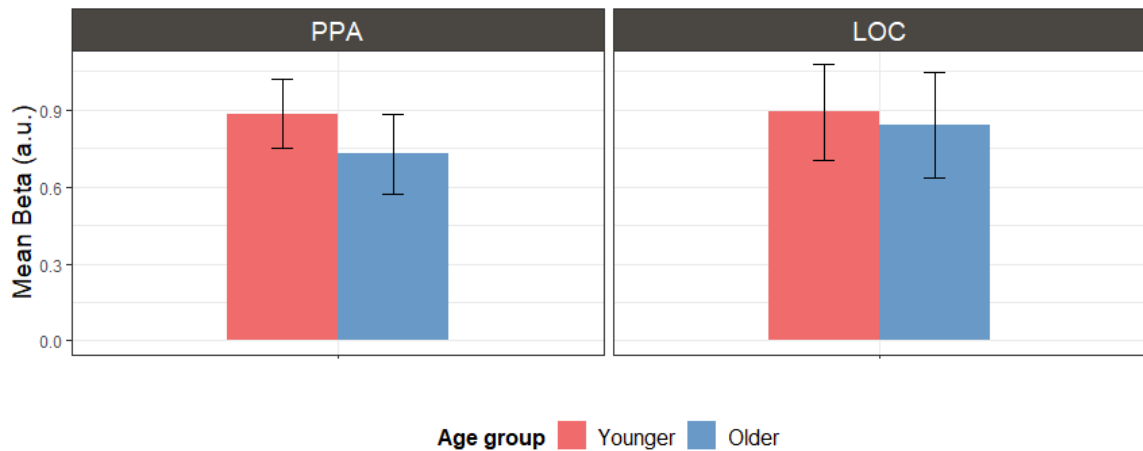
Figure 5.5. Selectivity for scene stimuli in the PPA and object-selectivity in the LOC plotted separately younger and older adults. Error bars reflect the 95% confidence interval.

5.3.3 Region of Interest Analysis: Neural Differentiation at the Item Level

Repetition effects were operationalized at the individual subject level in each ROI by computing the difference between the fMRI BOLD activity elicited by the 'first presentation' trials and the activity elicited by the second presentation (lure or exact repeat). Accordingly, reliable repetition suppression effects are reflective of a reduction in fMRI BOLD activity elicited by the second presentation. The first and second presentation trials were always binned according to their image category and trial type, resulting in repetition effects being operationalized for scene repeats, scene lures, object repeats, and object lures. Repetition effects are illustrated in Figure 5.6 and Table 5.4 illustrates one-sample t-tests testing whether the repetition effects reliably differed from zero. As can be seen from the table, all ROIs demonstrated reliable repetition suppression effects (repetition effect significantly above zero) in at least one of the trial conditions. In no cases were repetition effects significantly less than zero.

Table 5.4. One-sample t-tests against zero to examine the reliability of repetition suppression effects.

	Younger Adults	*Older Adults*
Parahippocampal Place Area		
Object Repeat	t = 6.404, p < 0.001	t = 7.520, p < 0.001
Object Lure	t = 2.670, p = 0.014	t = 1.638, p = 0.115
Scene Repeat	t = 5.042, p < 0.001	t = 4.440, p < 0.001

Scene Lure	**t = 2.716, p = 0.012**	**t = 3.963, p < 0.001**
Lateral Occipital Complex		
Object Repeat	**t = 4.322, p < 0.001**	**t = 5.455, p < 0.001**
Object Lure	t = 1.513, p = 0.144	t = 1.823, p = 0.081
Scene Repeat	t = 1.430, p = 0.166	t = 1.920, p = 0.067
Scene Lure	t = 1.267, p = 0.218	t = 1.841, p = 0.079
Anterior Hippocampus		
Object Repeat	t = 2.017, p = 0.056	t = 1.401, p = 0.175
Object Lure	**t = 2.459, p = 0.022**	t = 0.212, p = 0.834
Scene Repeat	**t = 2.178, p = 0.040**	**t = 3.204, p = 0.004**
Scene Lure	t = 2.440, p = 0.023	t = 1.212, p = 0.238
Posterior Hippocampus		
Object Repeat	t = 1.659, p = 0.111	**t = 3.213, p = 0.004**
Object Lure	t = 1.459, p = 0.158	t = 0.198, p = 0.845
Scene Repeat	**t = 2.584, p = 0.017**	t = -0.056, p = 0.956
Scene Lure	t = 1.735, p = 0.096	t = -0.981, p = 0.337

To examine whether repetition suppression varied according to age, image category, trial type, or ROI, we performed a 2 (age group: younger/older) x 2 (ROI) x 2 (image category: scene/object) x 2 (trial type: repeat/lure) mixed effects ANOVA on the repetition effects in the LOC and PPA, the two category-selective cortical regions. As can be seen in Table 5.5-A, the ANOVA revealed a main effect of trial type and a ROI x Category interaction, while all remaining effects were non-significant. Follow-up pairwise comparisons revealed that the main effect of trial type was due to greater repetition effects for identical repeats (M = 0.487) relative to lures (M = 0.200) across all ROIs and image categories. The ROI x Category interaction was indicative of the fact that repetition suppression effects in the PPA did not differ between scene and object stimuli ($t_{(47)} = 0.069$, p = 0.945), whereas the suppression effects in the LOC were greater for objects than for scenes ($t_{(47)} = 2.205$, p = 0.032). These findings suggest that the strength of suppression effects in the PPA, but not in the LOC, are independent of stimulus category. Lastly, the ANOVA also revealed that none of the identified effects differed by age. According to the hypotheses outlined in the introduction, we expected to identify null effects of age on repetition suppression for exact repeats, but an age-related increase in repetition suppression for lure pairs. However, the effect size for the age group x trial type interaction approached zero (partial-$\eta^2 < 0.001$), speaking against the hypothesis that increasing age results in an increase in repetition suppression effects for perceptually similar images.

An analogous ANOVA was employed for the hippocampal ROIs (with the factor of ROI: aHPC and pHPC). The results of this analysis are illustrated in Table 5.5-B. The ANOVA revealed a main effect of ROI, an ROI x category interaction, and an age group x ROI x category interaction. Follow up analyses demonstrated that the effect of ROI was driven by greater repetition suppression effects in the aHPC (M = 0.147) than in the pHPC (M = 0.062). The ROI x category interaction was driven by numerically greater repetition effects for scenes relative to objects in the aHPC, with the opposite pattern (objects greater than scenes) in the pHPC; however, in neither of these comparisons was the difference in the size of the effects statistically significant ($t_{(47)} = 1.327$, $p = 0.191$ and $t_{(47)} = -1.345$, $p = 0.185$, respectively). Next, this analysis was followed-up with two 2-way ROI x category ANOVAs performed separately for each age group to elucidate the age group x ROI x category interaction. These analyses are described below.

In the older adult group, the ANOVA revealed a significant main effect of ROI ($F_{(1, 23)} = 13.300$, $p = 0.001$, partial-$\eta^2 = 0.366$), arising from greater repetition effects in the aHPC relative to the pHPC (Ms = 0.127 and 0.034), and a null effect of category ($F_{(1, 23)} = 0.010$, $p = 0.923$, partial-$\eta^2 < 0.001$). The ROI x category interaction was significant ($F_{(1, 23)} = 12.630$, $p = 0.002$, partial-$\eta^2 = 0.354$), and follow-up pairwise comparisons revealed results similar to those for the original 4-way ANOVA: the aHPC demonstrated numerically stronger repetition effects for scenes relative to objects, and the reverse effect was observed in the pHPC, although neither of the comparisons reached statistical significance ($t_{(47)} = 1.640$, $p = 0.115$ and $t_{(47)} = -1.843$, $p = 0.078$, respectively). The analogous ANOVA of the data from the younger adult group revealed a significant effect of ROI ($F_{(1, 23)} = 5.810$, $p = 0.024$, partial-$\eta^2 = 0.202$), which reflected greater repetition effects in the aHPC than pHPC, but a null effect of category ($F_{(1, 23)} = 0.020$, $p = 0.892$, partial-$\eta^2 < 0.001$) and a non-significant ROI x category interaction ($F_{(1, 23)} = 0.010$, $p = 0.927$, partial-$\eta^2 < 0.001$).

In summary, as was the case for the analysis of repetition effects in the LOC and PPA, analysis of the effects in the hippocampus did not reveal any age differences in repetition suppression for either lures or repeats. Thus, these results also speak against the notion that age-related neural dedifferentiation takes the form of an increase in repetition suppression effects for perceptually similar lures in older relative to younger adults.

Table 5.5. The outcomes of the 2 (age group) x 2 (ROI) x 2 (image category) x 2 (trial type) mixed effects ANOVA on repetition suppression.

A: ROI: LOC/PPA	df	F	partial-η^2	p-value
Age group	1,46	0.232	0.005	0.632
ROI (LOC / PPA)	1,46	0.028	0.001	0.867
Category	1,46	2.346	0.049	0.132
Trial Type	**1,46**	**21.251**	**0.316**	**< 0.001**
Age x ROI	1,46	1.593	0.033	0.213
Age x Category	1,46	0.020	< 0.001	0.887
Age x Trial Type	1,46	0.004	< 0.001	0.952
ROI x Category	**1,46**	**10.359**	**0.184**	**0.002**
ROI x Trial Type	1,46	0.001	< 0.001	0.974
Category x Trial Type	1,46	1.891	0.039	0.179
Age x ROI x Category	1,46	< 0.001	< 0.001	0.987
Age x ROI x Trial Type	1,46	0.157	0.003	0.693
Age x Category x Trial Type	1,46	0.099	0.002	0.754
ROI x Category x Trial type	1,46	2.604	0.054	0.113
Age x ROI x Category x Trial Type	1,46	0.060	0.001	0.808

B: ROI: aHPC / pHPC	df	F	partial-η^2	p-value
Age group	1,46	1.054	0.022	0.310
ROI (aHPC / pHPC)	**1,46**	**17.152**	**0.272**	**< 0.001**
Category	1,46	0.027	0.001	0.871
Trial Type	1,46	3.653	0.074	0.062
Age x ROI	1,46	0.113	0.002	0.739
Age x Category	1,46	< 0.001	< 0.001	0.988
Age x Trial Type	1,46	3.048	0.062	0.087
ROI x Category	**1,46**	**7.720**	**0.144**	**0.008**
ROI x Trial Type	1,46	0.459	0.010	0.502
Category x Trial Type	1,46	< 0.001	< 0.001	0.996
Age x ROI x Category	**1,46**	**7.070**	**0.133**	**0.011**
Age x ROI x Trial Type	1,46	0.980	0.021	0.327
Age x Category x Trial Type	1,46	0.008	< 0.001	0.927
ROI x Category x Trial type	1,46	1.820	0.038	0.184
Age x ROI x Category x Trial Type	1,46	1.211	0.026	0.277
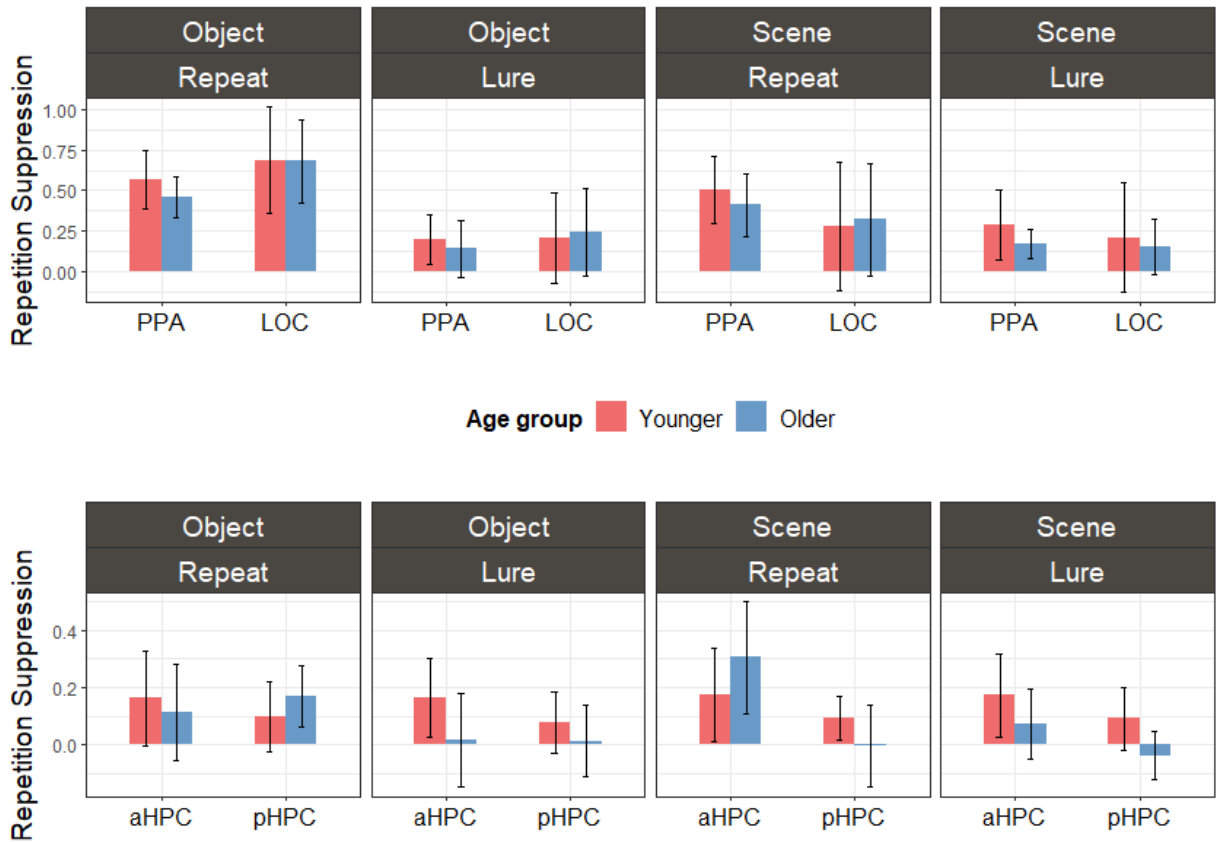
Figure 5.6. Repetition effects plotted separately according to ROI, image category, trial type, and age group. Values significantly above zero reflect reliable repetition suppression effects. Error bars reflect the 95% confidence interval.

5.3.4 Whole-brain Analysis: Neural Differentiation at the Category Level

First, we examined which brain regions were preferentially recruited during object and scene trials. Figure 5.7-A and Table 5.6-A depict the scene > object (in red) and object > scene (in blue) t-contrasts collapsed across age groups. In all cases, the scene and object effects were collapsed across to-be-tested items and first presentation trials. Because our pre-experimentally defined threshold of $p < 0.001$ produced large clusters spanning numerous cortical regions, we reduced the threshold to a more stringent threshold of FWE-corrected $p < 0.05$ to better understand the results. Scene-selective regions encompassed the fusiform and parahippocampal gyri extending into the hippocampus bilaterally. A large cluster was identified in the retrosplenial

complex extending into the precuneus and the posterior cingulate cortex. Scene-selective clusters were also identified in the middle occipital gyri extending into the inferior intraparietal lobule and the intraparietal sulcus. Object-selective clusters were identified in the lateral occipital cortices spanning the fusiform gyri and the right perirhinal cortex. Additional clusters were present in the calcarine sulcus and the bilateral angular gyrus. In frontal regions, object-selective clusters were largely left-lateralized and were observed in left superior frontal gyri, the dorsolateral prefrontal cortex, and the ventrolateral prefrontal cortex extending posteriorly into the insula.

Given prior findings from our laboratory (Koen et al., 2019), we expected to find reduced selectivity in older relative to younger adults in the scene-selective but not object-selective contrasts. Therefore, we constructed a younger (scene > object) > older (scene > object) contrast and a younger (object > scene) > older (object > scene) contrast using our pre-defined threshold of p < 0.001, cluster-wise correction at p < 0.05 (75 voxels). The outcomes of these analyses are illustrated in Figure 5.7-B and in Table 5.6-B. Scene-selectivity was greater in younger relative to older adults in the bilateral parahippocampal cortices, the right middle occipital cortex extending into the inferior parietal lobule, and in the right retrosplenial complex. The object-selective younger (object > scene) > older (object > scene) contrasts revealed no suprathreshold clusters. These results indicate that, at the whole-brain level, scene-selectivity but not object-selectivity is greater in younger than older adults.

Table 5.6. The outcomes of the scene- and object-selective contrasts and associated age differences.

A: Scene > Object	X	Y	Z	Peak Z	Cluster Size
Fusiform gyrus	**-24**	**-46**	**-8**	**Inf**	**5213**
Middle occipital gyrus	-34	-88	18	Inf	
Retrosplenial complex	-16	-60	12	Inf	
Fusiform gyrus	**28**	**-46**	**-10**	**Inf**	**8739**
Parahippocampal cortex	24	-38	-14	Inf	
Middle occipital gyrus	42	-80	22	Inf	
Cerebellum	**-14**	**-50**	**-50**	**Inf**	**138**
A: Object > Scene					
Lateral occipital complex	**-46**	**-70**	**-6**	**Inf**	**1725**
Fusiform gyrus	-44	-50	-18	Inf	

Fusiform gyrus	-44	-58	-16	Inf	
Lateral occipital cortex	**46**	**-74**	**-10**	**Inf**	**927**
Fusiform gyrus	46	-44	-16	7.06	
Angular gyrus	**-40**	**-78**	**40**	**Inf**	**658**
Angular gyrus	-36	-76	50	Inf	
Angular gyrus	-52	-70	24	6.62	
Superior frontal gyrus	**-28**	**16**	**50**	**Inf**	**2301**
Superior frontal gyrus	-4	18	52	Inf	
Dorsal anterior cingulate cortex	-4	22	44	Inf	
Ventrolateral prefrontal cortex	**-34**	**32**	**-14**	**Inf**	**2671**
Inferior frontal gyrus	-40	32	12	Inf	
Anterior insula	-30	20	0	Inf	
Superior frontal gyrus	**24**	**30**	**54**	**7.53**	**133**
Primary visual cortex	**2**	**-82**	**12**	**7.34**	**604**
Cuneus	2	-82	24	6.53	
Calcarine sulcus	-4	-64	0	6.01	
Cerebellum	**10**	**-84**	**-38**	**7.25**	**171**
Cerebellum	16	-84	-44	6.56	
Cerebellum	14	-82	-30	6.06	
Angular gyrus	**48**	**-68**	**46**	**7.02**	**164**
Angular gyrus	48	-64	32	6.02	
Cerebellum	**38**	**-70**	**-38**	**6.50**	**278**
Cerebellum	38	-70	-48	6.48	
Cerebellum	42	-76	-34	5.75	

B: Younger > Older: Scene-selectivity

Parahippocampal gyrus	**34**	**-40**	**-10**	**5.91**	**164**
Retrosplenial complex	**22**	**-58**	**20**	**5.85**	**184**
Middle occipital cortex	**46**	**-70**	**26**	**5.76**	**449**
Middle occipital cortex	28	-80	40	4.60	
Inferior parietal lobule	24	-80	52	4.48	
Parahippocampal gyrus	**-30**	**-44**	**-8**	**5.63**	**99**

B: Younger > Older: Object-selectivity

No suprathreshold clusters	
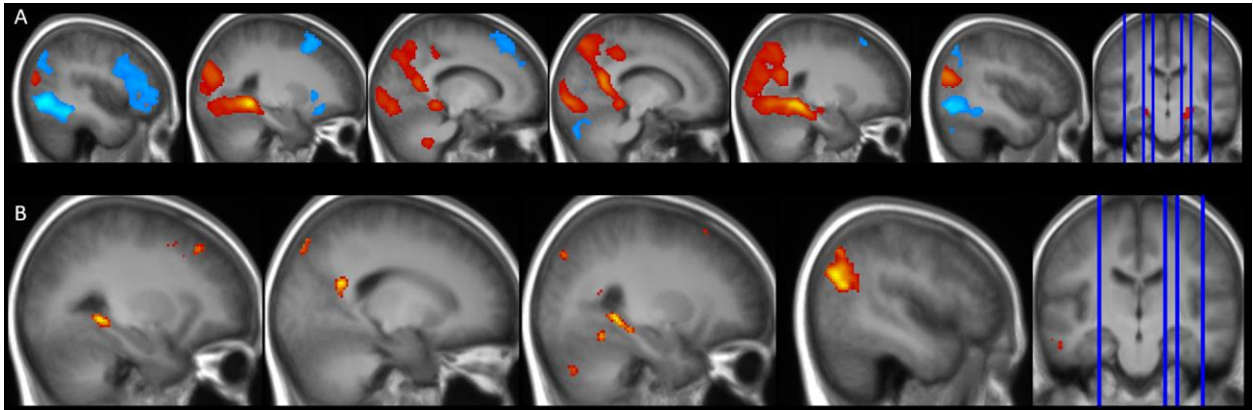
Figure 5.7. (A) Object-selective (blue) and Scene-selective (red) clusters identified collapsing across both age groups. **(B)** Clusters that evoked greater scene-selectivity in younger relative to older adults. No age differences were observed for object-selectivity.

5.3.5 Whole-brain Results: Neural Differentiation at the Item Level

The analyses of item-level neural differentiation were performed by examining the effects of trial type (exact repeat vs lure) and age group (younger vs older adults) on repetition suppression effects. Table 5.7 and Figure 5.8 report the main effects of scene and object repetition collapsing across trial type and age group (note that because of the large number of clusters identified, Table 5.7 reports main effects of scene and object repetition at a FWE-height-threshold of $p < 0.05$). For scene trials, robust repetition effects were evident in the fusiform and parahippocampal cortices, middle occipital gyrus, dorsolateral and dorsomedial prefrontal cortices, and the inferior frontal gyri. The pattern was highly similar for objects: repetition effects were identified in inferior occipital gyrus, middle occipital gyrus, parahippocampal gyrus, retrosplenial complex. orbitofrontal, dorsomedial, and dorsolateral prefrontal cortices, and inferior frontal gyri.

To examine trial type effects, we employed two F-contrasts comparing repetition for exact repeats vs. repetition for lures. These contrasts were constructed separately for objects and scenes. For the scene trials no clusters of *a priori* interest were identified where repetition suppression would differ by trial type. For the object trials, several clusters were identified across the inferior frontal regions and the left fusiform cortex. To elucidate these effects, we performed two directional contrasts: object exact repetition > object lure repetition, and vice-versa, employing the F-contrast as an inclusive mask. These contrasts revealed that the clusters identified by the F-contrast were driven by significantly greater repetition effects for exact repeats relative to lures.

To examine effects of age, we constructed repetition contrasts between younger vs older adults, separately for each trial type and image category (e.g., Older adults scene lures > Younger adults scene lures. In no case did any of these contrasts reveal clusters in which repetition effects differed by age group. These results indicate that the fidelity of neural representations (as operationalized with repetition suppression) did not differ between younger and older adults.

Table 5.7. Main effect of scene / object repetition and differences in repetition suppression between trial type (exact repeat / lure) for objects and scenes.

Main effect of scene repetition [1]	X	Y	Z	Peak Z	Cluster Size
Middle occipital gyrus	**42**	**-80**	**22**	**6.18**	**111**
Middle occipital gyrus	44	-72	22	5.90	
Parahippocampal gyrus	**30**	**-36**	**-20**	**6.16**	**76**
Parahippocampal gyrus	28	-28	-22	5.43	
Middle occipital gyrus	**-44**	**-78**	**22**	**6.08**	**87**
Middle occipital gyrus	-32	-86	26	5.36	
Parahippocampal gyrus	**-28**	**-36**	**-20**	**6.02**	**92**
Fusiform gyrus	-32	-44	-18	5.67	
Parahippocampal gyrus	-20	-42	-16	5.09	

Main effect of object repetition [1]					
Orbitofrontal cortex	**-36**	**32**	**-14**	**Inf**	**145**
Fusiform gyrus	**-44**	**-58**	**-16**	**Inf**	**1046**
Inferior temporal gyrus	-50	-50	-14	Inf	
Inferior temporal gyrus	-52	-58	-10	7.33	
Lingual gyrus	**-6**	**-54**	**4**	**7.58**	**341**
Retrosplenial complex	-4	-60	10	7.45	
Inferior frontal gyrus	**-40**	**26**	**16**	**7.51**	**760**
Dorsolateral prefrontal cortex	-46	34	10	6.94	
Precentral gyrus	-46	4	26	6.91	
Middle occipital gyrus	**-42**	**-78**	**26**	**7.49**	**531**
Middle occipital gyrus	-30	-80	32	6.30	
Middle occipital gyrus	-40	-70	20	6.00	
Fusiform cortex	**32**	**-26**	**-26**	**6.89**	**131**
Parahippocampal cortex	30	-36	-20	6.45	
Orbitofrontal cortex	**-2**	**38**	**-16**	**6.73**	**124**
Middle occipital gyrus	**42**	**-70**	**28**	**6.47**	**80**
Inferior occipital gyrus	**48**	**-54**	**-14**	**6.22**	**98**
Inferior occipital gyrus	**52**	**-64**	**-10**	**5.27**	**145**

Scene exact repeats vs. scene lures [2]

No suprathreshold clusters

Object exact repeats > object lures[3]

Fusiform cortex	**-34**	**-44**	**-18**	**5.06**	**151**
Cerebellum	-30	-48	-28	4.46	
Fusiform cortex	-48	-50	-20	3.99	
Precentral gyrus	**44**	**8**	**26**	**4.61**	**107**
Precentral gyrus	50	6	34	3.44	
Precentral gyrus	**-54**	**4**	**36**	**4.48**	**236**
Central sulcus	-48	-4	24	4.13	
Central sulcus	-50	10	24	4.09	
Inferior temporal gyrus	**-50**	**-62**	**-10**	**4.24**	**88**
Fusiform cortex	-36	-60	-2	4.12	
Inferior frontal gyrus	**-40**	**24**	**18**	**4.04**	**152**
Inferior frontal gyrus	-54	28	18	3.84	
Inferior frontal gyrus	-42	30	10	3.67	
Ventrolateral prefrontal cortex	**32**	**38**	**-12**	**4.02**	**78**
Ventrolateral prefrontal cortex	36	30	-12	3.57	
Postcentral gyrus	**-54**	**-10**	**50**	**3.97**	**91**
Postcentral gyrus	-56	-20	46	3.93	
Postcentral gyrus	-50	-26	42	3.88	

1 Note that for the sake of being concise, the main effects of repetition are reported at a FWE-corrected height-threshold of $p < 0.05$.

2 For either repeat > lure or lure > repeat

3 Inclusively masked with the trial type F-contrast. No effects observed with the reverse contrast.
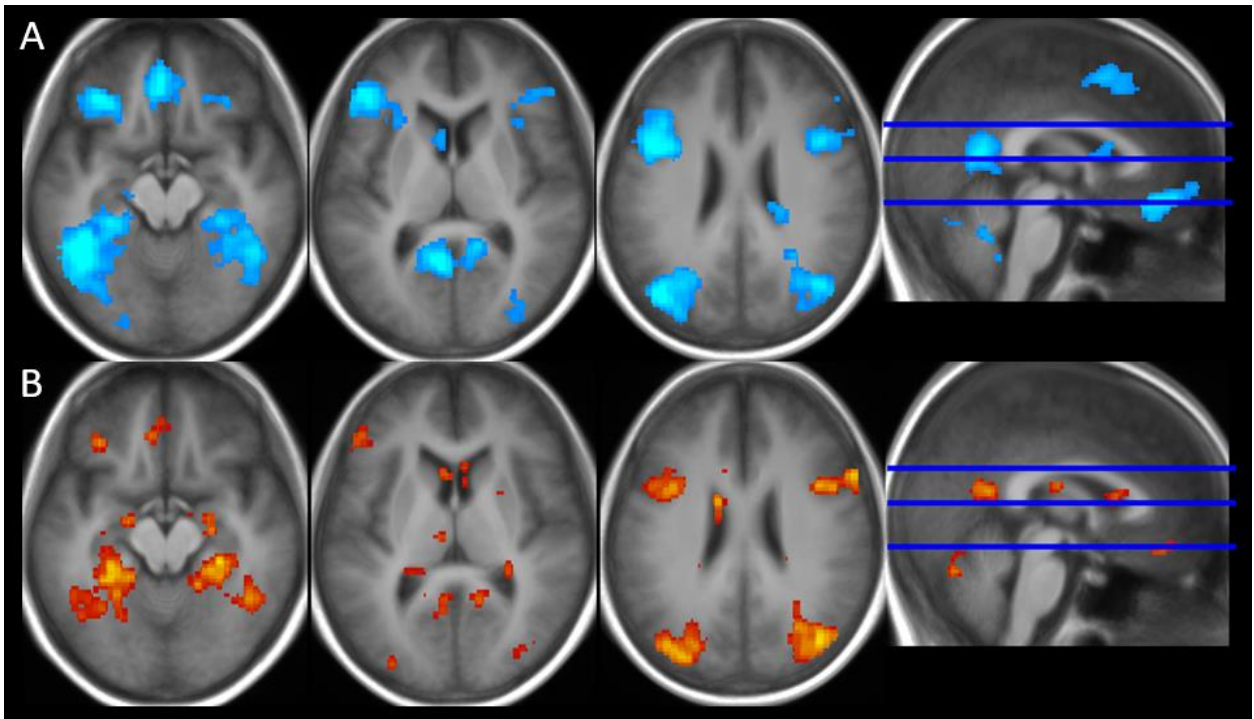
Figure 5.8. Main effects of repetition across age groups and trial types for scene **(A)** and object **(B)** stimuli. The data are illustrated on the mean T1 image of the entire sample at p < 0.001 and a voxel threshold of k > 74.

5.4   Discussion

In the present study, we examined age differences in neural differentiation at the level of visual stimulus categories and individual exemplars. At the category level, the whole brain analyses revealed reduced selectivity for scenes, but not for objects, in older relative to younger adults, although no age differences in category selectivity were evident in the ROI analyses. At the item level, the whole brain and ROI analyses provided highly convergent results demonstrating null effects of age on repetition effects for both exact repeats and perceptually similar lure images. Thus, contrary to the hypotheses outlined in the introduction, the present findings suggest that age-related neural dedifferentiation at the category-level does not extend to a reduction in the fidelity of neural representations for individual stimuli, at least when operationalized as an increase in repetition suppression effects for perceptually similar items. Below we discuss the implications of these findings for the understanding of age-related neural dedifferentiation.

In the present study, we employed a mnemonic similarity task, a paradigm commonly used to examine the behavioral and neural correlates of mnemonic discriminability in younger and older adults (Stark et al., 2013; Stark & Stark, 2017; Stark et al., 2019). Turning first to our behavioral results, we observed no age differences in item memory for object and scene stimuli, while memory for scenes was worse than memory for objects in both age groups. By contrast, we found that the LDI (the 'lure discrimination index', see Methods) differed as a function of both age (lower LDI scores in older relative to younger adults) and category (lower LDI for scenes relative to objects), and that the age-related reduction in mnemonic discriminability was equivalent for both stimulus categories. These findings align well with the prior literature. The null effects of age on item memory are consistent with numerous prior reports that item memory is relatively impervious to increasing age (Koen & Yonelinas, 2014; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995), while lower LDI scores in older adults have frequently been reported in studies that employed the mnemonic similarity task (Stark et al., 2013, 2015; Stark and Stark, 2017). Our findings are also consistent with the broader literature indicating an age-related decline in the ability to recollect detailed information about an experienced event (Koen & Yonelinas, 2014; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995), and a reduction in the precision and specificity of the retrieved content (Nilakantan et al., 2018; Korkki et al., 2020).

The mnemonic similarity task was designed with the aim of taxing the hippocampal pattern separation processes that are thought to decline in older age (for review, see Yassa et al., 2011). Pattern separation refers to a process whereby neural representations underlying perceptually similar visual stimuli (or similar events) are transformed into highly differentiated, orthogonal representations, a process thought to be critical for episodic memory and mnemonic discriminability. It is held to depend heavily on the dentate gyrus (DG) of the hippocampus, a region which has been shown to be particularly vulnerable to the effects of aging (Yassa et al., 2010), forming the basis of the assumption that a failure to pattern separate will impair mnemonic discriminability performance. Yassa and colleagues (2010) reported that hyperactivity in the CA3/DG region (interpreted as a correlate of deficient pattern separation) was associated with lower mnemonic discriminability in healthy older adults.

Studies examining age differences in hippocampal pattern separation have typically failed to account for potential age differences in the fidelity of the neural representations supported by the extrastriate visual cortex 'upstream' of the hippocampus. By contrast, in the present study we examined potential age differences in the fidelity and specificity of the neural representations arising not only in the hippocampus but in extra-hippocampal category-selective cortical regions also. To do this, we operationalized neural differentiation at the level of individual stimulus exemplars in terms of repetition suppression effects to exact repeats and perceptually similar lures. Prior findings indicate that, compared with younger individuals, older adults are more prone to retrieve relatively undifferentiated (gist-based) rather than highly detailed memories (for review, see Grilli & Sheldon, 2022). However, for the reasons noted above, whether this is a consequence of inadequate pattern separation in the hippocampus or, rather, low fidelity input to the hippocampus is unclear (but see Hill et al., 2021). The repetition suppression approach employed here is based on the assumption that as they become more dedifferentiated, perceptual representations will become more 'confusable', leading to an enhancement of suppression effects for perceptually similar items (Grill-Spector et al., 2006). Thus, to the extent that perceptual representations are indeed dedifferentiated in older relative to younger adults (see Introduction) we expected to observe null effects of age in repetition suppression effects for exact item repetitions, but an age-related increase in the effects for perceptually similar lure exemplars (cf. Goh et al., 2010). In stark contradiction to this expectation, however, we failed to detect any effect of age on the magnitude of repetition suppression effects for either exact repeats or similar lures.

The present findings add to the already inconsistent literature concerning the effects of age on the precision of item-specific perceptual representations. Whilst some prior studies have reported an absence of age differences in metrics of item-level neural differentiation (St-Laurent, 2014; 2019; Zheng et al., 2018), effects of age have also been reported (Bowman et al., 2019; Trelle et al., 2019; Goh et al., 2010). For example, in one study, null effects of age were observed for repetition effects elicited by brief movie clips during an encoding task (St-Laurent, 2014), and in another study (Zheng et al., 2018), multivoxel pattern similarity was employed to reveal null effects of age on the neural similarity of neural patterns elicited by repetitions of visual stimuli (after accounting for 'baseline' similarity, an important consideration for across-group

comparisons in pattern similarity analyses). Of importance, our results are inconsistent with those of Goh and colleagues (2010), who reported an age-related increase in repetition suppression effects for perceptually similar faces in the face-selective FFA. Two other studies inconsistent with our findings, neither of which employed the repetition suppression paradigm, are those of Bowman et al., (2019) and Trelle et al (2019). Both studies report evidence for age differences in item-level neural differentiation during an item recognition task. However, it is worth nothing that in the case of Trelle et al. (2019), this conclusion was based solely on the fact neural pattern similarity between consecutive item representations differed from zero in younger but not older adults, as opposed to a direct comparison between the age groups.

The present results suggest that the presence of age-related neural dedifferentiation at the categorical level does not necessarily imply dedifferentiation at the item level. However, null effects on neural dedifferentiation at the categorical level have also been reported, and the ubiquity of this phenomenon has been called to question (Koen et al., 2020; see Chapter 2). As described in more detail in Chapter 2 (see discussion), age differences in neural differentiation are hard to detect in certain task conditions (e.g., tasks requiring each item to be actively attended), and are in any case harder to find for some perceptual categories than others. Since the factors that determine the presence of age differences in differentiation are currently obscure, it is unclear whether the present null effects of age on lure repetition suppression effects should be attributed to the insensitivity of our experimental procedure, or whether they should be interpreted as further evidence against the 'dedifferentiation hypothesis' (see Chapters 1 and 2).

To our knowledge, the study by Goh et al. (2010) is the only other study to examine age differences in lure repetition suppression effects. We cannot rule out the possibility that the inconsistency between the present findings and those of Goh et al. is a consequence of differences in stimulus materials: Goh et al. (2010) employed as lures faces that were morphed to resemble the first presentation of the 'parent' face, while we employed images of objects and scenes that were judged as perceptually similar (the same approach that was employed by Stark et al., 2013). Moreover, in the task of Goh and colleagues, participants had to actively attend to the stimuli and make perceptual discriminations. In contrast, although the indoor/outdoor task in our study did require participants to attend to the stimuli, it is possible that participants engaged less attention

and were more likely to 'zone out'. As mentioned previously, we have hypothesized that age-related neural dedifferentiation is moderated by the demands of the task (i.e., whether the task is 'active' or 'passive').

Other studies that are inconsistent with our findings are those of Bowman and colleagues (2019), and Trelle and colleagues (2019), both of which examined neural differentiation between encoding trials and their associated repeats during a recognition memory test. Beyond the fact that participants may have attended more to the stimuli during recognition memory than during an indoor/outdoor task (see above), we conjecture that the greater temporal delay between item repeats in their tasks may have enhanced age differences in item-level neural differentiation. A potential finding of moderating effects of delay on item-level neural dedifferentiation would suggest that the age differences in encoding-retrieval similarity between item repeats may reflect time-dependent processes that occur post-encoding. Lastly, despite the robust effects of age on LDI, and repetition suppression effects for both scenes and faces, we were also unable to find any evidence for an age effect in repetition suppression in the hippocampus (a proxy for hippocampal pattern separation; Yassa et al., 2011). Of course, we cannot rule out the possibility that we would have detected age differences in pattern separation had we looked directly in the DG/CA3 subfield (Yassa et al., 2010). The spatial resolution of our data prevents us from measuring repetition effects at the hippocampal subfield level, and this may in turn have reduced the sensitivity of our analyses to detect an age effect in the hippocampus.

Some additional limitations of the study should be noted. First, as in the other studies reported in this dissertation, we employed a cross-sectional design with two extreme age groups. Therefore, any age effects cannot be attributed to the process of aging, as previously noted. Second, it is unclear to what extent our analyses are confounded by the well-documented age differences in the gain of the hemodynamic response function (Tsetanov et al., 2020). Lastly, the analyses described above depend on the assumption that repetition suppression effects for similar lures are indeed a (negative) correlate of representational specificity.

In summary, in the present study we found no age difference in the magnitude of repetition suppression effects to similar lures relative to exact repeats. These findings are inconsistent with some prior literature reporting age differences in neural differentiation at the item level. We

conjecture that potential causes for this inconsistency include differential task demands, effects of stimulus category, or a relatively short delay between first and second presentations of repeats or lures. Alternatively, these findings could suggest that the repetition suppression paradigm is not sensitive to age differences in the specificity of perceptual representations. Given the relatively mixed findings to date, future research should aim to elucidate the factors that contribute to the ability to detect age-related neural dedifferentiation at the level of individual stimulus exemplars.

CHAPTER 6

GENERAL DISCUSSION AND CONCLUSIONS

The experiments comprising this dissertation were dedicated to advancing our understanding of the relationship between age, cognition and the neural correlates of episodic memory encoding and retrieval. The four empirical chapters describe studies that examined age differences on three correlates of episodic memory function: neural differentiation (at both category and item levels), retrieval gating, and the retrieval-related anterior shift. The studies examining neural differentiation (Chapters 2 and 5) enhance understanding of the factors underpinning age-related neural dedifferentiation and the associations between neural differentiation and cognition that exist independently of age. The dissertation also contributes to the field with two highly novel findings in Chapters 3 and 4, whereby we were the first to report that the phenomena of retrieval gating and the retrieval-related anterior shift are sensitive to increasing age. Below, I summarize the main take-aways from the four empirical chapters. For each chapter, I highlight the significance and broader impact of the study to the field of memory and cognitive aging. Then I present some outstanding questions and elaborate on future directions that would further our insights into the factors contributing to age-related decline in episodic memory. In the case of the published manuscripts, Chapters 2 through 4, the described results have already served as a basis for new research projects and grant proposals. This highlights the significance of the empirical work described here to the field and the impact of our results on current understanding of the neural and behavioral correlates of memory and cognitive aging.

6.1   Age-related Neural Dedifferentiation

Chapter 2 describes a study that provides evidence for age-related neural dedifferentiation at the category-level in scene-selective but not face-selective cortical regions. The analyses also demonstrate that neural differentiation in the PPA during encoding is predictive of subsequent memory performance across both younger and older adults. The findings support the notion that neural differentiation is associated with two sources of variance: one due to age, and the other to memory performance independently of age.

The existence of age-related neural dedifferentiation at the category level does not imply that differentiation will also be evident at the level of individual exemplars. Chapter 5 reports a study which examined neural differentiation in younger and older adults at the item-level by comparing repetition suppression effects for exact repeats of objects or scenes, versus repetition effects for perceptually similar foils. Although robust repetition suppression was observed, we found no evidence for the predicted age-related increase in suppression effects for perceptually similar lures (held to be a proxy for neural dedifferentiation), speaking against our hypothesis that age-related neural dedifferentiation would manifest at the item as well as the category level.

The studies described above add to the evidence that neural dedifferentiation is not ubiquitous, and that the ability to detect reduced neural differentiation in older adults may be dependent on the task demands, the perceptual attributes of a given stimulus category, or the metrics by which it is operationalized. As noted throughout this dissertation and discussed at length in the discussion of Chapter 2, the factors that contribute to age-related neural dedifferentiation are currently unknown. This challenge motivated a currently ongoing empirical project which examines the potential relationship between age-related neural dedifferentiation and age differences in exploratory viewing behaviors. In this follow-up study, participants perform a source memory task closely similar to that of Chapter 2 while they undergo fMRI with simultaneous eye-tracking. The study is motivated by research that demonstrates that memory-based eye movements during encoding and retrieval are correlated with memory performance (Loftus, 1972; Molitor et al., 2014; Olsen et al., 2016; Voss et al., 2017; Damiano & Walther, 2019), and that these patterns of eye movements are sensitive to increasing age (for reviews, see Ryan et al., 2020; Wynn et al., 2019; 2020). It has been reported that the number of gaze fixations during the encoding of a visual stimulus modulates neural activity in visually responsive cortex and the hippocampus (Liu et al., 2017, 2020; Henderson & Choi, 2014; Henderson et al., 2020), and this raises the possibility that differences in eye movements during memory encoding underlie age differences in neural differentiation. In this upcoming research, we aim to examine whether age differences in the pattern and frequency of eye movements relate to age differences in neural differentiation at encoding. This will contribute to the understanding of factors that mediate

reduced neural selectivity in older age, and will also provide critical insight into the neural correlates of age differences in viewing behaviors. Given that age differences in eye movements and neural correlates of memory function have been largely studied in separation, findings from this research will make a significant contribution to the field of cognitive neuroscience of memory and aging.

6.2   Age Differences in Retrieval Gating

Chapter 3 examines age differences in the ability to modulate the retrieval of mnemonic features according to their relevance to task goals (i.e., retrieval gating). This work builds on prior research demonstrating that younger adults can 'gate' the content of a retrieved memory episode if the content is irrelevant to the retrieval goal (Elward et al., 2015). In the reported study, retrieval gating was operationalized as the difference in the cortical reinstatement of scene information during a 'background' task (when the scene was relevant) relative to reinstatement during a 'location' task (when the scene was task-irrelevant). The findings demonstrated, for the first time, that retrieval gating does not necessarily extend to older adults.

As noted in the discussion in Chapter 3, under the assumption that retrieval gating reflects an active inhibitory process, the findings suggest that older adults 'clutter' their memories with irrelevant information, which has a detrimental impact on the retrieval of task-relevant information. It is entirely possible, however, that instead of 'cluttering' their memories with irrelevant information, older adults might be attempting to retrieve seemingly irrelevant information as a means of compensating for their relatively weak memories for the goal-relevant information. Indeed, in the task employed in our study, the locations of both the retrieval cues and their associated scenes were varied. Therefore, older adults might have attempted to retrieve scene information to maximize their success during the location task. To address this question, future research should unconfound the location and background tasks by presenting the scene backgrounds in a single location.

We currently have no hypothesis as to whether retrieval gating depends on active inhibition of a retrieved memory representation or simply a bias that favors the retrieval of the goal relevant information. Thus, the term should be considered purely descriptive and agnostic as to the

underlying mechanism. Future research should address whether retrieval gating does indeed reflect a process whereby task-irrelevant information is retrieved and subsequently inhibited, or alternatively, is not retrieved in the first place. The temporal resolution of fMRI makes it challenging to examine this issue by tracking the BOLD signal. Reinstatement could also be operationalized with electroencephalography, affording the ability to adjudicate between the aforementioned 'inhibition' and 'passive search' accounts.

Lastly, it is worth noting that whereas current findings demonstrate robust retrieval gating for scenes in younger adults, it is unknown whether gating extends to other stimulus categories. The experiment described in chapter 3 has motivated a new project to examine whether retrieval gating is detectable for object stimuli. The finding that younger but not older adults 'gate' object as well as scene reinstatement would strengthen the notion that the absence of retrieval gating in older adults reflects a generic age-related impairment of episodic memory function.

6.3 Age Differences in the Retrieval-related Anterior Shift

Chapter 4 describes the phenomenon of the retrieval-related anterior shift. We developed a novel approach to quantifying the shift at the participant level which allowed us to identify robust anterior shift effects in four scene- and face-selective regions of interest. The analyses revealed that the shift is greater in older than younger adults, and that the magnitude of the shift in the PPA was associated with worse memory for the image associates of the retrieval cues regardless of age. In light of the strong evidence for a posterior (perceptual) to anterior (conceptual) gradient in the ventral visual pathway, these findings are consistent with the proposal that the anterior shift reflects a transformation from a perceptually detailed representation of the study event towards a less detailed, more conceptually-weighted mnemonic representation. This proposal is highly consistent with findings that older adults retrieve less detailed, more gist-based memories than younger individuals (for review, see Grilli and Sheldon, 2022).

The proposal that cortical reinstatement reflects retrieved mnemonic content has been a dogma for at least two decades (for reviews see Danker and Anderson, 2010; Rissman and Wagner, 2012; Rugg et al., 2015; Xue, 2018). The study described in chapter 4, however, adds to other evidence that retrieval entails more than just the reactivation of the same neural populations that

were active during encoding. Rather, our findings are consistent with the notion that retrieval-related reinstatement involves a representational 'transformation' of the encoded memory (Favilla et al., 2021), which carries important implications for the interpretation of prior studies of cortical reinstatement. Some of these studies (e.g., Hill et al., 2020; Srokova et al., 2021), analyzed the strength of cortical reinstatement from *a priori* ROIs defined from data acquired during the encoding task or from a functional localizer (as in Chapter 3). Moreover, in studies testing for age differences in cortical reinstatement, the ROIs are often defined from data collapsed across age groups. As a result, age differences in the strength of cortical reinstatement can be confounded by the magnitude of anterior shift in younger and older adults. It is also important to note that the anterior shift may be overlooked when data are analyzed at the group level. Thus, the findings reported in chapter 4 might motivate researchers to re-analyze previously published cortical reinstatement data to examine whether they previously missed evidence for the shift and its modulation by age.

Some fruitful avenues for future research would be to directly test the hypothesis that the anterior shift reflects a transformation from detailed perceptual to more gist-based mnemonic representations. In our data, successful retrieval did not require the reactivation of high-fidelity information about the study event, and thus we cannot determine whether the shift would have been smaller had the test required the retrieval of more detailed information. Therefore, an obvious follow-up experiment would be to construct a memory test in which half the trials require participants to indicate the stimulus category of the cued image associate (as in our case), whereas the rest of the trials require retrieval of specific perceptual details of the image (e.g., "did the scene contain buildings?"). If our hypothesis is correct, the retrieval of perceptual details should be associated with a smaller anterior shift.

6.4   General Conclusions and Broader Impact

Age-related memory decline is greatly exacerbated in conditions such as mild cognitive impairment and Alzheimer's disease. Understanding the factors that contribute to memory changes in healthy aging is an essential precursor to understanding these much more severe memory declines that are characteristic of age-related neurodegenerative disease. For that reason, it is worth

highlighting one important commonality among the studies described above, and that is the sensitivity of fMRI-based metrics of the neural activity within the PPA to the variance associated with age and cognitive performance. Metrics of neural differentiation (Chapter 2), cortical reinstatement, (Chapter 3) and anterior shift (Chapter 4) derived from the PPA were all found to be sensitive to increasing age, and to predict memory performance in an age-invariant manner. Additionally, the findings in Chapter 5 demonstrated that although the object-selective LOC was sensitive to repetitions for objects only, the scene-selective PPA demonstrated repetition suppression effects for both scenes and objects. These and related findings are consistent with evidence indicating that the parahippocampal cortex supports a range of processes other than those contributing to scene perception, most notably, the representation of both spatial and non-spatial contextual information (Eichenbaum et al., 2007; Ritchey et al., 2019). An impactful avenue for future research would be enhance our understanding of the functional significance of these fMRI effects, and to examine whether they are sensitive to pathological aging. This line of research may potentially prove to have value for the early detection of mild cognitive impairment or Alzheimer's disease.

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BIOGRAPHICAL SKETCH

Sabina Srokova was born in Bratislava, Slovakia, in 1995. Sabina and her younger brother were raised by their mother, Helena, a schoolteacher, who taught her kids to have a passion for knowledge and a natural curiosity for the unknown. Sabina earned a BSc in Psychology from the University of Essex, United Kingdom, in 2017. Her undergraduate work led her to develop an interest in the cognitive neuroscience of episodic memory and cognitive aging, and this later motivated her to pursue a career in research. Sabina joined the laboratory of Dr. Michael Rugg at The University of Texas at Dallas as a doctoral student in 2018, where she continues her work on the behavioral and neural correlates of cognitive aging and episodic memory decline.

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    Research: Cognitive, social, emotional development of infants during first year of life

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Tutor of Statistics and Research Methods – University of Essex   2016 - 2017
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PUBLICATIONS

Srokova, S., Hill, P. F., & Rugg, M. D. (2022). The retrieval-related anterior shift is moderated by age and correlates with memory performance. Journal of Neuroscience, 42(9), 1765-1776. https://doi.org/10.1523/JNEUROSCI.1763-21.2021

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PREPRINTS AND MANUSCRIPTS IN PREPARATION

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de Chastelaine, M., **Srokova, S**., Hou, M., Kidwai, A., Kafafi, S., Racenstein, M., & Rugg, M. (2022; under review). Cortical thickness, gray matter volume and cognitive performance: a cross-sectional study of the moderating effects of age on their inter-relationships. bioRxiv. https://doi.org/10.1101/2022.09.29.510169

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Rugg, M.D., & **Srokova, S.,** (in prep). Age-related differences in cortical reinstatement (invited book chapter; to appear in the Encyclopedia of Human Brain, 2nd edition, Elsevier)

Olivier, J.M.*, **Srokova, S**., & Rugg, M. D. (in prep). Age and retrieval-related scene reinstatement: moderating effects of cortical thickness.

Aktas. A.N.Z.*, **Srokova, S**., & Rugg, M. D. (in prep). The effects of age on neural differentiation are moderated by global cortical thickness.

CONFERENCE PRESENTATIONS

Talks:

Srokova, S, Hill, P.F., & Rugg, M.D. *The Retrieval-related Anterior shift is Moderated by Age and Correlates with Memory Performance.* Dallas Austin Area Memory Meeting, Virtual, 2021

Srokova, S., Hill, P. F., Elward, R. L., & Rugg, M. D. *Effects of age on goal-dependent modulation of episodic memory retrieval.* Psychology Lecture Series Brownbag, UT Dallas, 2020

Srokova, S., Hill, P.F., Koen, J.D., King D.R., Rugg, M.D. *Neural differentiation at encoding predicts subsequent source memory performance in young and older adults.* Dallas Austin Area Memory Meeting, Waco, TX, 2019

Poster presentations:

Srokova, S., Aktas, A. N. Z, Koen, J.D., & Rugg, M.D., Age-related neural dedifferentiation at the level of individual stimulus items. Society for Neuroscience, 2022

Srokova, S., Aktas, A. N. Z, & Rugg, M.D. *The effects of age on neural differentiation are moderated by global cortical thickness.* New Perspectives on Declarative Memory Conference (University of East Anglia, UK), 2022.

Srokova, S., Hill, P. F., Rugg, M. D. *Scene-selective increases in the functional connectivity of the parahippocampal place area are greater in young than older adults during encoding but are age-invariant at retrieval.* Cognitive Aging Conference, 2022

Srokova, S., Hill, P. F., Rugg, M. D. *Retrieval-related anterior shift is moderated by age and relates to memory performance.* Dallas Aging and Cognition Conference, 2022 (Abstract accepted, conference cancelled due to Covid-19)

Srokova, S., Hill, P. F., Rugg, M. D. *Age differences in Retrieval-related Anterior shift in the Parahippocampal Place Area.* Cognitive Neuroscience Society, 2021

Srokova, S., Hill, P.F., Koen, J.D., King D.R., Rugg, M.D. *Age-related neural dedifferentiation in scene-selective cortical regions varies according to perceptual sub-category.* Cognitive Aging Conference, 2020 (Abstract accepted, conference cancelled due to Covid-19)

Srokova, S., Hill, P.F., Koen, J.D., King D.R., Rugg, M.D. *Neural differentiation is moderated by age in scene-selective but not face-selective cortical regions.* Society for Neuroscience 2019

Srokova, S., Hill, P.F., Koen, J.D., King D.R., Rugg, M.D. *Neural differentiation at encoding predicts subsequent source memory performance in young and older adults.* Cognitive Neuroscience Society 2019

Srokova, S., Loaiza, V. M., *Semantic relatedness corrects the age-related binding deficit in working memory and episodic memory* Cognitive Aging Conference, 2018

Srokova, S. *The impact of 10Hz fronto-parietal tACS on Working Memory capacity: neural or retinal effects?* Undergraduate Research Conference, University of Essex, 2017

MENTORING (STUDENTS / RESEARCH ASSISTANTS)

Ambereen Kidwai – PhD student, fMRI methods and analysis

Ayse Aktas – Research assistant, fMRI data collection and analysis, Freesurfer

Joshua Olivier – Research assistant, fMRI data analysis, Freesurfer

Nehal Shahanawaz – Research assistant, fMRI data collection, Eye-tracking

Sandra Girgis – Masters Student, Freesurfer data analysis

Salwa Shahid – Undergraduate student, supervision on a behavioral study

Miguel Talamo – Undergraduate student, supervision on a behavioral study

Harish Suryadevara – Undergraduate student, Freesurfer data analysis

Muneeza Sheikh – Undergraduate student, Freesurfer data analysis

PUBLIC OUTREACH

Center for Vital Longevity Advisory Council – *Age differences in the control of recollected content and neural selectivity,* talk in October 2021

Garland Retired School Personnel – *Dementia, memory, and healthy aging*, public talk in November 2019

Celebration Senior Magazine – *Dementia, memory, and healthy aging*, public talk in May 2019

UPCOMING RESEARCH PROJECTS

Effects of age on neural selectivity at memory encoding and retrieval and the relationship with memory performance and eye movement behaviors

> **My contributions:** Conceptualization, Methodology, Software, Analysis, Project administration, Write-up (1st author)

> **Current status:** fMRI & Eye-tracking data collection ongoing

Effects of age on the control of recollected content for scene and object stimuli using fMRI.

My contributions: Methodology, Software, Supervision, Write-up (2nd author)

(Project led by a supervised student, Ambereen Kidwai)

Current status: fMRI data collection ongoing

EXTRACURRICULAR ACTIVITIES AND VOLUNTEERING

Assistant Adviser – University of Essex Student's Advice Centre	2014 – 2017
Residents' Assistant – University of Essex Student Support	2016 – 2017
Psychology Peer Mentor – University of Essex Student Support	2015 – 2016
President – University of Essex Psychology Society	2015 – 2016
First Year Representative – University of Essex Psychology Society	2014 – 2015

HONORS, AWARDS, AND GRANTS

Nancy M. O'Neil and John Q. Stilwell, JD, PhD Fellowship – UT Dallas ($1,000)	2022
Dissertation Research Award – UT Dallas ($2,420)	2022
Reserve and Resilience in Cognitive Aging and Dementia Travel Award ($750)	2021
The British Psychological Society Undergraduate Award	2017
The Michael Lodge Memorial Prize, 1st place – University of Essex	2017
The highest overall grade of the Psychology graduating class	
The Ray Meddis Prize – University of Essex	2017
The best final undergraduate research project in Psychology	
The Margaret Bell Prize – University of Essex	2017
Outstanding contribution to the Psychology department	
The Big Essex Award - Platinum Award – University of Essex	2017
Undergraduate Research Opportunities Placement – University of Essex ($2,000)	2016
Frontrunners Plus Research Placement – University of Essex ($2,000)	2016
The Psychology Prize, 2nd Place – University of Essex	2016
The 2nd highest final grade among 2nd year Psychology undergraduates	
Dean's list – University of Essex	2014 – 2017

Functional & structural MRI data collection and analysis
SPM, MATLAB, R, Python, Freesurfer, SPSS, JASP

Eye-tracking data collection and analysis
Eyelink 1000 Plus, SR-Research Data Viewer

Programming and administration of experimental tasks
PsychoPy (fMRI and Eyelink integration), PsychoJS, Pavlovia, Prolific

Data visualization
R, MATLAB

Certified independent MR operator
Siemens Prisma 3T at The Sammons Center for BrainHealth (UT Dallas)

AFFILIATIONS

Cognitive Neuroscience Society

Society for Neuroscience