Interactions between performance monitoring and memory formation:

Multimodal studies on ageing and the role of muscarinic cholinergic signaling

Thesis

for the degree of

doctor rerum naturalium (Dr. rer. nat.)

approved by the Faculty of Natural Sciences of Otto von Guericke University Magdeburg

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submitted on 27/09/2022

defended on 26/01/2023

Zusammenfassung

Interactions between performance monitoring and memory formation: Multimodal studies on ageing and the role of muscarinic cholinergic signaling. M.Sc. Psychologie, M.Sc. Translational Neuroscience, Alexander Weuthen.

Nicht jeder Versuch sich etwas zu merken gelingt auf Anhieb. Nach wie vor ist jedoch umstritten, ob erkannte Erinnerungsmisserfolge einen lernförderlichen oder lernhinderlichen Effekt auf die Leistung folgender Lernversuche haben. Ein besseres Verständnis der Detektions-Mechanismen gescheiterter Erinnerungsversuche könnte Aufschluss darüber geben, welche neurokognitiven Mechanismen das Gelingen erneuter Einspeicherungsversuche begünstigen, und inwiefern altersbedingte Gedächtnisverschlechterung mit verschlechterter Fehlererkennung und gescheiterten Anpassungsprozessen einhergeht. Studie 1 verfolgte das Ziel, neurophysiologische Grundlagen der Handlungsüberwachung von Gedächtnisfehlern zu verstehen. Studie 2 befasste sich mit Alterungsprozessen der Interaktion von Handlungsüberwachung und assoziativer Gedächtnisleistung und verglich 25 ältere Probanden (50-80 Jahre, 10 männlich) mit 30 jüngeren Probanden (18-35 Jahre, 15 männlich) aus Studie 1. In Studie 3 erhielten 30 männliche Probanden (18-30 Jahre) den muskarinergen Antagonisten Biperiden (4 mg), um herauszufinden, wie das cholinerge System in oben genannte Interaktion involviert ist. Ergebnisse der Studie 1 konnten zeigen, dass der posteriore mediale frontale Kortex mit der Überwachung unvollständiger Gedächtnisrepräsentationen sowie Schwankungen der Repräsentativität zu lernender Gesichter assoziiert ist. Die Ergebnisse der Studien 2 und 3 deuten darauf hin, dass Alterung und muskarinerg-cholinerge Blockade Überschneidungen verschlechterter Gedächtnisleistung und höherer Unsicherheit bei erfolgreichen Erinnerungsabrufen aufweisen. Weitere Studien erscheinen notwendig, um die Spezifität eines cholinergen Defizits durch Integritätsverlust anderer neuromodulatorischer Systeme auf Gedächtnisfehler-Erkennung und Einspeicherungserfolg abzugrenzen.

Abstract

Interactions between performance monitoring and memory formation: Multimodal studies on ageing and the role of muscarinic cholinergic signaling. M.Sc. Psychologie, M.Sc. Translational Neuroscience, Alexander Weuthen.

Not every attempt to memorize something succeeds at the first attempt. However, it is still debated whether recognized memory errors have a learning-promoting or learning-hindering effect on the performance of subsequent learning attempts. A better understanding of the detection mechanisms of failed memory recall attempts could shed light on which neurocognitive mechanisms are involved in promoting the success of new learning attempts and could explain the extent to which age-related memory decline is associated with diminished memory error detection and failed post-error adaptation processes. Study 1 aimed to understand neurophysiological basis of how the brain monitors memory errors. Study 2 addressed age-related differences of interactions between performance monitoring and associative memory in 25 older (50-80 years, 10 male) compared to 30 younger (18-35 years, 15 male) adults of Study 1. In Study 3, 30 men (18-30 years) received the muscarinic antagonist biperiden (4 mg) to determine how the cholinergic system is involved in this interaction. Results of Study 1 showed that the posterior medial frontal cortex is associated with monitoring incomplete memory representations as well as fluctuations in the representativity of to-be-learned faces. Results of Study 2 and Study 3 suggest that ageing and muscarinic-cholinergic blockage show overlaps with respect to deteriorated memory performance and decreased confidence on successfully remembered memories. Further studies are necessary to delineate the specificity of cholinergic deficits compared to integrity loss of other neuromodulatory systems on memory error detection and successful memory formation.

Table of Contents

List of Abbreviations

dlPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
ERN	Error-Related Negativity
FALT	Feedback Associative Learning Task
FFA	Fusiform Face Area
fMRI	Functional Magnetic Resonance Imaging
FRN	Feedback-Related Negativity
GLM	General Linear Model
MRI	Magnetic Resonance Imaging
PCC	Posterior Cingulate Cortex
pMFC	Posterior Medial Frontal Cortex
PPC	Posterior Parietal Cortex
SD	Standard Deviation
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex

Table of Figures

Table of Tables

I General Introduction

1 Scope

1.1 The fate of memory decline

Does not everyone occasionally experience memory failure, on which situational details are forgotten even though they are relevant to a current decision? Such memory deficits do not just dissolve on time passing but deficits in memory functioning increase with higher age. Prominent theories about brain and cognitive ageing discuss the decline in brain structure and function, as well as inhibitory deficits as main causes of memory performance decline (Grady, 2012). Furthermore, integrity loss in the basal forebrain cholinergic system during healthy ageing is assumed to explain age related decline in memory performance (Düzel et al., 2010), while other studies propose that pharmacological blockage of muscarinic acetylcholine receptors can be used to model memory decline in healthy adults (Blokland, 2022). Having subjective memory decline has shown to be predictive for individuals to have higher levels of neurodegeneration, while in later stages of a neurodegenerative pathology memory deteriorations may go unnoticed due to disease related anosognosia (Kuhn et al., 2021). But what underlies the ability to recognize failed learning attempts and how do individuals cope with a recognized insufficient memory quality?

1.2 Adaptive and non-adaptive accounts on memory errors

Cognitive control researchers are still debating about the perspective that perceived errors lead to increased attention and performance improvements (Botvinick et al., 2001; Maier et al., 2011; Ullsperger et al., 2014; Yeung et al., 2004) and the perspective that error detection is distracting from the main task and therefore leading to further memory errors (Decker et al.,

2020; Notebaert et al., 2009). Based on considerations of post-error memory impairments, it seems reasonable that strategies using error-less learning have been proposed to circumvent and compensate memory deficits on aged individuals with amnestic mild cognitive impairment (Roberts et al., 2018). But studies do not generally agree on advantages of error-less learning. For example, it has been suggested that such advantages may be the strongest in individuals with profound amnestic deficits (Metzler-Baddeley & Snowden, 2005), that this advantage is lower in individuals with better error detection abilities (Roberts et al., 2018), and that better error-full learning capabilities display a general advantage for working and recall memory (Fillingham et al., 2006). But are these perspectives on adaptive and non- or even mal-adaptive consequences of memory errors mutually exclusive? Studies investigating interindividual differences on the adaptivity of error detection seem to overlook that learning performance and, thus, also post-error learning improvements fluctuate within the same person over time. Besides findings of deteriorations in post-error memory formation, factors among the timing of post-error arousal responses have been suggested as relevant factors underlying whether memory errors are followed by adaptive or non-adaptive performance monitoring consequences (Decker et al., 2020). Neither of these perspectives may explain the abundance of results found in previous studies because different cascades of post-error processes may run simultaneously (Wessel, 2018). An improved understanding of how the brain's monitoring processes detect and adapt inaccurate memory representations may benefit from investigating moment-to-moment fluctuations of post-error memory formation success. Probably everyone has experienced such variations in occasional learning success and failure even on a second attempt for learning something. Respective research therefore does not rely on contrasting impaired with unimpaired individuals, but can use continuous learning designs with more than one chance for learning something to study what underlies the adaptiveness of post-error memory formation processes.

1.3 How does the brain detect memory errors?

The above considerations on how the brain up- or downregulates its resources for beneficial learning states, seem to imply accurate error detection processes. It therefore seems surprising that there is a lack on studies addressing how the brain monitors the insufficiency of memory representations. A sorrow understanding on how the brain monitors memory performance may be a necessary precondition for understanding moment-to-moment fluctuations in post-error improved or impaired learning successes. In principle, performance monitoring has been introduced as a domain general system accumulating internal or external evidence of whether increased effort is required (Ullsperger et al., 2014). For the memory domain, neurophysiological underpinnings of performance monitoring have not been systematically investigated so far. Therefore, the three experiments described in this dissertation investigated which neurophysiological processes are associated with the recognition of memory errors and underpinnings of the capability to shift into beneficial learning states.

1.4 Successful learning updates memory representations

When a target region or network has been found underlying monitoring of memory errors, the question arises how respective cognitive control processes can interact with the quality of following learning attempts. To understand the dynamic neurophysiological underpinnings of enhanced attention, multivariate classification on stimulus representations may estimate how much attention has been spent on stimulus characteristics, since the degree to which objects are attended has shown better decoding accuracies (Nelissen et al., 2013). Such analyses build on recent methodological developments in the field of neuroimaging on determining brain representations of cognitive processes. A big step forward in functional magnetic resonance imaging (fMRI) research was the shift from univariate to multivariate models, increasing the

interpretability on which brain regions may be involved in distinguishing between similar mental contents and operations (Haxby et al., 2014). For example, there is ample evidence that information on face identity is most robustly represented in right-lateralized posterior fusiform gyrus (Schwarz et al., 2019; Yovel, 2016). Right posterior fusiform gyrus further seems to show hemodynamic response profiles able to differentiate participant-specific face processing clusters (Schwarz et al., 2019), with fusiform face area (FFA) 1 in fusiform gyrus 2 and FFA 2 in fusiform gyrus 4 (Caspers et al., 2013). fMRI analyses presented in this dissertation used face stimuli and multivariate classification was based on cytoarchitectonic masks of right fusiform gyrus 2 and 4 regions, the current dissertation will refer to FFA when topographical results in posterior fusiform gyrus are discussed. In this regard, it has been suggested that participant-specific models should be used for an accurate detection of FFA (Rossion et al., 2012). Based on an individual's FFA model of face-representativity it will be investigated what underlies adaptive post-error memory amplification. Such developments of fMRI analyses have paved the way to investigate how the brain monitors memory errors and determine what underlies fluctuations on the representativity of stimuli intended to be later remembered. The current dissertation will address these questions by using multivariate cross-classification of face-representativity.

1.5 Ageing and neuromodulatory deficits

Upon understanding on how the brain detects memory errors, and what underlies enhanced stimulus representations during memory formation, one may ask to which degree memory decline during ageing may share a neurophysiological basis with deficits in memory error detection processes and consequently a decreased likelihood of adaptive brain state changes. Life span differences on performance monitoring showed that older adults have slower reaction times particularly during response conflicts and that age-related deficits in performance

monitoring are evident on tasks where participants have to differentiate the valence of action outcome representations (Hämmerer et al., 2014). Another study suggested that less stable task representations may be compensated by an increased tendency to use external cues for performance evaluation (Hämmerer et al., 2019). For monitoring the adequacy of memory representations, this suggests that with increasing age adults become less capable of evaluating whether a particular memory is accessible or inaccessible, although this leaves open whether older adults may underestimate or overestimate their memories quality. Age-related deficits in guiding attention to distinct task-relevant stimuli and updating task representations have been explained by reduced efficiency of acetylcholine and dopamine neuromodulatory systems across the adult lifespan (Störmer et al., 2012). As some studies propose the idea that acetylcholine mediates post-error behavioral performance improvements (Danielmeier et al., 2015; Hester et al., 2012), this suggests that reduced efficiency in the cholinergic system can explain why monitoring memory errors has less strong effects on attentional upregulation and post-error improved memory formation. The current dissertation will address questions on how ageing affects this interplay and examine, how the muscarinic-cholinergic antagonist biperiden diminishes memory performance and the ability to recognize quality differences of memory representations.

2 Theoretical background

2.1 Key concepts

In the following chapters, several key concepts are introduced, such as how memory formation and performance monitoring can be investigated, how brain regions and networks may be understood from a systems neuroscience perspective, and how these dynamics may be

changing upon brain ageing process including a less efficient neuromodulation by acetylcholine.

2.1.1 The subsequent memory effect

To understand what underlies successful memory formation one typically has to rely on whether later retrieval failed or was successful. Using the subsequent memory effect, previous studies have investigated which neurophysiological underpinnings during encoding of memories can explain later retrieval success and consequently indicate good memory formation. In a meta-analysis on 74 fMRI studies (Kim, 2011), the most consistent brain regions involved in the subsequent memory effect have been related to three different cognitive processes: content processing in posterior fusiform gyrus and left ventrolateral prefrontal cortex (vlPFC); attention during encoding in a region overlapping with intraparietal sulcus and posterior parietal cortex (PPC), premotor cortex and posterior medial frontal cortex (pMFC); and storage in medial temporal lobe. Furthermore, subsequent forgetting has been related to posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (vmPFC) which show higher hemodynamic responses for later unsuccessful compared to successful retrieval and trial-to-trial functional connectivity patterns have been suggested to explain fluctuations in memory performance. Another meta-analysis has investigated how subsequent memory effects are related to healthy ageing and suggested over-recruitment of middle frontal gyrus and superior frontal gyrus, precuneus and inferior parietal lobe, and under-recruitment of fusiform and occipital gyri as potential basis of for worse memory performance in older adults (Maillet & Rajah, 2014). But what is meant by under- and over-recruitment of brain regions and how does the brain decide on which areas to recruit for a particular cognitive demand?

2.1.2 Performance monitoring and error detection

Recognizing unsuccessful goal-oriented actions and cognitive processes – such as failed memory retrieval – represents an important precondition for beneficial performance adaptations to follow. Electroencephalography (EEG) studies have investigated neurophysiological underpinnings on the accumulation process of error evidence with high temporal resolution and could reveal two frontocentral EEG components related to different sources of error detection, namely the error-related negativity (ERN) and the feedback-related negativity (FRN), while both have been source-localized to pMFC (Debener et al., 2005; Gruendler et al., 2011). The ERN has been related to internal signals accompanying erroneous actions and the FRN to external error evidence by the presentation of negative performance feedback (Ullsperger et al., 2014). Although the exact mechanism on how pMFC accumulates evidence is still debated, fMRI studies have shown that signals within pMFC can predict post-error performance improvements (Hester et al., 2008; Klein et al., 2007). Besides these neuroimaging signals related to performance monitoring, participants typically slow down their behavioral responses after error evidence, a phenomenon called post-error slowing (Danielmeier & Ullsperger, 2011; Debener et al., 2005; Rabbitt, 1966). But do these error signatures in brain and behavior indicate the implementation of successful adaptation processes? Both perspectives have been brought up to the field of cognitive neuroscience. Adaptive perspectives on error-related brain signals and slowing of behavioral responses suggest that error detection improves task-related processes and improves following behavioral responses (Botvinick et al., 2001; Yeung et al., 2004). On the other hand, non-adaptive perspectives view error-related signals as orientation responses without benefits for task improvement (Notebaert et al., 2009) or even suggest task impairments due task-engagement competing process, such as rumination and inward orientation (Decker et al., 2020).

2.1.3 From brain regions to brain network

In the past two decades, voices have been risen that the brain can be better understood by assigning brain regions to brain networks (Power et al., 2011; Yeo et al., 2011). Regarding the above-mentioned inward orientation, some studies speak of task-positive and task-negative networks, meaning regions which typically show increased hemodynamic responses during active task engagement – such as central-executive and salience networks – and regions which have higher hemodynamic signals during passive states and resting state sequences – such as default mode network. Although the number of brain networks is a matter of debate and naming of network is ambiguous, three of the most investigated brain networks are the default network, salience (or ventral attention) network and executive control (or frontoparietal or central executive) network. Furthermore, it has been suggested that the salience network regulates switches between default mode and executive control networks (Menon, 2015) depending on whether the locus of attention is internal – such as during memory retrieval or rumination – or external such as when attending visual stimulus features for memory encoding. The salience network includes regions among anterior insula and anterior midcingulate cortex (Seeley et al., 2007), while the latter largely overlaps with the pMFC region assumed to be a central node for performance monitoring functions (Ullsperger et al., 2014). pMFC, however, displays considerable morphological variability in regard to presence or absence of a paracingulate gyrus which complicates the anatomical specificity and differentiation between anterior midcingulate cortex and pre-supplementary motor cortex regions – but respective variability can also explain differences on the topography of feedback-related hemodynamic responses in pMFC (Amiez et al., 2013). Due to this morphological variability between individuals, the current dissertation will refer to pMFC even when reporting results of other studies on anterior midcingulate cortex, pre-supplementary motor cortex or rostral cingulate zone. Increased hemodynamic responses in pMFC have also been found in the subsequent memory effect,

suggesting that pMFC and the salience network may also fulfill switch functions of default mode and executive control networks during memory encoding. The executive control network includes regions such as dorsolateral prefrontal cortex (dlPFC), vlPFC and PPC (Seeley et al., 2007). While dlPFC is assumed to interact with PPC during high working memory load and sustained attention (Curtis & D'Esposito, 2003), executive control network regions to a large proportion represent cortical regions found during successful memory formation (Kim, 2011). On the other hand, the default mode network includes vmPFC, PCC and precuneus and is typically related to resting conditions (Raichle et al., 2001), and has been related to subsequent forgetting with increased hemodynamic responses for forgotten compared to successfully retrieved memories (Kim, 2011). It is, however, important to note that the meta-analysis on the subsequent memory effect investigated hemodynamic responses differences during encoding (Kim, 2011), and that other periods during a memory task such as during retrieval may show a different involvement of these default mode network regions (Piccoli et al., 2015). This is also in line with the view that brain network's functional connectivity changes according to task demands (Gerchen & Kirsch, 2017) and suggest that the interplay of brain regions and networks involved in memory formation may better be understood by investigating moment-to-moment fluctuations of memory-relevant stimulus representations.

2.1.4 Age-related decline in brain structure and function

Episodic memory deficits are among the first observed symptoms of normal ageing (Tromp et al., 2015) and suggest that the brain network dynamics underlying successful memory formation and retrieval are not sufficiently compensated by the brain's reserves. Brain structural decline on gray and white matter has especially been found in frontal regions (Kaup et al., 2011) and longitudinal age effects have also found hippocampal volume decrease to explain a decrease in memory performance (Persson et al., 2006). From a brain functional

perspective, the idea has been proposed that the brain dedifferentiates during ageing (Lindenberger & Baltes, 1994), which may explain why hemodynamic responses found in fMRI studies are more diffuse (Grady, 2012). One of the most influential theories on age-related cognitive and memory decline is the inhibition deficit (Hasher & Zacks, 1988), which suggests that the brain becomes worse in suppressing unimportant information and distinct memories are consequently less accessible in older age. Such a deficit is in line with the posterior-anterior shift in ageing theory, which proposes that neural resources in the frontal cortex are upregulated because of sensory stimulus processing deficits (Davis et al., 2008). In other words, such deficits may increase working memory load – associated with the upregulation of executive control network with nodes in dlPFC and PPC – and therefore explain why older adults show increased hemodynamic responses in frontal regions. This is also what the meta-analyses on ageing effects on subsequent memory has found: frontoparietal increased and occipitotemporal decreased hemodynamic responses (Maillet & Rajah, 2014). This leads to the hypothesis that age-related executive control network upregulation is initiated by salience network nodes upon demand dependent recruitment. Intact error detection may be a relevant factor moderating the ability to learn from mistakes, in order to not rely on error-less learning environments (Roberts et al., 2018). Interestingly, a review on the link between pMFC function and goal-oriented behavior suggest that pMFC integrity and its role in task engagement may be a crucial protective factor to keep youthful cognition into old age (Touroutoglou et al., 2020).

2.1.5 Acetylcholine and neuromodulation

When investigating what underlies age-related differences of interactions between performance monitoring and memory formation, pharmacological interventions used to counteract age-related memory decline may hint to potentially involved neuromodulators. Do

these drugs modulate outward-directed attention related to increased recruiting of executive control network regions? In order to compensate for cognitive and memory decline in mild and moderate stages of Alzheimer's disease, acetylcholine esterase inhibitors are a major treatment strategy to restore healthy levels of functioning, with the assumption that acetylcholine levels in the synaptic cleft are increased and therefore better able to enhance efficiency of cholinergic neurotransmission (Majidazar et al., 2022). Other studies suggested that basal forebrain degeneration precedes and predicts further neurodegeneration in entorhinal cortex and neocortical regions (Fernández-Cabello et al., 2020; Schmitz & Nathan Spreng, 2016). Studies on individuals without neurodegenerative pathology have also related MRI markers of decreased basal forebrain integrity with declining memory functions (Düzel et al., 2010). Although basal forebrain has not often been investigated in fMRI (Markello et al., 2018), studies on rodents emphasized the crucial role cholinergic neurons of the medial septum subregion in the basal forebrain have for hippocampal functioning and memory formation (Mikulovic et al., 2018). While non-invasive studies on humans may not have the specificity to target the basal forebrain cholinergic system as done in rodent studies, oral intake of cholinergic drugs may help elucidate general cholinergic neuromodulatory effects on brain and behavior during task performance. The use of the muscarinergic-1-receptor antagonist biperiden is proposed to cause episodic memory deficits (Blokland, 2022) and diminished post-error adaptations on brain and behavior (Danielmeier et al., 2015). Therefore, the current dissertation aims to investigate whether adaptive post-error improvements on memory formation are less likely after oral intake of biperiden.

2.2 Key methods

As there is currently no suitable method available to conduct neurophysiological studies with high spatial, temporal, as well as neurochemical resolution simultaneously, the current

dissertation chose to address these perspectives on interactions between performance monitoring and memory formation in three different studies. Respective conclusion will be drawn from investigating intra- and interindividual behavioral differences on task performance and reaction times, pharmacological effects and different neuroimaging modalities assessing brain function related to behavioral performance.

2.2.1 Functional magnetic resonance imaging

Magnetic resonance imaging (MRI) is a neuroimaging method with high spatial resolution and can generally be assessed within different modalities roughly distinguished into sequences for structural, functional and diffusion imaging. Structural MRI analyses focus on the principle that different brain tissues can be distinguished by their water content and magnetic relaxation profile, such that methods like voxel-based-morphometry can estimate the contribution of gray matter, white matter and cerebrospinal fluid to the recorded magnetic resonance signal. On the other hand, fMRI is based on the Blood-Oxygen-Level-Dependent effect and brain regions involvement in particular cognitive processes are determined by their estimated metabolic demand and respective consumption of oxygen. A typical hemodynamic response is several seconds delayed compared to the cognitive event. Effects of these events on blood oxygen level dependent (BOLD) effects are estimated with the convolution of a so-called hemodynamic response function. Since all regions have a particular value of BOLD signal at any time, a systematic analysis of cognitive processes related effects requires to subtract two similar events hemodynamic responses from each other. At best, underlying cognitive processes only differ in particular feature of interest, such as when comparing holistic visual recognition processes of gray-scaled face and house images. Multivariate analyses have further influenced the field in the past 20 years, such that nowadays respective tools can be integrated on analyses pipelines

and compare how voxels in the same brain region differ in their hemodynamic response weights used to distinguish two similar stimuli such as faces or houses (Haxby et al., 2014).

2.2.2 Cross-sectional age effects

Using cross-sectional studies has advantages but also drawbacks compared to longitudinal analyses on ageing processes. A major advantage of cross-sectional studies, is that they are more efficient if larger age differences are investigated. The current dissertation aimed to identify memory formation and performance monitoring differences and their neurophysiological underpinnings during healthy ageing and compared to adults who are not expected to show strong age effects. Therefore, a cross-sectional design has been chosen with younger adults in the age of 18 and 35 years and older adults between 50 and 80 years. This cross-sectional comparison may be sufficient to determine age-related behavioral and neurophysiological differences, and allow to compare whether pharmacological blockage of the cholinergic system generates similar differences as expected for healthy ageing.

2.2.3 Pharmacology

Since cross-sectional comparisons investigate age group differences, they are potentially affected by cohort-effects and systematic different life events shared by age groups. Pharmacology can go beyond correlational influences when used in randomized, double-blind, placebo-controlled studies. For the current study selective muscarine-1-receptor antagonist Biperiden was chosen to be applied within 4 mg oral intake. Biperiden is more strictly related to age-related episodic memory decline than scopolamine which has a much less selective muscarine-1-receptor binding profile (Blokland, 2022). In order to simulate ageing effects of the basal forebrain cholinergic system, the use of muscarinic antagonists in pharmacological challenge studies might provide a suitable model of brain ageing effects (Klinkenberg &

Blokland, 2010). A previous study has found diminished error-driven improvements induced by biperiden (Danielmeier et al., 2015). In order to determine effects of cholinergic neuromodulation on interactions between performance monitoring and memory formation, Study 3 used a pharmacological randomized double-blind placebo-controlled cross-over design, giving the same individuals biperiden and placebo on different sessions with sufficient wash-out time of at least five days in between.

2.3 Study design

The current dissertation consists of three studies which dealt with the topics general brain network interplay during for successful adaptive memory formation in study 1, modulation by ageing in Study 2 and the role of cholinergic deficits in Study 3. Study 1 was is based on a cohort of 30 young healthy adults aged between 18 and 35 years which participated in an fMRI study during simultaneous performance of behavioral tasks. Study 2 used the same paradigms in older adults within an age range between 50 and 80 years, while in Study 3, slight changes for optimizing experimental efficiency and task duration were implemented.

2.3.1 Behavioral task design

The current dissertation aimed to determine interactions between performance monitoring and the quality of memory representations, including respective memory formation processes. Compared to other studies investigating the subsequent memory effect, the role of detecting memory errors has been relatively unexplored and requires evaluation of internal or external evidence accumulation processes on memory errors.

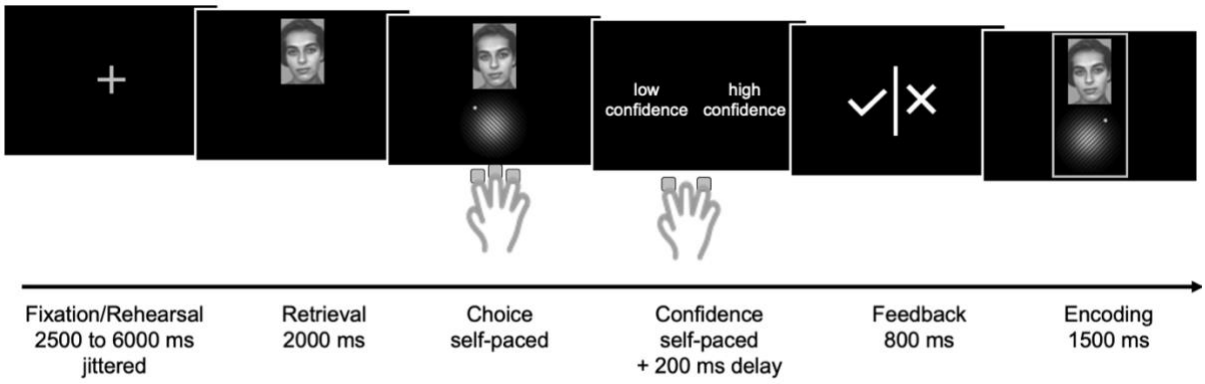

Figure 1. Overview on the trial design in FALT.

FALT. In the feedback associative learning task (FALT) (see Figure 1), error detection was inferred from low-confidence selection and the presentation of negative feedback. Participants had to rate their retrieval confidence on a binary scale by left or right keyboard presses and later obtained informative performance-based feedback on the correctness of their choice during retrieval. Each trial began with a fixation cross in the middle of the screen with a jittered duration between 2500 and 6000 milliseconds (ms). Then, a face stimulus was presented and 1000 ms later a gabor patch appeared in a random but incorrect orientation (out of the eight possible orientations). Participants then had to choose the matching orientation with their right index finger (left directed rotation) and right ring finger (right directed orientation). If they saw a face for the first time, they were instructed to make a guess. On subsequent encounters of the face, they should recall the associated orientation from their memory. After confirming their choice with the right middle finger, a visual confidence rating was presented on screen, such that participants could determine the confidence in their rating with respective finger presses towards low (left) and high (right) certainty. The side of presentation on low and high confidence was altered for each next trial. After a 200 ms delay period, either positive or negative feedback was presented for 800 ms according to correctness of the chosen orientation. At the end of each trial, there was a 1500 ms encoding screen showing the correct combination

of face and gabor patch. Each face was presented four times, with at least two and a maximum of 15 trials until the next trial with the same face. As shown in Figure 2, the FALT consisted of five independent runs with each eight new faces, summing up to 160 trials in total.

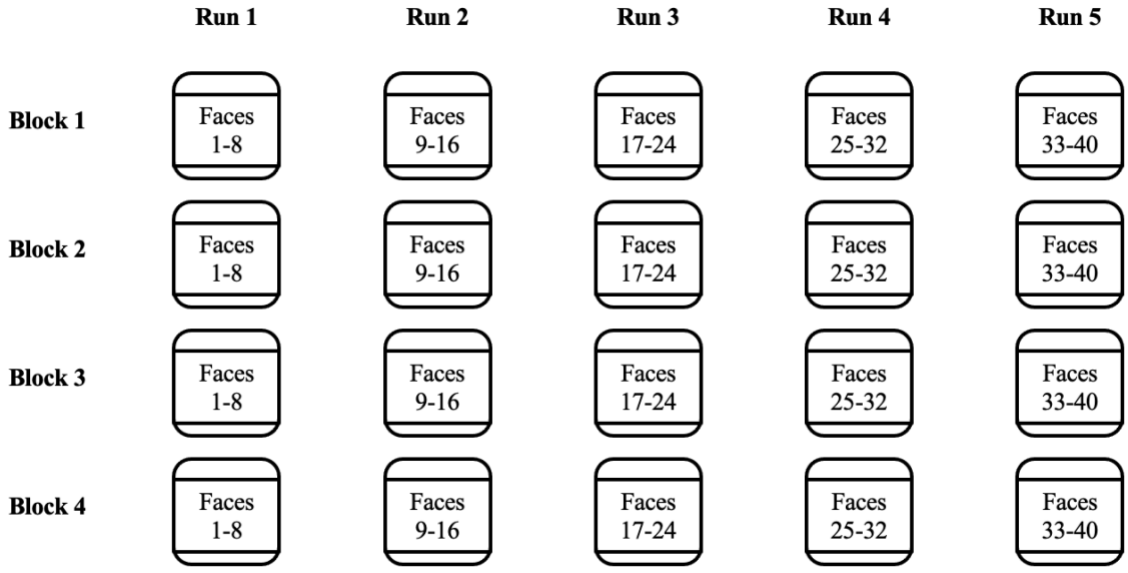

Figure 2. Overview of FALT blocks and runs.

Between runs, participants were presented with a pause screen on which the relative number of correct trials was displayed. The next run with eight new face stimuli was resumed with a confirmation button press. There were 120 trials in which participants could successfully remember the correct associated gabor patch orientation from past learning opportunities, because they guessed in block 1. As shown in Figure 3, trials were differentiated based on performance of current and future retrieval as being *ErrorError*, *ErrorCorrect*, *CorrectCorrect* or *CorrectError* trials. The subsequent memory effect typically contrasts encoding-related hemodynamic responses for trials which are later correct compared to incorrect remembered trials. The current dissertation further specified this contrast in a continuous learning

experiment with four learning opportunities per face such that the post-error subsequent memory effect contrasts *ErrorCorrect* and *ErrorError* trials.

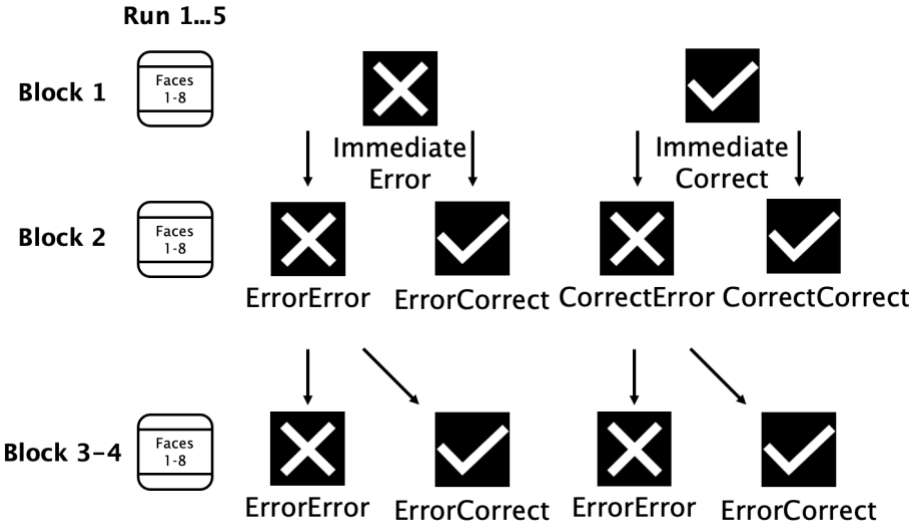

Figure 3. Schematic overview of different trial types in FALT.

Table 1. Signal detection theory analysis on the match between confidence and correctness.

	Correct	Error
High confidence	Hits (H)	False alarms (FA)
Low confidence	Misses (M)	Correct rejections (CR)
	$\text{Sensitivity} = \frac{H}{H + M}$	$\text{Specificity} = \frac{CR}{CR + FA}$

To determine whether not only memory but also memory monitoring is affected by age or cholinergic blockage, *d*' (*DPrime)* detection accuracy and response bias (*DBias*) were calculated in Study 2 and Study 3 by applying Z-transformed probability functions of sensitivity and specificity rates (see Table 1):

$$DPrime = Z(sensitivity) - Z(1- specificity)$$

$$DBias = -(Z(sensitivity) + Z(1- specificity))/2$$

Localizer. For the 1-back localizer task, participants had to press the confirmation key as fast as possible when the presented stimulus combination was a direct repetition of the immediately preceding trial (see Figure 4). Participants were instructed to attend and compare both stimuli, although faces and houses kept their assigned gabor patch orientations in all repetitions. As shown in Figure 4, on the third stimulus presentation participants needed to press the confirmation key because house and orientation were the same as in the preceding trial. Presentation times were analog to the fixation and encoding times in FALT. Within each run, face and house stimuli were presented four times, summing up to 80 trials for five runs in total. Direct repetitions occurred in two of 16 trials per run to keep participants engaged with attending, encoding and rehearsing the presented stimuli. The localizer task served to build fMRI-based participant-specific face recognition models. The relatively low proportion of 12.5 % repetition trials was chosen to maximize the number of suitable trials unaffected by motor responses. For each participant, a multivariate model was trained to distinguish encoding of face and house trials in the localizer task based on an individual's fMRI voxels in FFA. These models were applied to epochs in FALT – such as encoding, fixation and retrieval – to evaluate how pronounced face processing was indicated by hemodynamic response patterns in FFA. Based on previous studies, it was assumed that higher stimulus representation estimates indicate increased selective attention (Leong et al., 2017; Nelissen et al., 2013). Therefore, the first two studies in the current dissertation investigated which brain region are related to the estimated representativity of face stimuli during memory formation. During the inter-trial-interval a fixation cross was presented – which have been used by participants to rehearse the to-be-learned stimuli in their working memory. Because this fixation or rehearsal period may also contribute to memory formation, it was also included in analyses of face representations. Throughout the dissertation, the predicted estimates of the applied face recognition models will

be termed face-representativity. In Study 3, FALT and localizer paradigms were slightly adapted for simultaneous EEG instead of fMRI recording, although only behavioral data were investigated in the current dissertation. Changes in the paradigms will be described in the respective methods section.

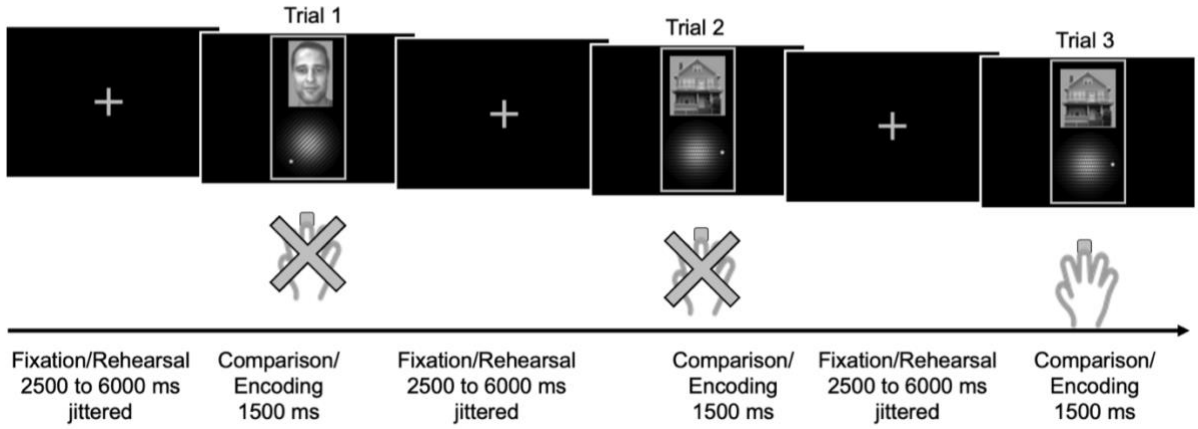

Figure 4. Three example trials of the 1-back localizer task.

2.3.2 Conducted analyses

The current dissertation aimed to determine interactions between performance monitoring and associative memory formation. In total, 115 experimental sessions went into the analyses of three studies, with 30 participants (15 females, 15 males, 18-35 years) in Study 1, 25 participants (15 females, 10 males, 50-80 years) in Study 2 and 30 participants (30 males, 18-30 years) joining twice in Study 3, once for the placebo and once for the verum session. In Study 3, only male participants were recruited due to the invasiveness of blood tests for pregnancy exclusion and to rule out potential influences of varying hormone levels throughout the menstrual cycle. All three studies investigated non-smokers with a body-mass index between 20 and 30 kg/m^2 to increase comparability of the three studies and to exclude interactions between the drugs muscarinic and self-administered of nicotinic cholinergic actions in Study 3. Behavioral and neuroimaging parameters have been analyzed, such as

memory accuracy and confidence ratings with respective reaction times, fMRI effects of memory success, error detection and stimulus representations in comparison between older and younger adults. Study 1 focused on fMRI analyses determining error detection processes of memory retrieval and used multivariate cross-classification to infer stimulus representativity during post-error memory formation. Study 2 assessed which memory and error detection performances distinguish younger and older adults based on behavioral and hemodynamic differences. And in Study 3, behavioral effects upon muscarine-1-receptor blockage on interactions between performance monitoring and memory formation were investigated and compared to age effects found in Study 2, to evaluate which age-related performance differences may be due to cholinergic deficits.

I Empirical Studies

3 Study 1: Interactions between performance monitoring and memory formation – an fMRI study on younger adults

3.1 Introduction

A major cognitive capability is to form memories and make use of acquired knowledge when required again. While memory formation is not always successful, the current study investigates how the brain monitors failed retrieval and improves memory formation in following learning situations. Studies focusing on neurophysiological network interplay underlying successful cognitive performances highlighted that the ventral-attention/salience network switches between upregulated central-executive/frontoparietal network on situations of externally required attention and upregulated default-mode network on situations requiring internally guided attention. To regulate network dynamics for performance improvements it seems necessary, that evidence has been accumulated whether there is a need for shifts in the

locus of attention. It has repeatedly been suggested that the brain dwells a domain general performance monitoring system based in pMFC (Gruendler et al., 2011; Ullsperger et al., 2014) and some studies have proposed that error-related hemodynamic signals in pMFC are predictive for successful performance adaptations (Klein et al., 2007) and post-error improved associative learning (Hester et al., 2008). For post-error memory formation, EEG signals at time of the FRN have shown to be predictive for whether following re-encoding succeeds or fails (de Bruijn et al., 2020). Although there is a debate about whether recognized memory errors lead to adaptive or non-adaptive consequences for further learning situations (Decker et al., 2020), it seems surprising that previous studies have not specifically investigated how the brain detects inaccurate memories and upregulates processing of memory-relevant stimuli. The current study aims to determine whether pMFC is systematically related to evidence for memory errors and related to increased stimulus representations in the ventral visual stream.

Three phases of memory processes are typically distinguished: encoding, consolidation and retrieval. When retrieval fails, it is questionable in which of the memory phases stimulus representations are diminished. Although successful encoding and consolidation do not guarantee successful retrieval – such as under high cognitive load conditions and distraction – later retrieval success requires encoding and maintenance quality to be sufficiently high for memory representations to not vanish before recollection. Based on this logic of the subsequent memory effect, previous neuroimaging studies have investigated which neurophysiological signals at time of encoding predict later retrieval success. Cognitive processes and brain regions contributing to the subsequent memory effect have been differentiated into content processing in FFA and left vlPFC, storage function in medial temporal lobe and attention during encoding in PMC, pMFC and PPC (Kim, 2011). This perspective leaves open how these regions are related to the recognition process on attentional upregulation demands, which may follow

failed retrieval and lead to adaptive cognitive state changes. pMFC has been related to performance monitoring and adaptive behavioral changes (Ullsperger et al., 2014), which may explain pMFC involvement in studies investigating the subsequent memory effect. While increased hemodynamic responses in executive control network are related to working memory load and upregulated attention (Curtis & D'Esposito, 2003), other regions may signal the need for adaptations to these regions, such as salience network regions (Menon, 2015) and neuromodulators such as acetylcholine (Ljubojevic et al., 2018). In order to understand what underlies the enhanced processing of stimulus features for memory storage, multivariate decoding approaches can be a promising approach to evaluate the degree of respective behaviorally-relevant categories represented (Erez & Duncan, 2015; Leong et al., 2017). Stimulus decodability has also been related to the degree how much attention has been spent on by means of executive control network involvement (Nelissen et al., 2013). But where are stimulus representations located, which may be maintained by executive control network?

During consolidation and rehearsal processes it is commonly assumed that stimulus-specific regions in interaction with the medial temporal lobe are replaying memory contents and that this replay process is beneficial for later retrieval (Liu et al., 2022). Therefore, past achievements in the field of visual object recognition may help determining how the recognition of memory errors interacts with the quality of mental representations of to-be-learned stimuli. Stimuli from the face category have often been used for multivariate analyses and compared to more posterior face-selective regions among right lateralized FFA, of which face processing is assumed to indicate a holistic interpretation of faces (Ramon & Rossion, 2012; Yovel, 2016).

The current study aims to determine whether pMFC carries out performance monitoring during associative retrieval and is involved in improving memory formation by increasing stimulus representativity after memory errors. Therefore, a study was designed assuring that participants detected memory errors by using internal evidence using subjective retrieval confidence and external evidence with the presentation of negative feedback. To further differentiate the degree of representativity on face stimuli during the post-error encoding period, multivariate cross-classification on a separate 1-back localizer task was used by fitting a respective face-representativity model on voxels on form fusiform gyrus 2 and 4. Following hypotheses are formulated:

Hypothesis 1: pMFC is involved in subsequent memory performance with higher hemodynamic response for encoding of *ErrorCorrect* than *ErrorError* trials.

Hypothesis 2: Performance monitoring related hemodynamic signals in pMFC are positively related to signatures of incomplete memory representations, being

(a) unsuccessful retrieval, namely higher for retrieval of unconfident *ErrorError* than high-confidence *ErrorCorrect*,

(b) memory error expectation, namely higher for selection for low than high confidence,

(c) memory error feedback, namely higher for presentation of negative than positive feedback.

Hypothesis 3: Increases in face-representativity in FFA brain regions is related to pMFC hemodynamic responses.

3.2 Methods

3.2.1 Participants and procedure

30 young adults (15 male, age 18-35 years) without history of neurological or psychiatric disorders participated in the current fMRI study after checking exclusion criteria (body mass index between 20 and 30 kg/m^2, non-smokers, no history of psychiatric or neurological disorders, no metal implants) via phone interview. Participants gave written informed consent before study begin and were compensated with study credits or money for their time. Participants obtained written instructions on the behavioral tasks and task comprehension was ensured by practice trials on a laptop computer outside the scanner. Next, they were positioned in the MRI scanner with cushions inside the head coil and under the arms to increase comfort and decrease excessive movement throughout the scan. The keyboard was placed under the right hand, the photoplethysmography sensor on the left middle finger and the breathing belt around the chest on the position of the highest elevation.

3.2.2 Stimuli

The cognitive paradigms presented during fMRI scanning used emotionally neutral faces from the Picture Database of Morphed Faces (Jäger et al., 2005) and house images from the Dalhouses sample (Filliter et al., 2016), on which the background color was replaced with the same grey scale as in the face images. The tasks also contained eight different gabor patch stimuli with an orientation point in extension of the middle white stripe rendered with Psychtoolbox 3 (Kleiner et al., 2007) with Matlab 2018a on a Windows 10 computer. For each of the two tasks, within 100 input files, randomization between jitter durations, gabor patch orientations and face stimuli was guaranteed by assessing decorrelation, respectively.

3.2.3 Experimental design

Data acquisition. MRI data were obtained by a 3 Tesla Siemens Prisma scanner with a 64-channel head coil. After brief anatomical scout images, structural MRI was assessed using magnetization prepared rapid gradient echo sequence in sagittal slices (voxel size = 1x1x1 mm, matrix size = 192 x 256 x 256, repetition time = 2.5 s, echo time = 0.00282 s, flip angle = 7°, multi band factor = 2). For the cognitive tasks, fMRI scans were recorded with field of view aligned to anterior and posterior commissures (voxel size = 2.2 x 2.2 x 2.2 mm, matrix size = 100 x 100 x 66, repetition time = 2.0 s, echo time = 0.03 s, flip angle = 80°, multi band factor = 2, interleaved order, no interslice gap), with single band reference images on the first scan and field maps for better alignment to the structural images during preprocessing. During continuous fMRI scanning, participants performed the FALT and localizer tasks, which have been described in chapter 2.3.1 Behavioral task design.

fMRI preprocessing. MRI data were converted using dcm2niix (version v1.0.20190902), and renamed in accordance with Brain-Imaging-Data-Structure format (Gorgolewski et al., 2016) using command line tools. Data were analyzed on a high-performance computing cluster using Linux Debian (version 4.9.0-16-amd64). For preprocessing, fMRIPrep version 20.2.0 (Esteban et al., 2019) was run with singularity (version 2.6.1-dist) wrapped around a docker container. Preprocessing encompassed slice time correction, susceptibility distortion correction, boundary-based registration and spatial normalization was applied to obtain images in MNI152CAsym_res-2 output space. Physiological regressors for retrospective image correction were obtained from PhysIO package in the TAPAS toolbox (Kasper et al., 2017). For simultaneous fitting of the hemodynamic response functions and denoising, GLMs on the fMRIPrep preprocessed images contained following confounds: 24 motion parameters (six rigid body motion parameters, six derivatives, and respective twelve squared parameters), 24

physiological regressors, 12 anatomical regressors (white matter and cerebrospinal fluid, as well as their derivatives and squared parameters), a cosine drift model and a constant intercept.

3.2.4 Statistical analyses

Behavioral and fMRI analyses were based on Python code within Jupyter Lab, using plotting functions from Matplotlib and Seaborn, numerical processing and statistical testing with Numpy, Scipy, Statsmodels and Pandas, and decoding tools from Scikitlearn and Nilearn (Abraham et al., 2014).

Behavioral analyses. A one-sample *t*-test against chance level of 12.5 % was performed for the relative number of correct trials per participant, to determine whether they successfully learned the presented face and gabor patch associations. Meta-memory parameters for sensitivity and specificity were calculate as respective detection accuracies on selecting high confidence on correct retrieval (sensitivity) and selecting low confidence on trials with failed retrieval (specificity) (see Table 1).

fMRI analyses. Univariate GLM results were obtained by simultaneously fitting the Glover hemodynamic function with respective events regressors during retrieval (*ErrorError, ErrorCorrect, CorrectCorrect, CorrectError*), confidence (low and high), feedback (positive and negative), encoding (*ErrorError, ErrorCorrect, CorrectCorrect, CorrectError*) and fixation. Conventional univariate GLM analyses were performed to determine whether pMFC is associated with the post-error subsequent memory effect (Hypothesis 1), and to determine memory error detection associated hemodynamic responses in pMFC during retrieval (Hypothesis 2a), confidence selection (Hypothesis 2b) and feedback presentation (Hypothesis 2c). For the post-error subsequent memory effect, hemodynamic response estimates during

error-related encoding success were compared (high-confidence *ErrorCorrect* > low-confidence *ErrorError*). Error-detection associated contrast were calculated during failed retrieval (low-confidence *ErrorError* > high-confidence *ErrorCorrect*), for low confidence (low > high confidence) and during error feedback (negative < positive feedback).

To investigate whether error detection related fMRI signals in pMFC can explain increases in FFA-related face-representativity (Hypothesis 3), participant-specific multivariate cross-classification models were trained in the localizer task and applied to memory-formation related epochs in FALT. For multivariate cross-classification the least-squares separate (Mumford et al., 2012) approach was used such that for a given epoch, like the encoding time of 1500 ms, each trial was fit with a hemodynamic response function as target regressor in a separate GLM. This led to 160 GLM results deriving *z*-standardized single-trial beta-weights for each trial while controlling for all other events such as in conventional GLM analyses. In the localizer, betaseries were derived from single-trial GLMs on the encoding of faces and houses, while only trials without required or undertaken motor response went into analyses contrasting faces and house. Additional regressors for the other trials were included as confounds. For multivariate cross-classification, a linear support vector machine with L2-penality was trained on single-trial beta-weight of these localizer correct rejection trials, within a 5-fold leave-one-run-out cross-validation scheme and based on FFA voxels to determine general predictive performance of multivariate classification. Next, a full model was fit to all respective trials and cross-classification of the single-trial beta-weights during encoding, fixation and retrieval epochs in the FALT was performed. Since the main task contained only face stimuli, multivariate cross-classification accuracy was determined by the total amount predicted face-category epochs divided by the total number of trials. To assess face-representativity during memory formation, the single-trial decision function based on FFA was

extracted for each trial and each of the three epochs. For each participant, a GLM was then used to fit the decision function scores with all other voxels in the brain to determine which regions outside FFA corresponded to fluctuations of face-representativity. Upon statistical testing of the group results, images were 6mm smoothed and cluster thresholded with a false-positive rate of alpha < .001 and a minimum distance of 5 mm between clusters images, while removing cluster with less than 10 voxels.

3.3 Results

3.3.1 Behavior

FALT. Participants correctly remembered face-gabor associations in 59.4 % of trials (> chance level 12.5 %, $t(29) = 16.88$, $p < .001$) and improved their memory performance with further face repetitions in later blocks (see). Correct trials were associated with high confidence ratings reaching a sensitivity of 80.14 % (*SD* = 14.28) on hits, namely selecting high confidence on correct trials, and a specificity of 76.22 % (*SD* = 17.68) on correct rejections, namely selecting low confidence on incorrect trials. Participants' meta-memory sensitivity and specificity were negatively linked to each other ($R_{Pearson}(29) = -.40$, $p = .030$). While sensitivity positively correlated with overall memory accuracy ($R_{Pearson}(29) = .65$, $p < .001$), there was no link between specificity and memory accuracy ($R_{Pearson}(29) = .07$, $p = .727$).

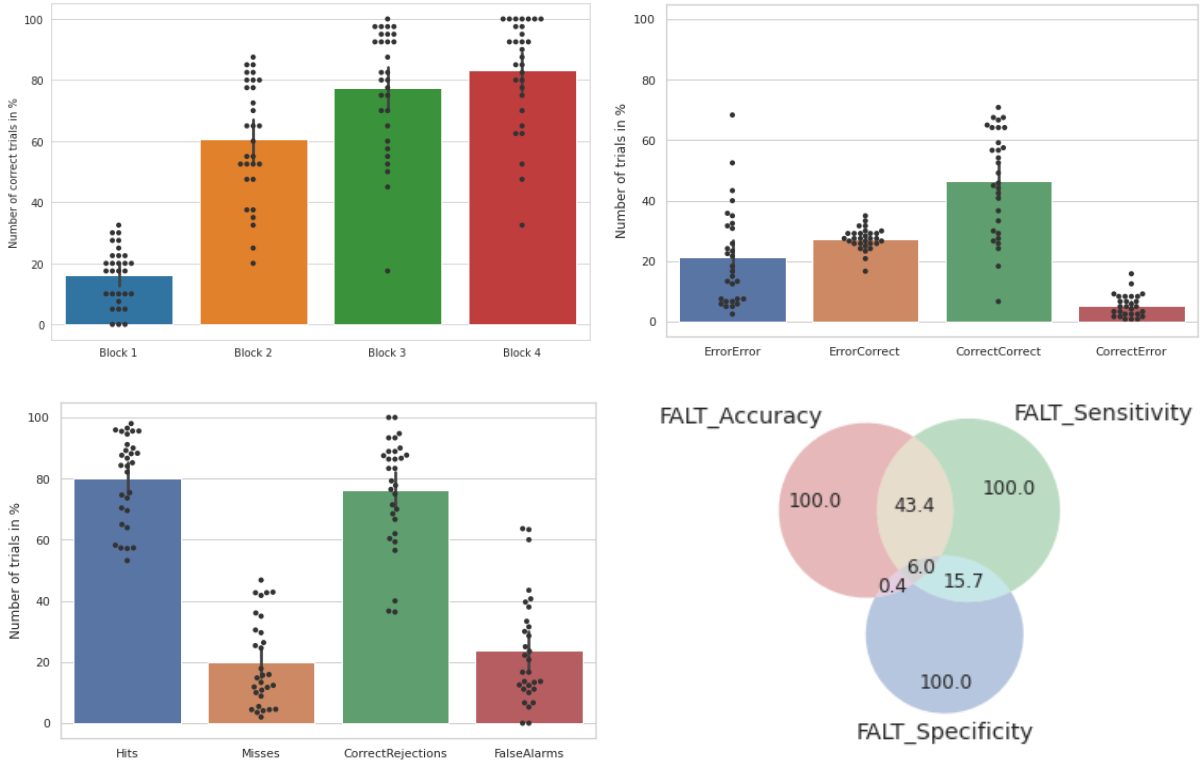

Figure 5. Performance in FALT. Correct association of face and gabor patch orientation per block (top left). Distribution of trial types in blocks 2, 3 and 4 (top right). Confidence ratings match retrieval correctness (bottom left). Overlap of memory accuracy with meta-memory sensitivity and specificity (bottom right).

Localizer. In the 1-back localizer task, 17 participants reached 100% accuracy, pressing the confirmation key on all direct repetitions and without wrong presses on non-repetition trials. Four participants lacked at least one trial to press the button on repetitions, six participants wrongly pressed during non-repetition trials and three participants performed both mistakes. Although this could indicate that participants who performed mistakes may have been inattentive, GLM fMRI analyses on the localizer did not show differences in the contrast between faces and houses for when respective participants were included or excluded.

3.3.2 fMRI

Post-error subsequent memory effect and memory error related signals

Univariate GLM results contrasting *ErrorCorrect* versus *ErrorError* trials showed higher hemodynamic responses in post-error trials for successful later retrieval compared to failed later retrieval during encoding regions left vlPFC, left FFA, right FFA, left PPC, and left pMFC and right pMFC (for the peak coordinates, see Figure 6). As shown in Figure 7, an overlapping pMFC region was also associated with contrasts on the detection of premature memory representations being either incorrect or unconfident during unsuccessful retrieval (*ErrorError* > *ErrorCorrect*, $z(29) = 4.270$, $p < .001$), presentation of negative larger positive feedback ($z(29) = 3.437$, $p < .001$) and low larger high confidence ($z(29) = 5.027$, $p < .001$).

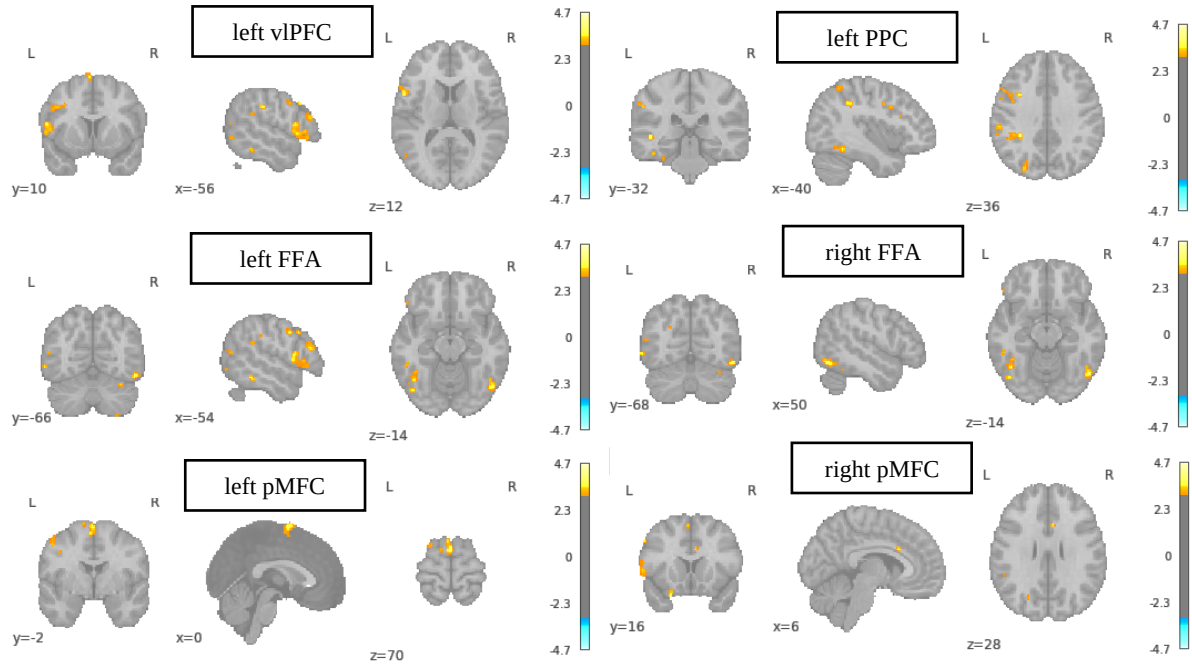

Figure 6. Post-error subsequent memory effect (ErrorCorrect > ErrorError).

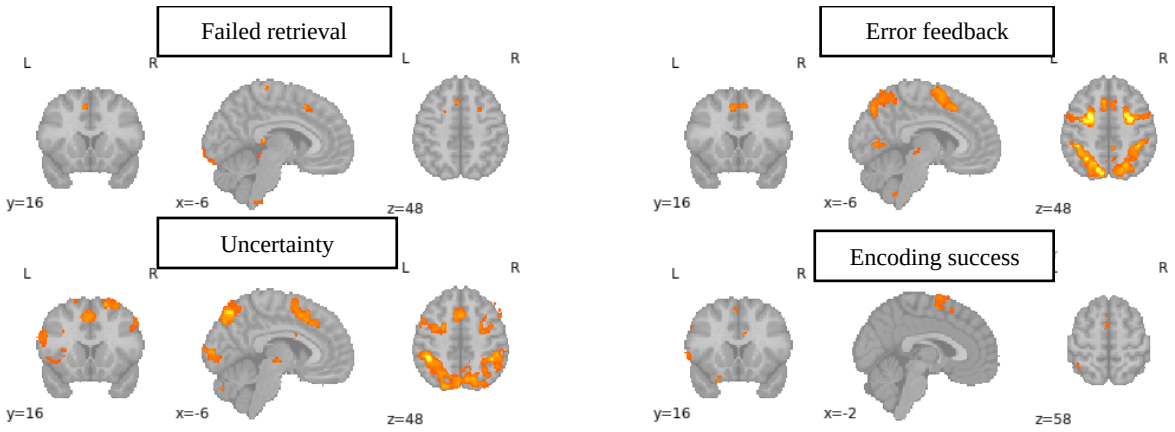

Figure 7. Performance monitoring and memory error associated hemodynamic responses for failed retrieval (ErrorError > ErrorCorrect), uncertainty (low > high confidence), error feedback (negative > positive feedback), and post-error encoding success (ErrorCorrect > ErrorError during encoding).

Face-representativity and face-selective regions

For multivariate cross-classification, the classifier was trained on trials in the localizer tasks using only voxels of the right FFA mask. Leave-on-run-out cross-validation showed a classifier performance of 76.56 % accuracy (*SD* = 14.6, $p < .001$), which was significantly above a chance level of 50 % ($t(29) =$, $p < .001$). The prediction of house and face category were balanced, showing no trend in the likelihood of face-representativity models to prefer faces or houses ($t(29) = 0.47$, $p = .642$). Memory formation may not only be determined based on stimulus encoding but face stimuli may also be rehearsed during intertrial interval. Therefore, the prediction of face-representativity in FALT also included the intervals during which a fixation cross was presented. Applying participant-specific face-representativity models trained to memory formation and retrieval epochs in FALT, the classifier predicted in 56.1 % (*SD* = 30.0, $p = .124$) of encoding betaseries, in 81.9 % (*SD* = 17.78, $p < .001$) of fixation betaseries and in 71.6 % (*SD* = 23.0, $p < .001$) of retrieval betaseries that faces were presented (see Figure 8). Assessing the relationship between FFA derived face-representativity and whole

brain hemodynamic responses in a GLM on FALT during encoding and fixation, respectively – the two periods related to memory formation – showed that hemodynamic responses in FFA were the most systematic fusiform association, while outside FFA different regions among pMFC (encoding: $z(29) = 3.559$, $p < .001$, fixation: $z(29) = 4.065$, $p < .001$), amygdala/basal forebrain (encoding: $z(29) = 3.622$, $p < .001$, fixation: $z(29) = 4.934$, $p < .001$) were systematically related to FFA face-representativity.

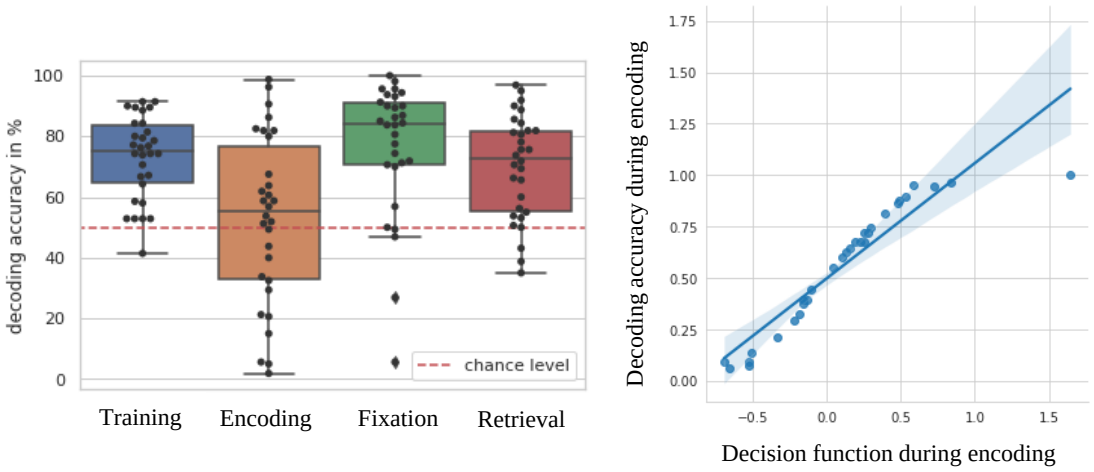

Figure 8. Left: Accuracies for the prediction of face stimuli using multivariate cross-classification (left) during training in the localizer and applied to three epochs in FALT. Right: Construct validity of face-representativity estimates suggested by linear relationship of participant-specific mean decision function (distance from multivariate hyperplane) and participants' decoding accuracy during encoding.

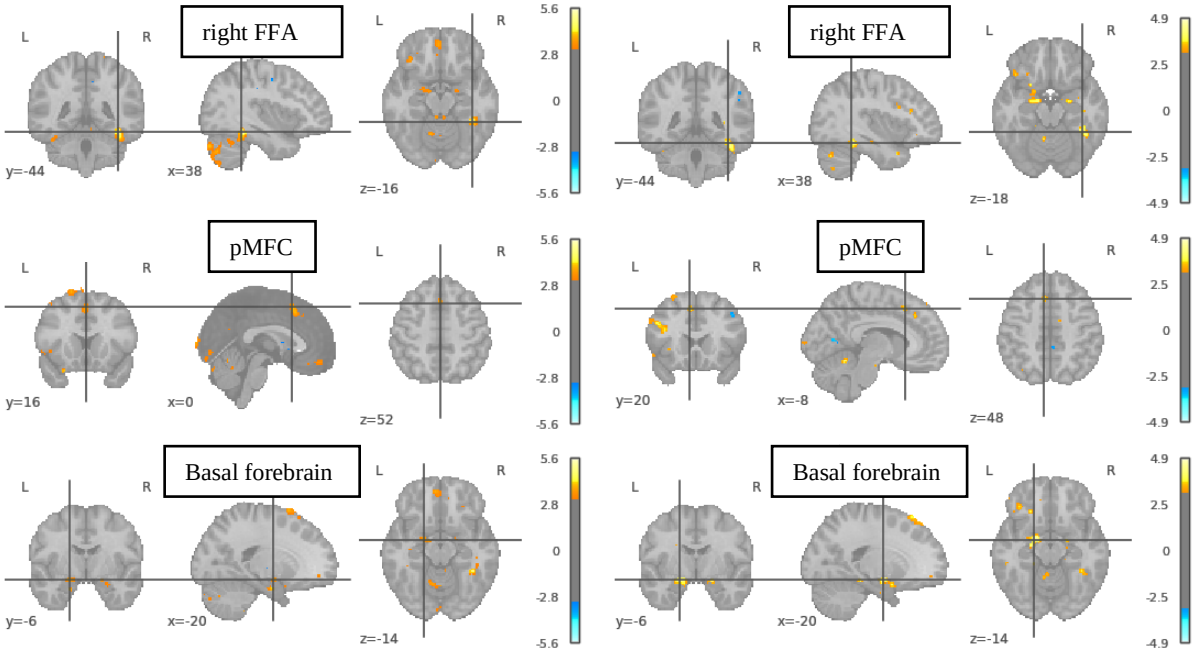

Figure 9. Face-representativity associations to hemodynamic responses during encoding (left) and fixation (right) single-trial betaseries.

3.4 Discussion

3.4.1 Brief summary

The results show that a pMFC is associated with accumulating evidence for a need of improving memory representations and that hemodynamic responses in this region explain variability in face-representativity of face-specific regions along the ventral visual stream, in line with the meta-analysis on the subsequent memory effect relating pMFC with attention during encoding (Kim, 2011). Face-representativity was most strongly related to fusiform cortex in FFA hemodynamic responses during all three epochs of encoding, fixation and retrieval, indicating the robustness of the face-representativity model. The decoding accuracies, however, varied considerably, showing the highest decodability during fixation. By exploring different topographies of FFA related hemodynamic responses, different proportions were

occupied: The localizer task showed the strongest right FFA hemodynamic response for face larger than houses in a similar anterior FFA cluster. The subsequent memory effect in FALT showed the strongest difference in fusiform cortex on posterior lateral FFA with a larger proportion in the transition to lateral occipital cortex. During fixation, FFA showed the most pronounced effect in FFA and during retrieval the difference between *ErrorCorrect* and *ErrorError* trials was most pronounced in medial posterior FFA.

pMFC – FFA interactions for post-error upregulation of stimulus representativity

These results favor the perspective that pMFC is involved in accumulating evidence of incorrect and low-confidence memory representations and that it may orchestrate brain networks involved in stimulus upregulation on post-error memory formation processes. Previous studies have found that decoding accuracies stimulus representations are strongest when a stimulus is in the focus of attention (Nelissen et al., 2013) and suggest that frontoparietal executive control areas enhance stimulus representations in occipitotemporal stimulus-specific areas. Other studies have used combinations of multivariate classification and eye tracking to develop markers for the amount on how much attention has been allocated (Leong et al., 2017). The current study aligns with these results by showing that single-trial face-representativity is associated with increased hemodynamic responses in pMFC, suggesting a link of cognitive processes leading from error monitoring to enhanced stimulus representations. But are these FFA based face-representativity direct effects of direct connections with pMFC? Rodent studies suggest that such connections do exist between frontal cingulate and visual cortex, and they explain post-error upregulation of visual attention (Norman et al., 2021). Other studies do, however, emphasize that executive control network regions are responsible for maintaining working memory stimulus representations (Curtis & D'Esposito, 2003) and rather suggest indirect effects from salience network regions to stimulus

specific regions, such as mediated by executive control network upregulation by the salience network (Menon, 2015). In line with this assumption, the current study suggests that respective executive control network nodes may be upregulated due to salience network related evidence accumulation of insufficient memory representations. There were, however, also effects of face- representativity on a cluster overlapping with basal forebrain. Although basal forebrain has not often been investigated using fMRI, recent studies suggest that different portions of the basal forebrain can be determined by their functional connectivity profiles and by using cytoarchitectonic probability maps (Markello et al., 2018). In the current study, there was a pronounced overlap of hemodynamic responses related to face-representativity with cytoarchitectonic maps of the basal forebrain (Eickhoff et al., 2005; Zaborszky et al., 2008). Functional connectivity analyses of the basal forebrain subregion basal nucleus of Meynert suggests widespread coupling with cortical regions and amygdala (Markello et al., 2018) and may explain changes in arousal and associated global fMRI signals (Liu et al., 2018; Turchi et al., 2018). Although fMRI does not have the specificity to only record signals from cholinergic cells, there was a pharmacological fMRI study blocking muscarinic acetylcholine receptors, showing that acetylcholine mediates post-error attentional upregulation (Danielmeier et al., 2015). This suggests, that even if pMFC is involved in detecting evidence indicating the need for improved memory formation, potential mechanisms mediating effect between pMFC and stimulus-specific regions such as FFA may be manifold, such as direct single-synaptic connections (Norman et al., 2021), executive control network mediations (Menon, 2015) or even a modulation by basal forebrain cholinergic system.

Anterior/posterior topography differences in pMFC and FFA

While encoding success showed right fusiform effects most strongly in lateral posterior FFA, retrieval success was most strongly related to medial posterior FFA. On the other hand,

hemodynamic responses during encoding were most similar to FFA topography found in the localizer task for the contrast between faces and houses, explaining why the decoding accuracy may be highest during fixation betaseries. By inspecting constant effects of single-trial hemodynamic responses during fixation, there was an association of pMFC, vlPFC and vmPFC. This was surprising and deflects from single-trial hemodynamic responses during encoding, since vmPFC and dlPFC hemodynamic responses are typically anti-correlated. Based on these considerations, that the fixation epoch at the beginning of each trial may have been used by participants as rehearsal/replace opportunities for better memory formation respective preceding trials and analyses according to the representativity analyses of the encoding betaseries. Furthermore, this variation in the topography of fusiform effects between encoding, fixation and retrieval in FALT and face processing effects in the localizer task is in line with the notion that regions for perception and memory vary in their anterior/posterior topography. This effect has before been shown for the scene-processing parahippocampal regions but was not confirmed for face-associated regions in fusiform cortex (Steel et al., 2021). As the subsequent memory effect meta-analysis and the current study found both in fusiform regions and in pMFC, related to the subsequent memory effect and encoding. Both clusters are, however, more posterior than would be expected by the error-recognition contrast and the localizer task contrast for face-representativity. Are these more posterior hemodynamic responses directly linked to later more anterior effects of stimulus maintenance? Maybe they are directly related, as suggested by other studies suggesting travelling waves related to arousal fluctuations (Raut et al., 2021). Using fMRI, the current study does, however, not have the temporal specificity to cleanly disentangle encoding from stimulus rehearsal during fixation. For this purpose, combined fMRI and EEG studies may be more suitable to condense temporal and spatial topographies of post-error stimulus maintenance processes during memory formation. This regional variation found in the conventional analyses, does stand in stark

contrast with the stability of face-representativity model use for cross-classification in the current study, being consistently related to regions assumed to be involved in face-processing networks, such as amygdala and vlPFC (Müller et al., 2018). Further studies are needed to determine how differences in the topographies of stimulus-related processing are related to comparably stable stimulus-specific models, such as based on multivariate cross-classification.

3.4.2 Limitations and outlook

Prediction accuracies of face representations

Analyzing stimulus-representativity during encoding was based on recent developments of multivariate cross-classification. Although there is a general recommendation for using least-squares separate as method of choice in fast event-related fMRI designs, for many other analytical choices there is no consensus on gold standards yet (Kaplan et al., 2015). In light of the validity on the representativity measure different variants on using the decision function as the distance from the hyperplane, a respective sigmoidal likelihood transformation or a calibrated class probability measure using Platt-scaling, did show strong on-average correspondence of more than 90 % explained variance on predicting general decoding accuracy differences between participants – indicating that decision function as used in the current study is a valid approach on estimating single-trial stimulus-representativity. The robustness of face-representativity related hemodynamic responses outside FFA further underlines the reliability of the participant-specific face-representativity models. Besides, it has been stated that low classification accuracies are interpretable if they are generalizing across the population (Hebart & Baker, 2018). In this regard the current study may or may not be benefiting from the model's insufficiency to capture every distinct face or house, since the trial-to-trial variability was used as basis for stimulus representativity during memory formation. On the other hand, even for 100 % decoding accuracies, the decision function has no specific upper boundaries suggesting

that it may still explain variability in face-representations. For increasing the model's performance, future studies may attempt to use higher trial numbers in the localizer task.

House stimuli for double dissociation of representativity

Although in the FALT only faces have been used as stimulus category to associate gabor patches, control analyses using houses may further help displaying a double dissociation between face and house upregulation processes from their stimulus-specific target regions with domain general performance monitoring and attentional upregulation networks. In this regard, previous functional connectivity studies showed functional connectivity of posterior FFA with pre-SMA and dlPFC (Caspers et al., 2014), suggesting that posterior FFA could be an entry-point for pre-SMA guided stimulus upregulation. This may on the other hand be a confound by experimental procedures involving stimulus maintenance processes of face-stimuli. In this regard similar concerns for face-specificity may be drawn as for fusiform face-specific regions, such that this region is related to expertise in recognizing fine-grained visual features (Bilalić, 2016). Therefore, face-stimuli could also have higher emotional value than houses, in that faces are automatically processed regarding their trustworthiness, attractivity and emotional expression (although all face stimuli in the current study had a neutral expression) while houses may not. This may explain amygdala effects of larger hemodynamic responses for faces than houses and brings up the question, whether the fusiform cluster may have shifted the multivariate cross-classification model to predict face-stimuli in FALT, where only faces have been used as stimuli. Inspection of cross-validation predictions during training do, however, not support this concern, as the prediction for trials in the localizer tasks were balanced between faces and houses displayed no tendency for the algorithm to prefer one or the other. Since in the meta-analysis on the subsequent memory effect, fusiform regions have been shown to be among the most robust region founds displaying encoding quality, using another control

category would also benefit general understanding of more posterior fusiform effects found in the meta-analysis on the subsequent memory effect, in order to understand whether this region is already stimulus-specific for faces or a general entry point also for houses to remember.

Interactions between performance monitoring and memory formation during ageing

The current study highlighted how pMFC may be involved in monitoring insufficient states of memory representations and how brain network dynamics may enhance stimulus representativity. This favors a view where a domain-general performance monitoring system is involved in face-representativity upregulation, potentially mediated by executive control network or basal forebrain cholinergic processes related to attentional allocation on ventral visual stream regions. While memory performance declines with age, one study suggested that the interaction between salience network and ventral stream regions may underlie age-related memory deficits, as this may hinder consolidation (Faßbender et al., 2022). Some studies also show that older adults are worse on assessing their level of memory confidence by either overestimating their level of confidence upon memory formation (Dodson et al., 2007) or underestimating their memory performance such as in subjective memory decline (Kuhn et al., 2021), although others suggest, that memory-related metacognition does not show an age related decline beyond was is expected due to performance difference on a particular age (Palmer et al., 2014; Zakrzewski et al., 2021). This brings up the question of in which stages of the potential hierarchy on the neurophysiological interplay underlying memory error detection, attentional upregulation and memory storage these age-related deficits are observed, how they overlap and how they may impact each other.

4 Study 2: Cross-sectional age effects in associative memory performance and meta-memory of younger and older adults

4.1 Introduction

The first study provided evidence for a cluster in pMFC being systematically related to monitoring of low-confidence and unsuccessful retrieval, post-error improvements of learning success and increased stimulus representativity during encoding and fixation. These results suggest that pMFC – with domain general performance monitoring functions – may be relevant for modulating brain networks to achieve adaptive post-error improvements on memory formation. While studies on error-less learning approaches have suggested that memory performance can be improved through learning processes with less mistakes, respective advantages are suggested to lack in individuals with intact error detection (Roberts et al., 2018). Other studies suggested that successful recognition of declined memory performance in form of subjective memory complaints are predictive for later developments of neurodegenerative pathologies such as Alzheimer's disease and may therefore be used as screening for early interventions (Susana et al., 2021). But what underlies older adults' memory error detection capabilities and which brain region's structure and function are related to changes in recognizing successful and unsuccessful memory formation?

Studies on performance monitoring and studies on metacognition do not agree on whether monitoring processes are affected (Hämmerer et al., 2014; Hämmerer et al., 2019) or unaffected (Palmer et al., 2014; Zakrzewski et al., 2021) during ageing. On the one hand, representations of task states are found to diminish such that participants require more external cues to evaluate their performance with older age (Hämmerer et al., 2019). On the other hand, studies on metacognition of memory suggest that deficits on recognizing the quality of memory

do no decline beyond what is expected by respective memory deficits (Palmer et al., 2014; Zakrzewski et al., 2021). Another study found older adults to perform more high confidence errors on meta-memory judgements and states that these deficits are beyond what is expected by respective memory accuracies (Dodson et al., 2007). From these studies it seems unclear whether and in which direction expectations of success in memory formation change during ageing. It could be that healthy ageing is accompanied by expected levels of confidence or that it is related to under-confidence, namely low sensitivity and being too restrictive on choosing high confidence, or over-confidence, namely low specificity and choosing high confidence despite unsuccessful retrieval. To understand how interindividual variability in age-related expectations on memory formation may underlie previous study results, the current study aimed to determine whether and how behavioral and neurophysiological underpinnings of memory monitoring change with ageing.

In this respect, pMFC is a potential candidate for brain regions mediating preserved performance monitoring and memory formation capabilities. In the past years, several studies have suggested that pMFC contributes to successful ageing and maintenance of youthful cognitive and memory performance into older age (Gefen et al., 2015; Lin et al., 2017; Sun et al., 2016; Touroutoglou et al., 2020). Besides histological findings on pMFC's role for preservation of memory performance (Gefen et al., 2015), the functional role of pMFC in goal-oriented behavior and task engagement has been emphasized as factor contributing to brain and cognitive reserves (Sun et al., 2016; Touroutoglou et al., 2020). But there was also evidence from a study on functional connectivity showing a relationship between midcingulate functional connectivity and performance differences between older adults with and without preserved memory function (Lin et al., 2017). If successful memory formation requires outward guided attention on stimuli to be encoded, increased coupling of salience network with

executive control network and decreased coupling with default mode network would be expected (Menon, 2015). Furthermore, this leads to the hypothesis that age-related memory decline shows a disruption in the interplay of these network during memory formation. Such changes between these three network and ventral stream regions have been shown during memory consolidation (Faßbender et al., 2022). The authors of that study further showed that functional connectivity differences between salience and default mode networks explained age-related interference susceptibility (Faßbender et al., 2022), which is in line with the theory of inhibitory deficits (Hasher & Zacks, 1988). But in which situations are diminished inhibition abilities leading to performance differences showing up as increased error numbers? And how do individuals try to cope with inhibitory deficits?

Theoretically, age-related decreased reaction times (Salthouse, 1996) could be attempts to compensate for inhibition deficits. In studies on age-related behavioral slowing it is debated whether slower responses are a sign of response-conflicts (Hämmerer et al., 2014) and compensatory speed-accuracy changes (Staub et al., 2015), or caused by a general processing speed decline (Salthouse, 1996). In younger adults performing speeded reaction time tasks there is, however, also not a clear consensus on the adaptiveness of behavioral slowing (Notebaert et al., 2009; Ullsperger & Danielmeier, 2016). It could also be that reasons for slowed reaction times are not merely exclusive such that general slowing with age occurs and also response-conflict related slowing. At least conflict-related mechanisms may be associated with pMFC function, which has shown response-conflict related increased hemodynamic responses and functional connectivity changes (Langner et al., 2015). If an individual recognizes that memory representation are inaccurate or weak, this may represent such a conflict involving respective brain network modulation of pMFC with executive control and default mode networks (Menon, 2015). The current study aimed to investigate whether younger

and older adults show changes in performance monitoring of memory representations, and whether these changes were related to an age-related memory performance decline. To address these questions, memory performance, confidence ratings and reaction times were investigated in respect to their concordance and regarding respective hemodynamic responses upon memory formation, retrieval, confidence selection and feedback presentation.

Hypotheses 1: Older adults show worse memory performance, slower reaction times and decreased meta-memory, namely determining failed and successful retrieval by choosing respective confidence levels.

Hypotheses 2: Older adults are expected to show larger hemodynamic responses in anterior (pMFC, vlPFC and dlPFC) and lower hemodynamic responses in posterior regions (FFA, occipital cortex) on the post-error subsequent memory effect (*ErrorCorrect* > *ErrorError*).

4.2 Methods

4.2.1 Participants and procedure

25 older adults (10 male) between 50 and 80 years were recruited in a cross-sectional comparison with the 30 younger adults of Study 1. The desired sample size of 30 participants could not be reached due to lack a of volunteers and pandemic related restrictions. After a phone interview checking for exclusion criteria (body mass index between 20 and 30 kg/m^2, non-smokers, no history of psychiatric or neurological disorders, no metal implants), participants were invited for an in-person screening to assess cognitive health status by the mini-mental state examination, excluding participants with values < 28.

4.2.2 Stimuli

Participants performed the FALT and localizer task with the same parameters and stimuli as younger adults.

4.2.3 Experimental design

An overview on the experimental design has been described in 2.3.1 and in the methods section of Study 1.

4.2.4 Statistical analyses

Behavioral analyses. FALT memory performance (correct trials / total number of trials), meta-memory sensitivity (select high confidence on correct trials) and meta-memory specificity (low confidence on incorrect trials) were calculated and compared between younger and older adults via t-tests for independent samples. Interdependencies showing their Pearson correlation coefficients and incremental increased variance by using both sensitivity and specificity to predict of memory performance were determined and plotted on Venn diagrams using Matplotlib-Venn Python library. Reaction times were analyzed using single-trial linear mixed models with a participant factor of no interest and the predictors age, retrieval success and confidence, as well as their interactions.

fMRI analyses. Cross-sectional age effects on hemodynamic responses in the fMRI task were assessed by using second level model contrasts between older adults and younger adults in the three sets of analyses (1) conventional GLM, (2) representativity based on multivariate cross-classification and (3) task-based functional connectivity of FFA. Cluster-correction was performed as in Study 1, using false-positive rate of alpha < .001 and removing clusters with less than 10 voxels.

4.3 Results

4.3.1 Behavior

Memory performance. In the FALT, older adults had significantly lower memory accuracy with 40.04 % (SD = 18.50) correct trials compared to 73.78 % (SD = 15.26) in younger adults ($t(53) = 7.37$, $p < .001$). While both groups reached similar amounts of *ErrorCorrect* trials, younger adults had more *CorrectCorrect* trials and older adults more *ErrorError* trials, such that only one older participant reached above 80 % of correct trials in the last block compared to 19 younger adults (see Figure 10). Two older adults did not have high confidence *ErrorCorrect* trials and were therefore excluded from fMRI analyses on the subsequent memory effect.

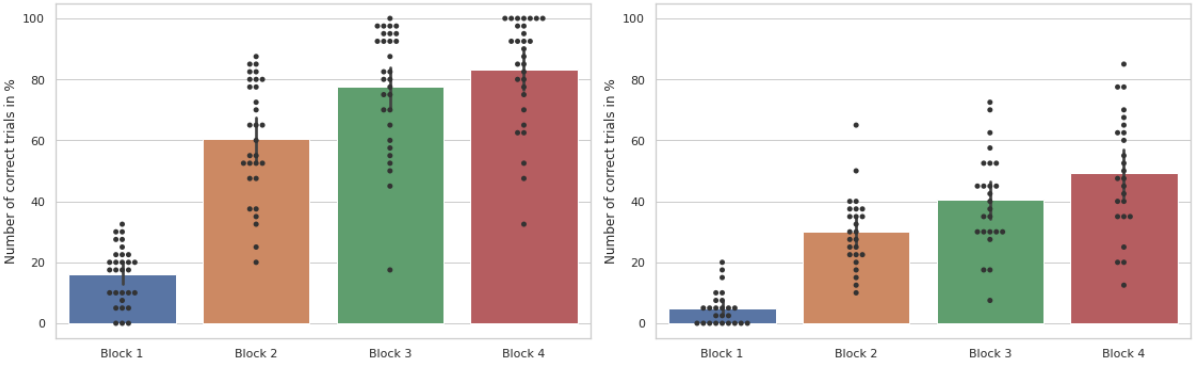

Figure 10. Block-wise memory accuracy of for younger (left) and older (right) adults..

Confidence ratings. Meta-memory sensitivity decreased from a hit rate of 80.14 % in younger adults to 56.24 % in older adults ($t(53) = 4.17$, $p < .001$), while specificity did not show age-related differences ($t(53) = 0.07$, $p = .94$). The relationship between sensitivity and memory accuracy decreased from younger to older adults, suggesting that low confidence predicted 30.7 % less variance of memory performance in older adults, while explained variance of sensitivity and specificity increased by 39.3 % (see Figure 11).

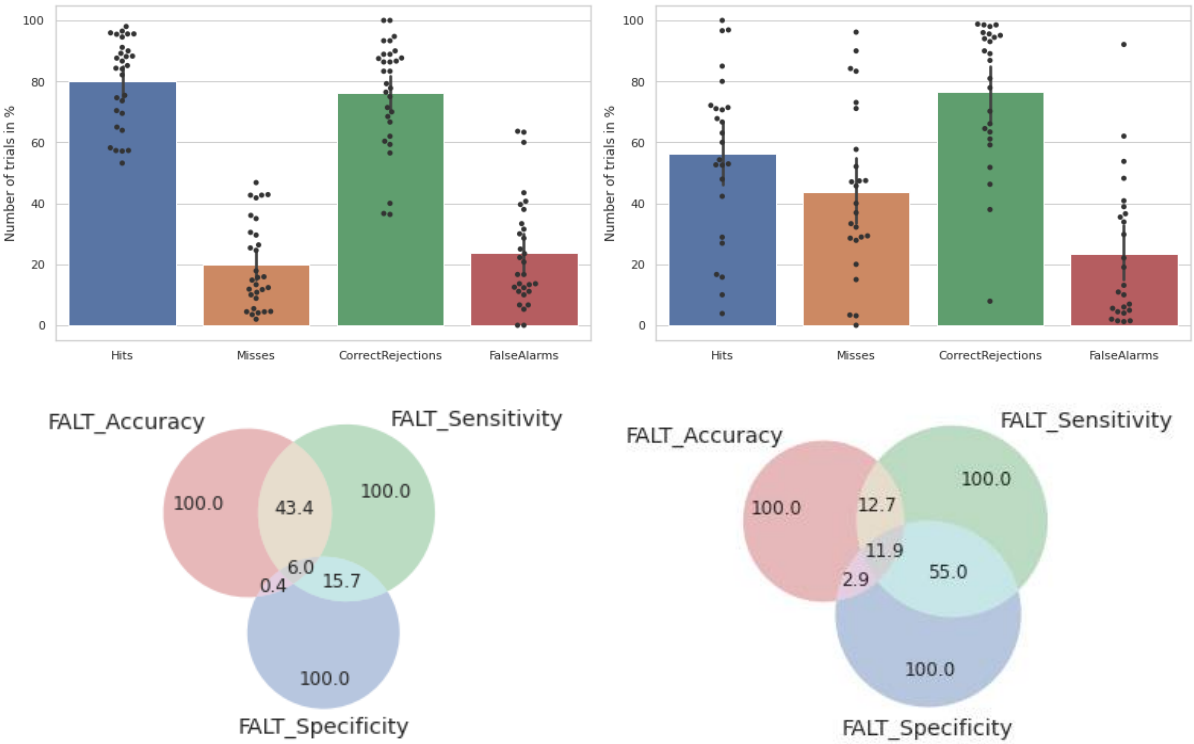

Figure 11. Meta-memory age group comparison of younger adults (left) and older adults (right). The bottom two plots show Venn diagrams displaying how much variance is explained by respective other parameters. The overlap of all three parameters indicates how much additional variance is explained, when memory accuracy is predicted by sensitivity, specificity and their interaction term.

Signal detection theory analyses indicated that both younger ($t(29) = 11.76$, $p < .001$) and older adults ($t(24) = 10.61$, $p < .001$) successfully differentiated retrieval success by respective confidence selection, while younger adults showed stronger detection accuracy ($t(53) = 3.28$, $p < .001$). Younger adults did not show a response bias ($t(29) = -0.24$, $p = .595$), while older adults showed a bias to report low confidence ($t(24) = 1.81$, $p = .042$), which was significantly higher for older compared to younger adults ($t(53) = 1.77$, $p = .041$).

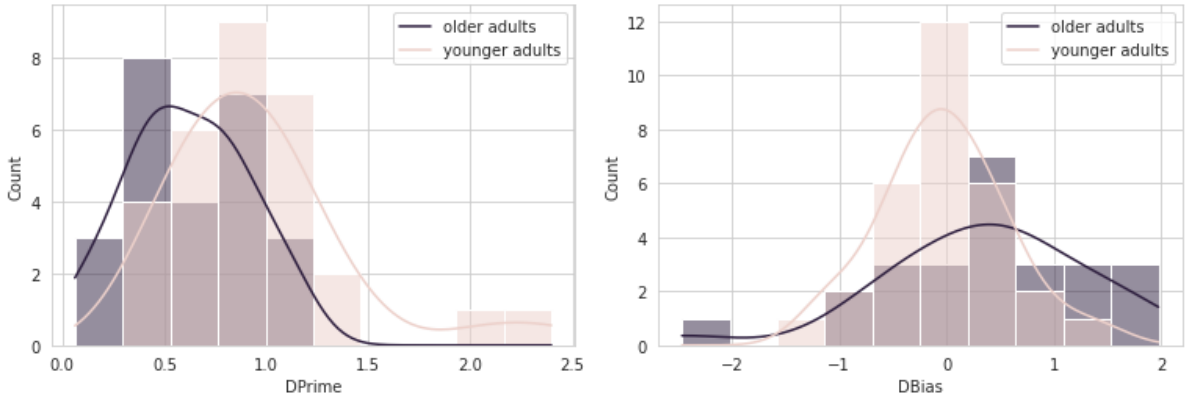

Figure 12. Signal detection theory parameters d' (left) and response bias (right). Higher d' is related to a better match between confidence ratings and retrieval success. Response bias = 0 indicates no bias, response bias > 0 indicates under-confidence and response bias < 0 indicates over-confidence.

Reaction times. Older adults generally had slower reaction times on confidence selection than younger adults ($t(53) = 7.99$, $p < .001$). for younger adults, single-trial linear mixed model results with confidence selection reaction time as criterion (see Figure 13) showed that a low-confidence, incorrect trial in the first block and run was estimated to take 1220 ms ($z(29) = 49.579$, $p < .001$) and a high-confidence correct retrieval on the last block and run was estimated to take 906 ms. Model coefficients showed that reaction times decreased 37 ms per block ($z(29) = -6.570$, $p < .001$), 25 ms per run ($z(29) = -6.957$, $p < .001$), 52 ms for correct retrieval ($z(29) = -3.733$, $p < .001$) and 77 ms for selecting high confidence ($z(29) = -5.416$, $p < .001$). In older adults, reaction times on confidence selection of low-confidence incorrect retrieval in the first block and run was estimated to take 1690 ms ($z(24) = 33.69$, $p < .001$), and confident, successful retrieval on the last block and run predicted a reaction time of 1070 ms. For older adults confidence selection reaction times decreased 58 ms for each block ($z(24) = -6.42$, $p < .001$), 69 ms for each run ($z(24) = -10.32$, $p < .001$) and 84 ms for correct retrieval ($z(24) = -3.55$, $p < .001$), but where independent for whether older adults selected confidence

($z(24) = 0.24$, $p = .814$). Older adults generally had slower reaction times than younger adults, they showed stronger benefits for later blocks and runs, but effects of high confidence on faster reaction times diminished.

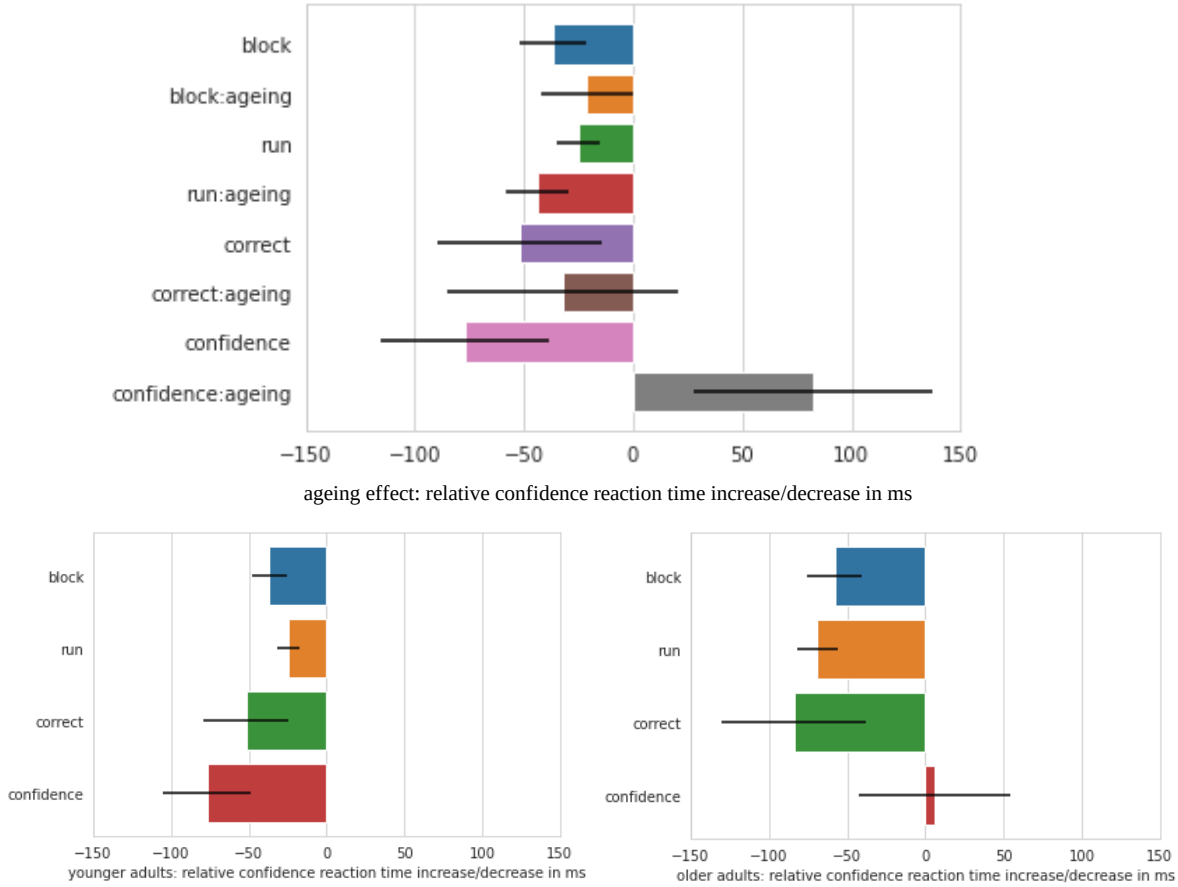

Figure 13. Single-trial linear mixed model results on the prediction of reaction times during confidence selection by block, run, retrieval correctness and confidence rating with nested participant factor in a full model (top), younger adults (bottom left) and older adults (bottom

4.3.2 fMRI

Post-error subsequent memory effect and memory error related signals

In older adults, the subsequent memory effect (*ErrorCorrect* > *ErrorError*) showed higher hemodynamic responses during encoding in PCC, precentral gyrus, angular gyrus, superior

temporal gyrus and cerebellum. Compared to younger adults, older adults showed higher hemodynamic responses in PCC and occipital cortex, while no region were found to be increased for younger compared to older adults.

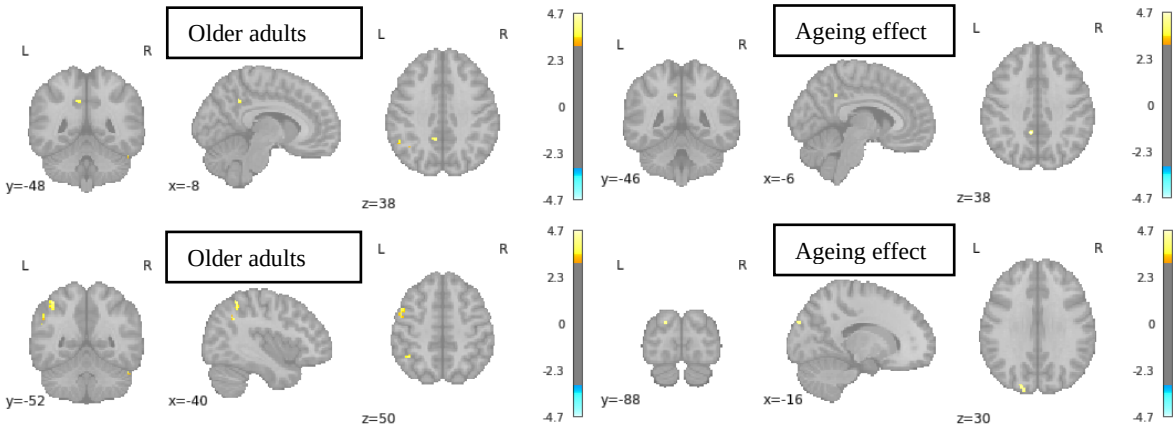

Figure 14. Post-error subsequent memory effect for older adults and age effects (older > younger adults).

Older adults only showed memory error related hemodynamic responses in pMFC upon receiving error feedback (negative > positive feedback) (see Figure 15 on the bottom right), but not for unsuccessful retrieval (*ErrorError* > *ErrorCorrect*) and error expectation (low > high) confidence. During unsuccessful retrieval (*ErrorError* > *ErrorCorrect*) older compared to younger adults showed higher hemodynamic responses in occipital cortex and middle insula, and lower hemodynamic responses in anterior thalamus and frontal eye field. Low compared to high confidence showed higher hemodynamic responses for older compared to younger adults in vmPFC, and lower hemodynamic responses in anterior insula, visual cortex and IPS. For negative larger positive feedback, older adults showed stronger hemodynamic responses in temporoparietal junction and lower hemodynamic responses in FFA and ventral striatum.

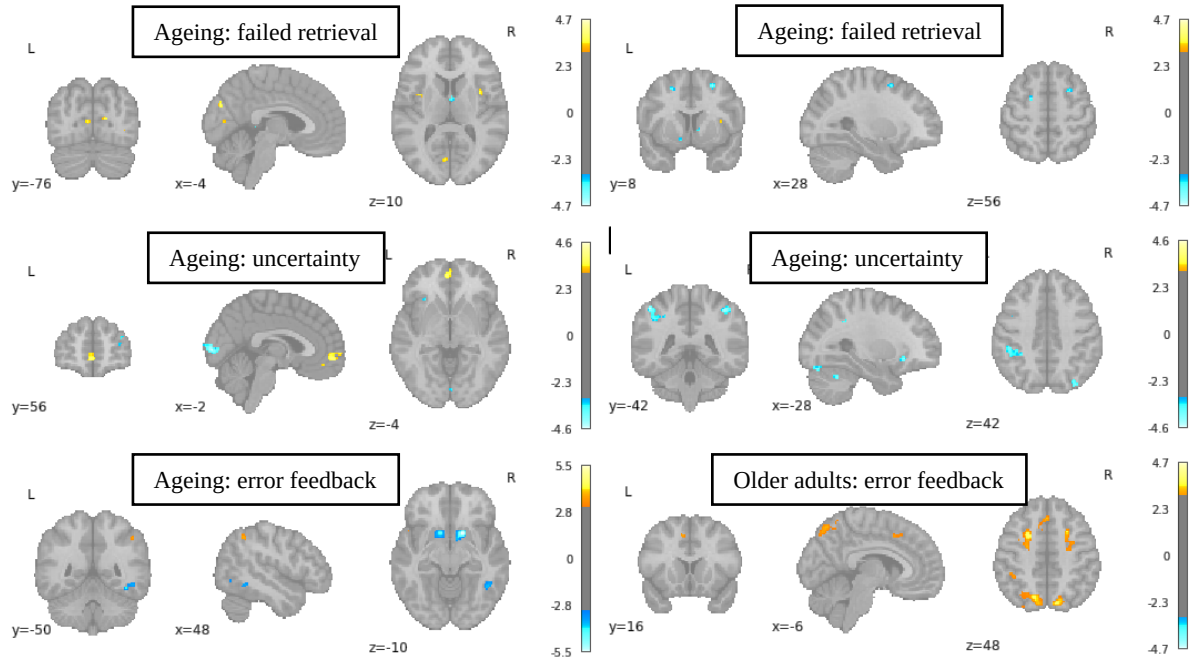

Figure 15. Age effects (older > younger adults) of failed retrieval (ErrorError > ErrorCorrect), uncertainty (low > high confidence) and error feedback (negative > positive feedback).

Face-representativity and face-selective regions

In the localizer task, the FFA topography for face-related hemodynamic responses (faces > houses) was comparable between younger and older adults and showed the most pronounced fusiform cortex effect in a cluster in right FFA, although older adults had larger face-related hemodynamic responses in left FFA and parahippocampal gyrus, as well as lower hemodynamic responses in left pMFC and dorsomedial PFC (see Figure 16). The overlap on right FFA underlines that spatial registration, realignment and normalization during preprocessing did not lead to age-related differences in FFA topography.

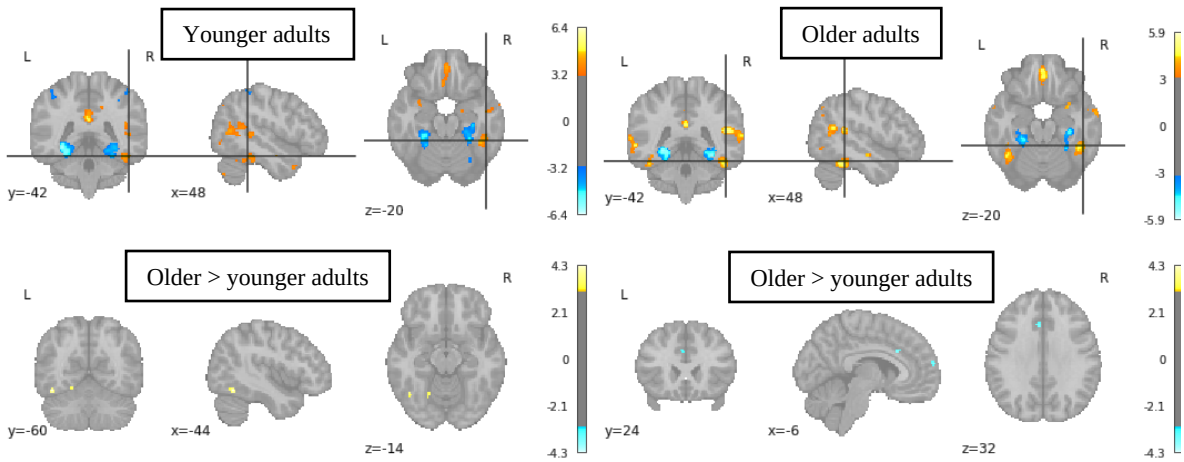

Figure 16. Hemodynamic responses for faces compared to houses in younger and older adults and the age group comparison in the localizer task.

In multivariate cross-classification, older adults had significant above chance accuracies during training in the localizer task ($t(24) = 6.62$, $p < .001$), while there was no indication that the model preferably predicted faces or houses ($t(24) = 0.87$, $p = .392$). Older adults generally showed significant classification performance on predicting faces in FALT during fixation ($t(24) = 3.38$, $p = .002$) and retrieval ($t(24) = 3.54$, $p = .002$), while below chance accuracy during encoding were found ($t(24) = 7.84$, $p < .001$). Older and younger adults showed no differences in cross-classification accuracy during fixation ($t(53) = 1.67$, $p = .101$) and retrieval ($t(53) = 1.13$ $p = .265$) but decreased accuracy during encoding ($t(53) = 4.745$, $p < .001$).

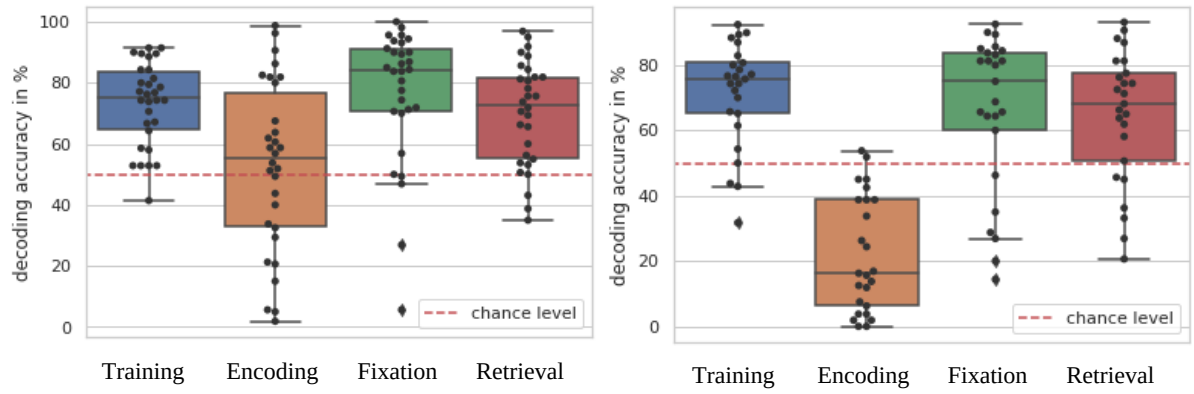

Figure 17. Comparison of classification accuracies in younger (left) and older adults (right). Decoding accuracies during encoding for both age groups did not show reasonable decoding accuracies.

Face-representativity during encoding showed a more extensive topography in occipitotemporal cortex than expected by the results of younger adults and the well-circumscribed FFA region in right FFA during presentation of faces in the localizer. Face-representativity during fixation resulted in stronger right FFA effects but was also related to more posterior occipitotemporal hemodynamic responses.

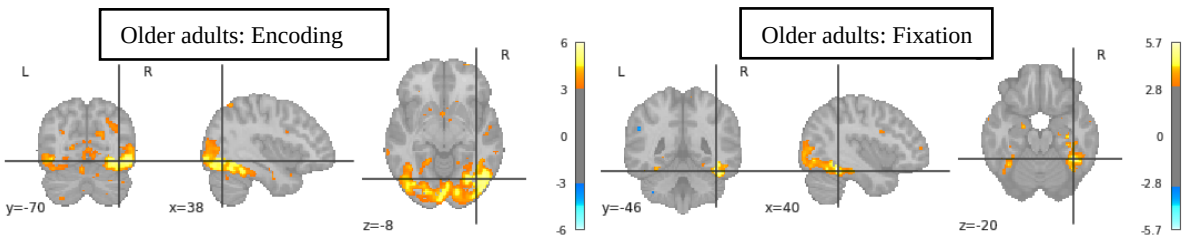

Figure 18. Face-representativity derived from multivariate cross-classification and its relationship during encoding (left) and fixation (right) single-trial hemodynamic responses.

4.4 Discussion

4.4.1 Brief summary

Memory performance and meta-memory sensitivity decreased in older compared to younger adults, while reaction times during confidence selection increased. The fMRI contrast on post-error successful encoding (*ErrorCorrect* > *ErrorError*) showed increased hemodynamic responses in default mode network regions, which is in line with previous meta-analysis results on age-related differences of the subsequent memory effect (Maillet & Rajah, 2014). In the localizer task, older adults showed higher left-hemispheric hemodynamic response for faces compared to houses, while decreased hemodynamic responses in pMFC and dorsomedial prefrontal cortex were found. Younger and older adults had comparable decodability for training of the face-representativity classifier and for fixation and retrieval during FALT. For encoding, classification showed systematic below chance accuracies, while single-trial face-representativity showed much less sparse topography to right FFA than during fixation and compared to the results found for younger adults. Older adults also showed weaker FFA effects during presentation of negative feedback although pMFC was still associated with error feedback presentation. This suggests lower correspondence between performance monitoring related pMFC signals and right FFA regions related to the processing of to be learned face-representations. For low confidence and for unsuccessful retrieval older adults did not show hemodynamic responses in pMFC. Older compared to younger adults, however, showed increased hemodynamic responses for low confidence in vmPFC and decreased hemodynamic responses in regions among occipital cortex – a pattern which was expected for age-related subsequent memory effects (Maillet & Rajah, 2014). This effect in hemodynamic responses was accompanied by behavioral age effects showing that older adults had biased selection of low confidence despite successful remembering and lacked reaction time advantages upon selecting high confidence levels.

It is not uncommon for studies on the subsequent memory effect that encoding related fMRI signals are contrasted between high confidence later successful retrieval with confidence-independent later failed retrieval (Duverne et al., 2008; Gutchess et al., 2005; Miller et al., 2008), while potentially overlapping performance monitoring processes among confidence evaluation and feedback processing are not well understood. In this regard, results of Study 1 showed hemodynamic responses in right FFA and subsequent-memory-related areas in pMFC and executive control network related to memory error evidence such as low confidence and negative feedback. Although the exact FFA topography varied between contrasts, an upregulation of stimulus representations may be related to increased attention towards a stimulus (Leong et al., 2017; Nelissen et al., 2013) and benefit successful memory formation. For older adults, face-representativity was decreased during encoding and the topography for hemodynamic responses associated with face-representativity showed stronger effects in broader occipitotemporal regions. This suggests that detection of failed memory formation and following encoding processes on stimulus representations become less related to one another in older age. Do aged individuals have deficits on preparing the brain for improved face encoding after a demand for memory formation has been recognized? And does the aged brain lack knowledge on which areas to recruit for successful task performance?

The meta-analysis on age-related subsequent memory effect differences suggested that older participants may use other strategies than younger adults – such as attempting to remember a similar looking familiar person – and therefore recruit retrieval related default mode network regions during memory formation (Maillet & Rajah, 2014). But why should older adults use other strategies associated with different brain networks? Are retrieval related strategies compensating deficits or are they in competition therefore part of the reasons leading to

respective memory deficits? Some studies suggest that older adults have contextual processing deficits leading to failed cognitive control (Braver et al., 2001) and that they show a compensatory shift to retroactive cognitive control (Paxton et al., 2007). Although the current study cannot disambiguate whether observed age-related changes on memory formation related hemodynamic responses are compensatory, it has been suggested that older adults lack to form task representations (Hämmerer et al., 2019) which may be necessary to seize the opportunity on improving memory formation after memory errors have been recognized. In this regard, the current study found memory error related hemodynamic responses in pMFC only during negative feedback presentation, while selected confidence levels were biased towards reporting low confidence despite successful retrieval. Insufficient task representations would explain age-related changes on reporting confidence levels and increased reliance on external performance feedback (Hämmerer et al., 2014).

Regarding brain ageing theories and compensatory changes on brain functions, the current study has emphasized the relationship between memory formation and memory error detection by confidence judgements and feedback presentation. The overlap of performance monitoring related signals, changes in stimulus representativity and success on memory formation may further contribute to a better understanding of factors contributing to adaptative post-error changes. The pattern observed in this study do, however, fit into several established theories on changes in neurophysiological process as observed by fMRI studies. Reduced right lateralization of face-related hemodynamic responses fits to hemispheric asymmetry reduction in older adults (Cabeza, 2002), while age-related hemodynamic response changes for low and high confidence display a posterior-anterior shift (Davis et al., 2008) pattern.

4.4.2 Limitations and outlook

The current study investigated neurophysiological and behavioral underpinnings of age-related differences in memory formation and performance monitoring. These results were based on a cross-sectional comparison between younger and older adults. It seems worth noting that the intended sample size of 30 older adults was not reached and five male participants lacked to be recruited for a fully balanced sample. The response bias on reporting low confidence found for older adults further decreased trial numbers in the subsequent memory task, such that two participants had no respective trials with later high confidence successful retrieval (*ErrorCorrect* > *ErrorError*). Several regions assumed to be involved in the subsequent memory effect in an age-independent manner – such as left vlPFC (Maillet & Rajah, 2014) – did neither show significant associations in older adults, nor age-related differences compared to significant effects of younger adults. A larger sample size may further increase sensitivity and allow to determine whether respective effects are similarly or differently present in older adults. For the decrease in confidence levels and respective influences on subsequent memory effect estimates, there however does not seem to be a straightforward solution. Further studies on the subsequent memory effect may be required to investigate to which degree performance monitoring processes during memory retrieval and memory formation overlap on neurophysiological underpinnings for successful updating of memory representations. Suitable task designs and analytical choices seem required to disentangle which neurophysiological underpinnings underlie age-related effects on interaction between performance monitoring and memory formation.

Behavioral differences for older and younger adults were found on memory performance, selected confidence levels and respective reaction times. Regarding finding on reaction times and the accuracy of selected confidence levels, it seems worth to remind that left and right

presentation sides for low and high confidence were switched between trials. Although this may counteract biased hemodynamic responses, it also introduces a task switching component potentially increasing reaction times in older adults. Similar changes in reaction times have been investigated on sustained attention task where older adults slowed down their responses particularly during go-trials (Vallesi et al., 2021).

Among the key findings of the current study is that older adults showed a bias in reporting low confidence despite successful retrieval, which may have implications for the understanding on which neurophysiological processes underlie reporting subjective memory decline during ageing. Furthermore, older adults did not show faster reaction times for reporting high compared to low confidence suggesting that internal models on the accuracy of memory representations decrease, making aged individuals to stronger rely on external performance feedback for adapting attention and stimulus processing during following encoding opportunities. While decline in different neuromodulatory systems has been related to deficits on memory formation (Störmer et al., 2012), Study 3 will investigate how impaired cholinergic integrity by using a pharmacological antagonist may resemble the age-related modulation of interaction between performance monitoring and memory formation found in the current study.

5 Study 3: Pharmacological intervention blocking muscarine-1-acetylcholine receptors in healthy young male adults

5.1 Introduction

The previous two studies have investigated neurophysiological associations and age-related changes of interactions between performance monitoring and memory formation. Although Study 1 found increased hemodynamic responses for face-representativity overlapping with a

cytoarchitectonic mask of the basal forebrain, fMRI lacks neurochemical specificity and can therefore not determine whether basal forebrain mediated acetylcholine release is involved in post-error enhancement of face-representations. However, declined efficiency of cholinergic neuromodulation has been proposed to explain age-related deficits on selective attention (Störmer et al., 2012) and may therefore have contributed to the behavioral and neurophysiological age differences in Study 2. In this regard, pharmacological blockage of acetylcholine receptors in younger adults may help elucidate which of these effects – such as lower memory performance, slower reaction times and lower confidence on the behavioral level – are mediated by impaired cholinergic neuromodulation. In a recent literature review on cholinergic models of memory impairment, it was claimed that the selective muscarine-1-receptor antagonist biperiden best captures age-related memory deficits (Blokland, 2022). Although voices have been raised that biperiden selectively causes memory impairments and leaves other cognitive functions intact (Blokland, 2022; Borghans et al., 2020), other studies using biperiden have also found deficits among impaired selective attention and working memory (Bakker et al., 2021; Klinkenberg et al., 2012). Episodic memory may strongly rely on intact selective attention when similar stimulus features need to be separated from one another, such that worse selective attention functions can explain compromised episodic memory as effect of biperiden. But if the cholinergic system is involved in the precise distinction of to-be-remembered stimuli, how does the cholinergic system detect the need to increase selective attention?

A domain general performance monitoring system (Ullsperger et al., 2014) may accumulate evidence on a need for improving memory formation and then interact with the cholinergic system to ensure required attention levels. In line with such a model are previous results of a pharmacological fMRI study, which showed that biperiden abolishes post-error behavioral

slowing and post-error increases in accuracy, as well as hemodynamic responses in task-related visual regions (Danielmeier et al., 2015). Based on these ideas that the cholinergic system obtains attentional upregulation commands from pMFC upon error detection, biperiden should diminish error-improved memory formation due to deficient cholinergic adaptation processes.

In the above study, biperiden also dampened post-error slowing (Danielmeier et al., 2015). If reaction time differences between correct and incorrect trials diminish, this indicates a disappearance of either a reaction time benefit for correct trials or a reaction time disadvantage for incorrect trials. In this regard, it has been suggested that pMFC is associated with a conflict-related interruption on contextually incompatible cued responses (Pastötter et al., 2010). If cholinergic upregulation occurs as consequence of pMFC related conflict detection, diminished post-error slowing under muscarinic cholinergic blockage should leave performance monitoring processes intact such that worse post-error improvements could lead to higher error expectations. For the FALT paradigm investigated in this dissertation, this may suggest that performance monitoring could shift levels of retrieval success expectations towards under-confidence and display more pronounced slowing. This may further increase boundaries for evidence levels to surpass for internally tagging available memory representations with high confidence. With lower success expectations on memory formation, high confidence levels may have to exceed a higher threshold such that attempted memory retrieval is not in conflict with an internal goal of good task performance.

Hypothesis 1: Worse memory performance is expected for sessions on which participants receive biperiden compared to placebo.

Hypothesis 2: Lower tendencies on reporting high confidence upon successful retrieval are expected under biperiden.

5.2 Methods

5.2.1 Participants and procedure

30 male participants between 18 and 30 years took part in a placebo-controlled double-blind study receiving 4 mg biperiden or a placebo in two separate sessions –15 participants received biperiden in session 1 and a placebo in session 2, and 15 other participants received a placebo in session 1 and biperiden in session 2. Exclusion criteria were the same as for the other two studies (body mass index between 20 and 30 kg/m^2, non-smokers, no history of psychiatric or neurological disorders), as well as further exclusion criteria for risk populations of drug adverse effects as described in the pharmaceutical specialist information (such as no intake of anti-histaminergic drugs and somatic disorders among specific cardiovascular or intestinal conditions). A medical examination was performed by a study physician who was present throughout participation. None of the participants had adverse effects leading to termination before completion. The study protocol was in accordance with the declaration of Helsinki and approved by the local ethics committee.

5.2.2 Stimuli

Although face and house stimuli were from the same stimulus samples as in Study 1 and Study 2, different presentation times and stimulus numbers in FALT and 1-back localizer were used (see Figure 19). Presentation times and particularly jittered inter-trial-intervals showing fixation crosses were decreased from durations between 2.5 and 6.0 s – optimized for efficient fitting of hemodynamic responses in fast event related fMRI designs – to durations between 1.5 and 2.5 s for increasing trials numbers and experimental efficiency. The FALT paradigm

was extended to six separate houses and faces runs with twelve different face or house stimuli each, which needed to be associated with twelve tilted gabor patches. The increased number of stimuli per run was used to counteract ceiling effects as observed in young participants of Study 1. Confidence selection was changed from binary choices (low and high confidence) and alternating presentations sides to continuous confidence ratings between low confidence (left side, index finger) and high confidence (right side, ring finger). Upon pressing respective keys with the right hand, the arrow position moved towards respective sides and reached the maximum position after 1000 ms of acceleration with a quadratic exponential function. Times of initial pressing of respective the confidence key as well as time of release were recorded, although the current study will use binarized confidence levels on respective left and right button presses and the duration between confidence screen presentation and initial confidence button press for comparability with the previous two studies in this dissertation. Compared to the earlier version of the localizer task, stimuli on the top and bottom were independently presented and for each run participants either received the instruction to press the confirmation key for direct stimulus repetitions on the top (face or house within the same runs) or bottom (one of twelve tilted gabor patches). There were three runs per condition (top or bottom) with each two direct stimulus repetition in the attended position but without repetitions on unattended stimuli. Attentional conditions were pseudo-randomly ordered. In total there were twelve different stimulus sets for each, FALT and localizer, using the first six stimulus sets on session 1 and the last six sets for session 2, such that independent face and house stimuli were used in placebo and biperiden sessions of the same participants.

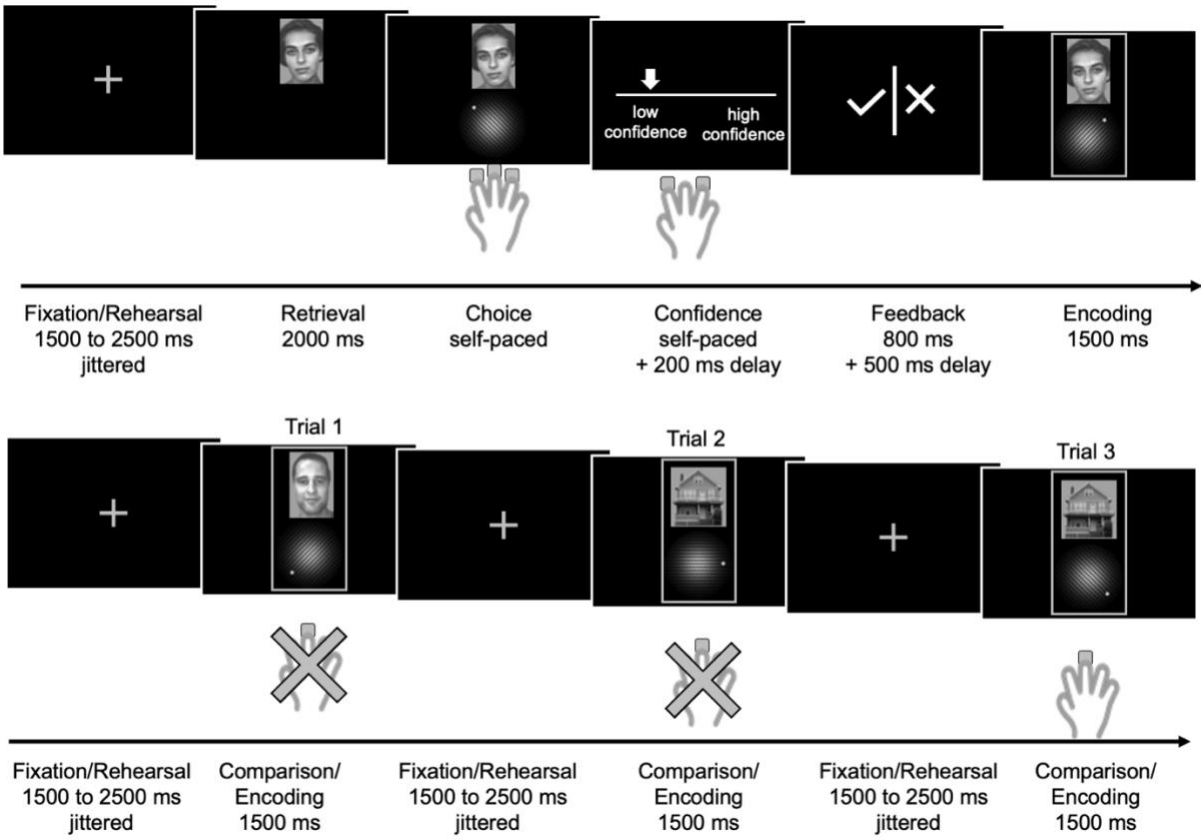

Figure 19. Paradigm adaptations in FALT (top) and localizer task (bottom). In Trial 3 of the localizer task participants needed to press the confirmation key.

5.2.3 Experimental design

After the study physician confirmed that none of the exclusion were present, participants obtained either the selective muscarine-1-acetylcholine receptor antagonist biperiden (4mg BIPERIDEN-neuraxpharm containing 3.58 mg biperiden), or a placebo in identical capsules. Participants were prepared for electroencephalography recording in the first 45 minutes, during which they received different questionnaires and written instructions for FALT and localizer. At around 50 minutes after oral intake of the capsule, participants watched the inscapes movie (Vanderwal et al., 2015) and after 60 minutes – which is the assumed time biperiden shows peak blood levels – participants started performing the FALT and subsequently the 1-back

localizer task. Before oral intake, before FALT and at the end of the session, blood pressure and heart rate were recorded, as well as questionnaires for fatigue and state anxiety.

5.2.4 Statistical analyses

To assess how biperiden affected memory and metamemory performances in FALT, ordinary least squares GLMs with the three factors drug (biperiden vs. placebo), session (first vs. second session) and their interaction effect were fit to overall memory accuracy (proportion correct trials from all trials), sensitivity (proportion high confidence selection on correct retrieval) and specificity (proportion low confidence selection on failed retrieval). Venn diagrams were used to display shared variance of memory accuracy, sensitivity and specificity. The direct overlap indicates determination coefficients (squared Pearson correlation coefficients) between respective to parameters, and the overlap between all three indicates how much additional variance on predicting memory accuracy is explained, when fitting an interaction effect of sensitivity and specificity compared to a GLM without their interaction. Respective fitting was performed separately for biperiden and placebo sessions. Single-trial analyses on the post-error subsequent memory effects were examined by predicting whether an incorrect trial was later successfully retrieved or repeatedly incorrect (*ErrorError* = 0, *ErrorCorrect* = 1) using interpretable regressors for drug (placebo = 0, biperiden = 1), session (session 1 = 0, session 2 = 1), block (block 1 = 0, …, block 4 = 3), run (run 1 = 0, …, run 6 = 5), confidence (low confidence = 0, high confidence = 1) and *z*-scored reaction times (duration in ms, excluding reaction times > 2 standard deviations from mean), with biperiden interaction effects and a nesting factor on participant. Significant differences of *d*’ and response bias were compared to zero and differences between biperiden and placebo sessions were assessed with respective t-tests.

5.3 Results

5.3.1 Behavior

Memory performance. As shown in Figure 20, the placebo session resulted in comparable numbers of *ErrorError*, *ErrorCorrect* and *CorrectCorrect* trial types, while in the biperiden session the highest number of trials was in the *ErrorError* category.

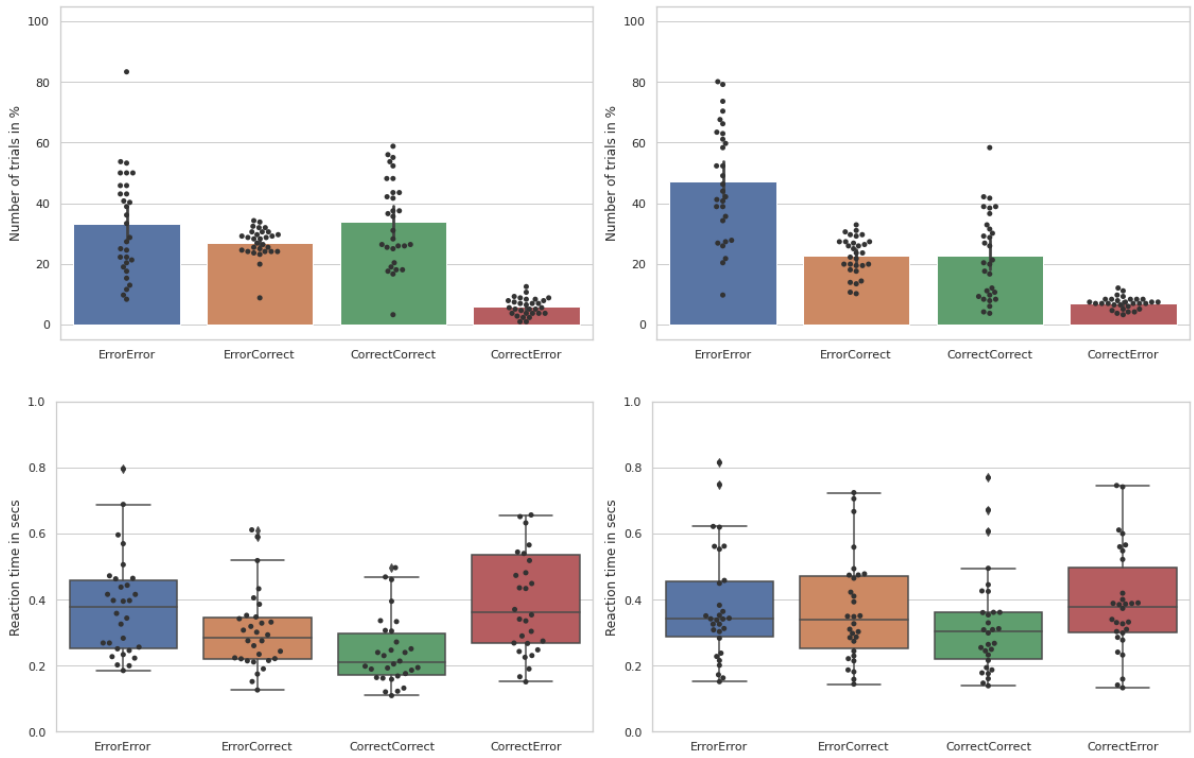

Figure 20. Proportion (top) and confidence selection reaction times (bottom) according to trial types in FALT for placebo (left) and biperiden (right)

When predicting overall memory accuracy in FALT using a GLM, there were significant biperiden ($t(58) = -3.29$, $p = .002$) and session effects ($t(58) = 2.49$, $p = .016$), but no indication for different biperiden effects on first or second sessions ($t(58) = -0.59$, $p = .560$) (see Figure 21). Meta-memory sensitivity was significantly predicted by biperiden ($t(58)= -2.72$, $p = .009$),

while session ($t(58) = 0.60$, $p = .553$) and session with biperiden interaction ($t(58) = -0.78$, $p = .436$) did no show significant effects.

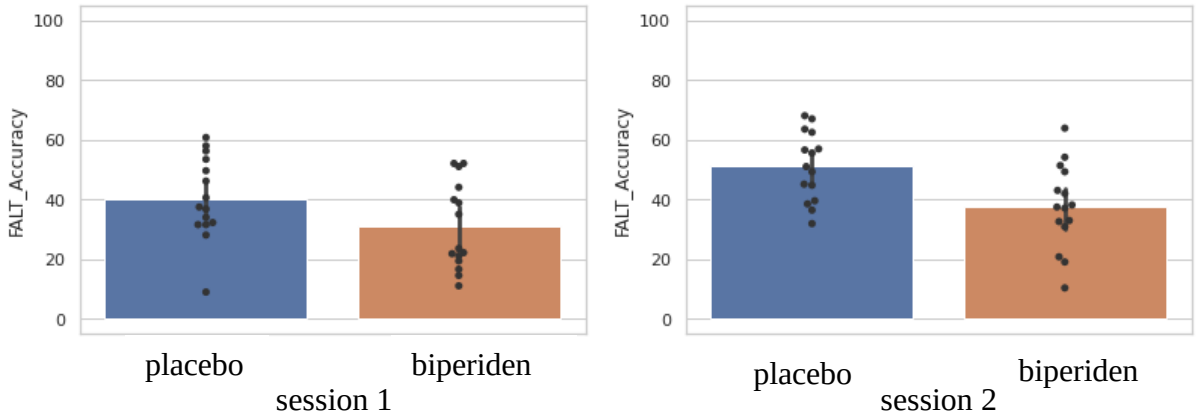

Figure 21. Biperiden and session effects for FALT memory accuracy.

Meta-memory specificity did not show any significant effect in relation to biperiden, session or the interaction term. The single-trial linear mixed model on post-error subsequent memory effect had an intercept of 34.2 % being the probability of later successful retrieval for a trial in session 1, block 1, run 1 and low confidence under placebo with an average confidence selection time. As shown in Figure 22, biperiden was related to 7.9 % lower likelihood of successful memory formation ($z(29) = -3.61$, $p < .001$), session with a 9.9 % increase ($z(29) = 9.42$, $p < .001$), each run with a 1.9 % increase ($z(29) = 4.19$, $p < .001$) and a 2.1 % decrease under biperiden ($z(29) = -3.45$, $p = .001$), high confidence with a 13.1 % increase ($z(29) = 3.48$, $p < .001$), longer reaction times with an increase of 2.0 % per standard deviation ($z(29) = 2.38$, $p = .017$) and a 2.4 % decrease for each reaction time standard deviation under biperiden ($z(29) = -2.20$, $p = .028$).

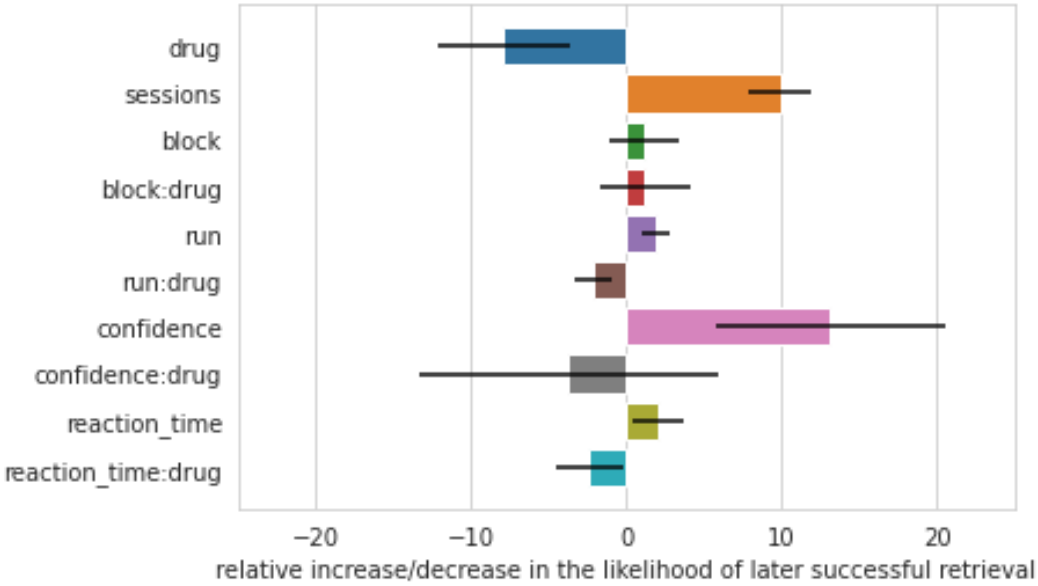

Figure 22. Single-trial linear mixed model of subsequent memory displaying changes in the likelihood of later retrieval success for higher values (right direction) and later unsuccessful retrieval (left direction) on error trials.

Confidence ratings. Participants successfully differentiated between failed and successful retrieval based on their confidence levels with $d' > 0$ both, when having received placebo ($t(29) = 17.44$, $p < .001$) and biperiden ($t(29) = 17.15$, $p < .001$), although the confidence ratings were more accurate in the placebo session ($t(58) = -2.17$, $p = .034$). As shown in Figure 24, the placebo session did not indicate a response bias on confidence ratings ($t(29) = 1.24$, $p = .223$), although under biperiden there was a response bias denoting under-confidence on predicting low confidence despite successful retrieval ($t(29) = 4.16$, $p < .001$), which was larger compared to placebo ($t(58) = 2.33$, $p = .023$). The response bias under biperiden also showed correlation coefficients between sensitivity and specificity (see Figure 25).

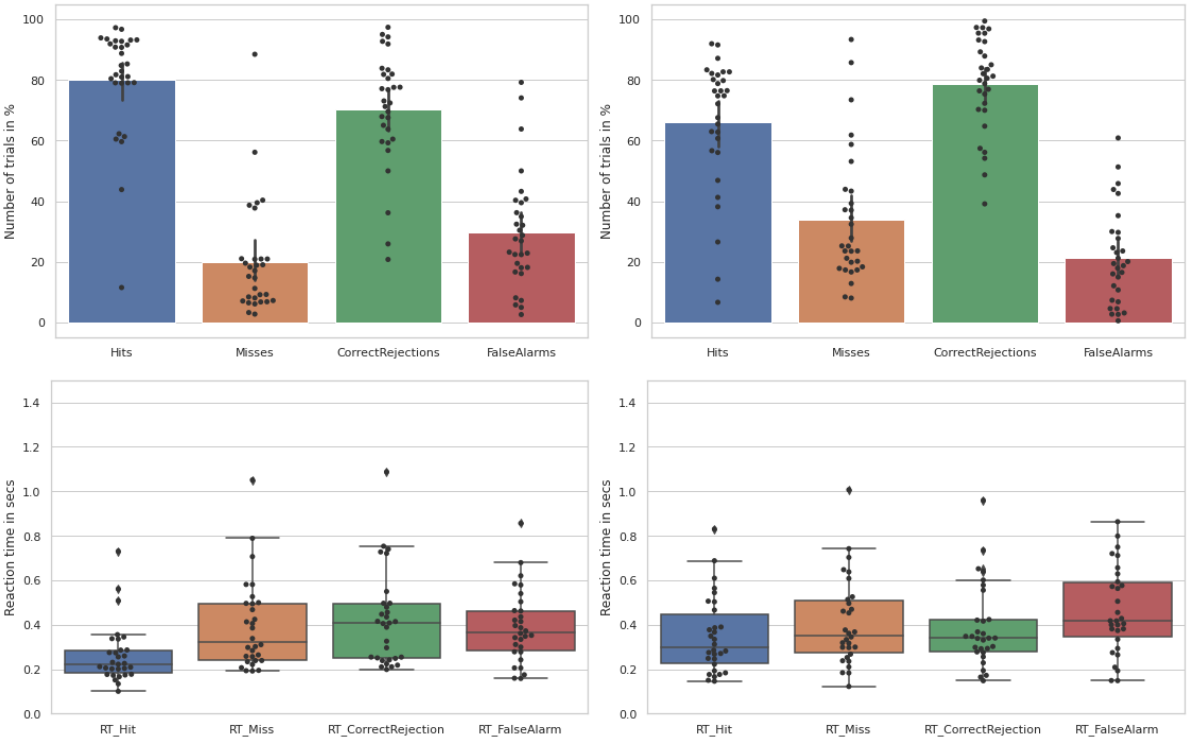

Figure 23. Confidence ratings and meta-memory trial types in FALT for placebo (left) and biperiden (right).

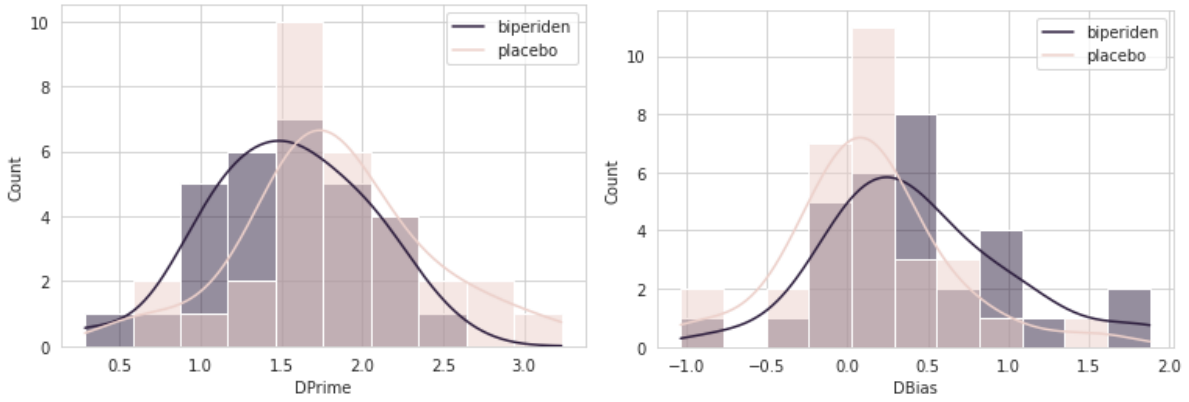

Figure 24. Signal detection theory parameters d' (left) and response bias (right). Higher d' is related to a better match between confidence ratings and retrieval success. Response bias = 0 indicates no bias, response bias > 0 indicates under-confidence and response bias < 0 indicates over-confidence.

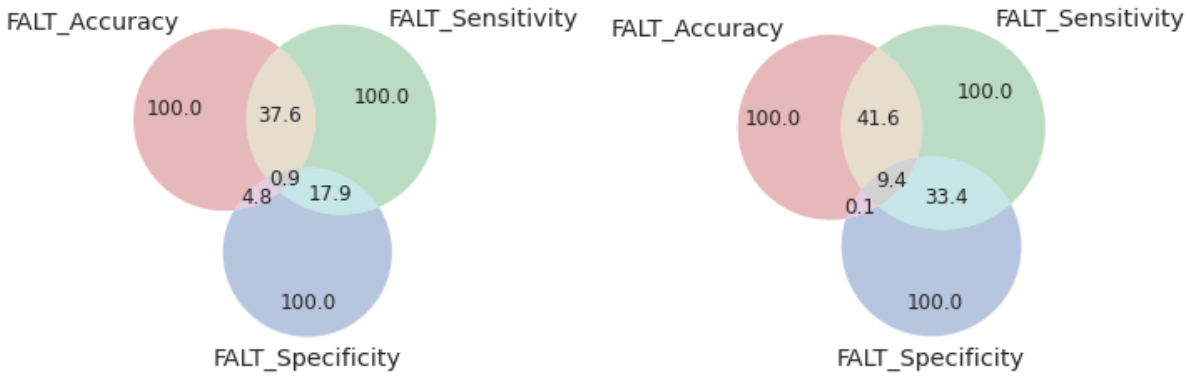

Figure 25. Overlap of memory and meta-memory in FALT for placebo (left) and biperiden (right).

Reaction times. The single-trial linear mixed model on raw reaction times (after exclusion of 3.2 % of trials with more than two standard deviations from average) estimated a mean reaction time of 456 ms. Respective results on the model coefficients are presented in Figure 26. While there was no biperiden main effect on confidence reaction times ($z(29) = 0.18$, $p = .861$), session 2 showed 96 ms faster reaction time estimates compared to the session 1 ($z(29) = -18.28$, $p = .039$). Each block was related to 9 ms slower reaction times ($z(29) = 2.07$, $p < .001$) and each run with 33 ms faster reaction times ($z(29) = -15.04$, $p < .001$), while run showed an interaction effect with biperiden of 6 ms slowing ($z(29) = 1.99$, $p = .047$). High confidence was related to 95 ms faster responses than low confidence ($z(29) = -6.06$, $p < .001$), while half of this effect dampened under biperiden showing 50 ms slower reaction times on high compared to low-confidence trials in the biperiden session ($z(29) = 2.31$, $p = .021$).

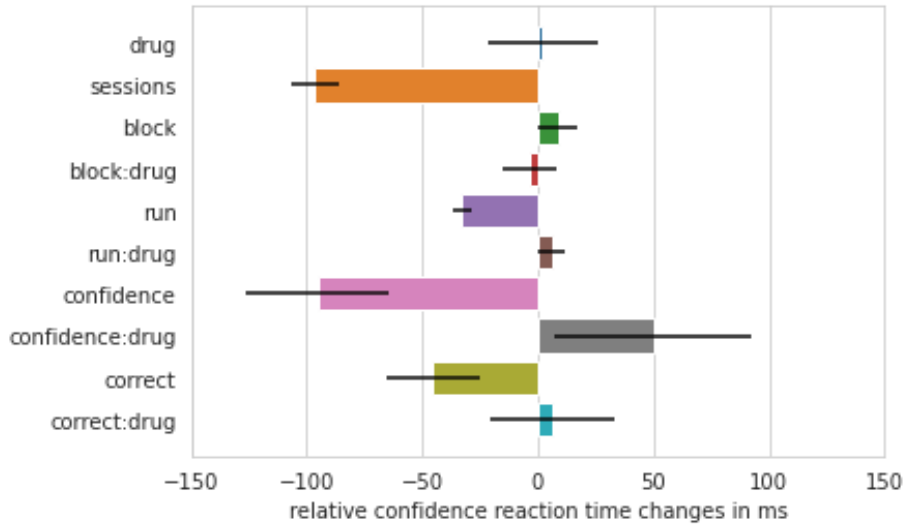

Figure 26. Linear mixed model results on the prediction of raw reaction times showing unstandardized regression coefficients.

5.4 Discussion

5.4.1 Brief summary

In the current study, biperiden lowered the chances of successful post-error memory formation. The decrease in memory performance was slightly stronger than participant's improvement from the first to the second session – while the latter could suggest effects such as strategy development. There was no indication for a memory accuracy related interaction effect between biperiden and the session it was administered, which underlines that session and biperiden effects have diverging mechanisms regarding task performance changes. In the biperiden session participants confidence ratings indicated under-confidence according to signal detection theory analyses, showing biased confidence selection and a restrained commitment to report high confidence upon successful retrieval. Reaction time analyses further complemented the under-confidence results, showing that biperiden diminished reaction time advantages of high confidence from almost 100 ms to less than half of it. Absolute reaction times did, however, not change under biperiden. While slower reaction times during confidence

selection represented an advantage in the success likelihood of post-error memory formation periods, this effect was deteriorated under biperiden, suggesting no memory formation benefits of slower reaction times when muscarine-1-acetylcholine receptors are blocked.

Cholinergic deficits on memory and memory monitoring. These results confirm the first hypothesis, that biperiden affects post-error memory formation processes and reaffirm a biperiden model for understanding age-related memory impairments (Blokland, 2022) but also suggest that they are accompanied by changes in performance monitoring – as reflected in confidence ratings and reaction times. Beyond impaired memory, biased confidence ratings were found as effect of biperiden, which may resemble increased thresholds memory representations have to surpass before high retrieval confidence is reported. Such considerations on changed decision boundaries have been suggested to be part of temporally overlapping post-error adaptation processes (Purcell & Kiani, 2016; Ullsperger & Danielmeier, 2016). The adaptivity of decreased sensitivity levels and low confidence could represent a change on decision boundaries in performance monitoring of memory representations. It, however, seems a matter of debate whether lower sensitivity levels impair or improve following memory formation periods. Explained variance between sensitivity and memory accuracy did not change between placebo and biperiden in the current study, although this was observed in age-related differences of Study 2. Furthermore, if lower sensitivity levels and response bias are interpreted as functional impairments and not as adaptive decision boundary changes, sensitivity and memory should decrease their interdependence. Since this has not been observed, the current study suggests that cholinergic blockage using biperiden leaves performance monitoring processes intact. This is in line with a previous study finding largely comparable performance-monitoring related hemodynamic responses but diminished post-error adaptations under biperiden (Danielmeier et al., 2015).

High confidence errors benefit memory formation independent of biperiden. Interestingly, a biperiden-independent effect was that high confidence on incorrect trials has been related to a 13.1 % increase in the likelihood that the post-error learning situations is successfully used for memory formation. While both, *ErrorCorrect* and *ErrorError* trials, have unsuccessful retrieval in common, the current results suggest that reporting a false alarm increases following learning performance substantially. Failures on selecting high confidence may, however, also have shown higher relevance for learning when compensatory mechanisms – such as lowered confidence levels – are recognized to be too weak. This effect did, however, not show an interaction with biperiden, suggesting that other neurophysiological networks involved may be bypassing at least muscarine-1-acetylcholine receptors. These results confirm the hypothesis that diminished cholinergic efficiency leaves performance monitoring and adaptation processes beyond cholinergic mediation intact – and support the idea that pMFC may be first is first in the signaling cascade with the cholinergic system (Danielmeier et al., 2015). Although it was not specifically hypothesized, high confidence errors may produce larger prediction errors and therefore boost following learning. This aligns with a study suggesting that surprise signals can boost learning even if they are not task-relevant (Wessel et al., 2016). It is, however, tempting to speculate that this effect – which was not changed by biperiden – may be based on other downstream regions modulated by pMFC such as the dopaminergic midbrain and respective projections (Hester et al., 2012). The paradigm was, however, not optimized to investigate high confidence errors and further studies on interactions between performance monitoring and associative memory formation may adapt the used paradigms to produce larger proportions of confidence-accuracy mismatches.

5.4.2 Limitations and outlook

While the current study found behavioral effects of performance monitoring and memory formation, different processes are simultaneously at play during post-error resolution (Purcell & Kiani, 2016). For example, the task at hand is not a typical cognitive control task in respect to speed-accuracy trade-offs which may be relevant for producing behavioral slowing on processes it has been better understood. The current study investigated biperiden effects on performance monitoring associated behavioral estimates – such as increased response times – because the interdependence between success expectation and response time represented an interaction regarding high confidence trials and faster responses. While longer reaction times were generally related to improved post-error learning success this effect showed the opposite pattern under biperiden. In line with the idea that error resolution may restrain cognitive capacities which otherwise could be beneficial for task performance (Ullsperger & Danielmeier, 2016), the way confidence was assessed in the current study may have allowed participants to self-pace their tempo according to their requirements for error resolution. Further studies may investigate timing differences between memory error monitoring processes – such as confidence ratings and performance feedback – and following encoding periods. Neuroimaging analyses may further help elucidate accompanying cognitive processes during feedback and encoding, on which behavioral parameters lack. While in a previous study the feedback period and respective early EEG components were more predictive for later retrieval than the following re-encoding period itself (de Bruijn et al., 2020), it remains to be investigated on which neurophysiological and neurochemical levels performance monitoring processes – such as feedback presentation or confidence ratings – start up respective memory formation processes for boosting later retrieval. The current study has contributed to the understanding how cholinergic integrity may not only underlie memory performance but also specific error-adaptation processes, with cholinergic antagonists leading to under-confidence

and reaction time changes. These results may help elucidate how memory error detection processes are operating and suggests that phenomena such as subjective memory decline – in form of lower retrieval success expectations – can be a consequence of impaired cholinergic signaling on muscarine-1-acetylcholine receptors.

6 General Discussion

The current dissertation sheds light on the functional neuroanatomy of memory error detection and suggests that performance monitoring processes associated with pMFC are involved in post-error improved memory formation. Cross-sectional age effects and muscarinic cholinergic blockage showed memory deterioration and increased retrieval uncertainty. Furthermore, reaction time advantages of high-confidence trials declined in older adults and diminished to half of their size under biperiden compared to placebo.

In the following, a theoretical framework for the observed results will be presented which is admittedly speculative and leaves different steps untested, but may support the conceptual understanding of the observed results and lead to new hypotheses to-be-tested in future studies: Upon detection of memory errors, pMFC interacts with cholinergic basal forebrain and executive control network, which, in turn, upregulate selective attention. Increased selective attention prepares stimulus-specific regions in the ventral visual stream such that memory-related medial temporal lobe regions can more successfully extract relevant stimulus features. Within ages between 50 to 80 years, memory performance declines due to reduced basal forebrain integrity such that acetylcholine-mediated selective attention is disturbed, leading to failures in separating memory-relevant from memory-irrelevant stimulus processing in the ventral visual stream. An impaired cholinergic system reduces the likelihood that acetylcholine-mediated selective attention can improve memory formation, while pMFC-

dependent error-monitoring processes remain intact. By recognizing weaker memory performance, further attempts are carried out to restore memory function based on available brain reserves. In this regard, confidence levels during memory retrieval decrease and errors in memory formation are expected increasingly. In the memory-impaired brain, high confidence selection stands in contrast to stronger expectancy of memory errors and therefore represents a metacognitive conflict slowing down respective confidence selection reaction times. In the following chapter, several key points of this theoretical framework are discussed and it is presented how the current dissertation contributes to a better understanding of interactions between performance monitoring and memory formation.

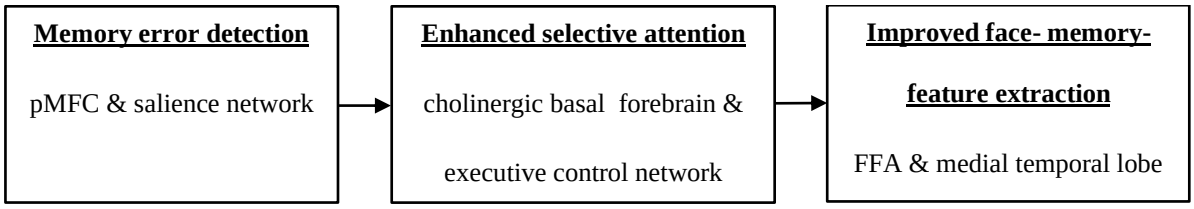

Figure 27. Potential mechanism of error-driven improvement in memory formation.

6.1 General summary

6.1.1 The basis of successful post-error memory formation

The neurophysiology of changes in stimulus representations and memory monitoring were investigated in Study 1. Regions involved in memory formation – as determined by fMRI studies on the subsequent memory effect (Kim, 2011) – were largely replicated in Study 1. Among these regions were vlPFC, FFA, PPC and pMFC. The post-error subsequent memory contrast (*ErrorCorrect* > *ErrorError*) replicated previous findings of pMFC's involvement (Hester et al., 2008) and underlines its role in post-error memory formation. Previous studies have emphasized right FFA's role in its specificity for face recognition (Caspers et al., 2013; Schwarz et al., 2019; Yovel, 2016), while the current study focused on face-related memory

formation processes. vlPFC and PPC are part of frontoparietal executive control network (Seeley et al., 2007) and have been related to increased selective attention levels (Nelissen et al., 2013). Previous studies have found pMFC hemodynamic responses in relation to post-error improved task performances (Hester et al., 2008; Klein et al., 2007) and pMFC has been proposed as an essential hub of performance monitoring processes (Ullsperger et al., 2014). In this regard, results of Study 1 found significant hemodynamic responses in pMFC not only during post-error successful encoding of face memories, but also showed increased hemodynamic responses for unsuccessful retrieval, low confidence and negative feedback. Memory-error related pMFC signals may indicate that a need for improved encoding has been recognized – a potential requirement for adaptive performance changes. Matching with this assumption, a previous EEG study has found frontocentral FRN to be predictive for post-error successful re-encoding (de Bruijn et al., 2020). While this suggests that there should be an interplay between pMFC and stimulus-specific regions upon post-error memory formation success, this step remained to be tested and was addressed in the current dissertation.

Recent studies have suggested that multivariate classification models can evaluate stimulus representativity, which may be used as estimate for selective attention (Leong et al., 2017; Nelissen et al., 2013). Regarding post-error improved memory formation, it was therefore hypothesized that stimulus representativity in ventral visual stream can be explained by pMFC hemodynamic responses. In line with the suggestion that participant-specific models are required for accurate detection of face-specific regions (Rossion et al., 2012), participants in Study 1 also performed an analog 1-back localizer task on which face and house stimuli needed to be compared with stimuli of the preceding trial. For each participant a multivariate classification model was trained on right FFA fMRI voxels in the localizer task to predict face-representativity during memory formation and retrieval in the main task (FALT). Predicted

face-representativity showed a robust FFA topography on single-trial hemodynamic responses during encoding, rehearsal and retrieval in FALT. This underlined the robustness of the model since it distinctly corresponded with the face compared to houses contrast of conventional GLM analyses in the localizer task. Face-representativity did, however, not only relate to right FFA - the region the face-representativity model was trained on – but also to pMFC hemodynamic responses. If multivariate representativity can be used as estimate for selective attention levels (Leong et al., 2017; Nelissen et al., 2013), these results support the assumption that pMFC coordinates post-error increased attention on face-specific stimulus features and suggests that cognitive control processes can explain stimulus processing in the ventral visual stream. Face-representativity related hemodynamic responses did, however, also overlap with a basal forebrain cytoarchitectonic mask (Zaborszky et al., 2008), which indicates a potential cholinergic involvement in face-representativity changes. The cholinergic basal forebrain has been hypothesized to mediate post-error behavioral and visual processing adaptations after pMFC related error detection (Danielmeier et al., 2015; Sarter et al., 2006). While it has been suggested that acetylcholine release in frontoparietal executive control regions presents a key mechanism for enhanced attention (Ljubojevic et al., 2018), other studies have suggested that salience network nodes in anterior insula and pMFC are relevant for increased executive control network recruitment (Menon, 2015). Another study on rodents suggested that direct projections from cingulate cortex to visual regions are involved in post-error improved visual processing (Norman et al., 2021). Therefore, it seems in question which pMFC projections are most relevant for error-driven enhanced stimulus processing for memory formation.

6.1.2 Ageing affects memory and increases uncertainty

In a cross-sectional comparison, accuracy of memory retrieval declined by almost 40 % from younger adults (18-35 years) to older adults (50-80 years). Although younger adults had a

higher benefit on using learning opportunities for their favor, they also had slightly above-chance accuracies in the first block indicating that they may have developed strategies to infer the orientation based on previous pairings in the same block (see Figure 28). In older adults, default mode network regions showed a higher involvement in post-error memory formation success, which was in line with meta-analytical findings of age differences on the subsequent memory effect (Maillet & Rajah, 2014). A respective pattern of increased vmPFC and decreased occipital cortex hemodynamic responses for high compared to low confidence selection did also fit into this pattern. Despite that many previous studies on the subsequent memory effect contrasted encoding periods of later correct compared to incorrect retrieval regarding their hemodynamic responses, substantial differences in contrast specifications remained (Maillet & Rajah, 2014). For example, some studies used combinations of trial conditions such as only high confidence later correct trials compared to later incorrect trials disregarding of confidence levels. This may confound hemodynamic responses of the subsequent memory effect with expectation mismatches on high-confidence memory errors. The current dissertation used the approach to contrast high confidence post-error later successful retrieval (*ErrorCorrect*) with low confidence post-error later failed retrieval (*ErrorError*). This approach may successfully differentiate between trials which are correctly remembered from trials which were guessed right, since there was a one in eight chance to guess the correct orientation in Study 1 and 2. However, the chosen contrast specification may be impacted by the reporting bias of older adults who more frequently chose low confidence than expected by their general confidence-related detection accuracy. This also lead two participants to be excluded from fMRI analyses on the subsequent memory effect, as they had no high-confidence post-error successful retrieval trials (*ErrorCorrect*) despite reasonable learning performance and sufficient high-confidence repeated successful trials (*CorrectCorrect*). Reaction time analyses on binary confidence ratings further supported the

conservative response bias regarding that high confidence did not have a reaction time advantage in older adults – although this was clearly observed in younger adults.

Compared to previous studies which investigated the subsequent memory effect, error detection processes such as failed retrieval, low confidence and negative feedback have been additionally investigated as contrasts for hemodynamic responses. In this regard, only negative feedback displayed significant hemodynamic responses in pMFC, supporting the idea that older adults have weaker task representations and therefore an increased requirement of external performance feedback (Hämmerer et al., 2019). At least for simple face recognition in the localizer task this conclusion may, however, not be supported since conventional GLM analyses showed comparable results for older and younger adults with topographically distinct hemodynamic responses in FFA for faces compared to houses. Classifier performance in cross-validation in the localizer and application in FALT during fixation/rehearsal and retrieval derived comparable decoding accuracies for younger and older adults, while both groups did not have above-chance decoding accuracies during encoding. Single-trial face-representativity was, however, not associated with pMFC hemodynamic responses in none of the epochs in older adults. This could suggest pMFC-associated performance monitoring and FFA-related face recognition processes are less linked in older adults. In younger adults negative feedback was – besides pMFC hemodynamic responses – also related to effects in FFA which could be linked with previous ideas that already during negative feedback the success of following re-encoding periods may be determined (de Bruijn et al., 2020). In older adults, the contrast for negative compared to positive feedback showed decreased hemodynamic responses in ventral striatum and FFA. While this may indicate lower FFA associations with negative feedback, it could also indicate increased hemodynamic responses for positive feedback and therefore a stronger benefit on learning through guessed correct trials than learning through mistakes in

older adults. Previous studies have suggested that older adults use different strategies such as trying to associate perceived faces with remembered familiar faces – which could explain increased default mode network hemodynamic responses (Maillet & Rajah, 2014). But are older adults getting worse in error-driven learning? Anecdotes of participants indicated roughly two different strategies which have been known in the field of spatial navigation as allocentric and ego-centric perspectives (see Figure 28). Is one of these stronger relying on age-related and cholinergic deficits? Are the strategies of older adults more related to egocentric than allocentric strategies? Further studies are needed to identify how different strategy usages may rely on different brain networks and available brain reserves.

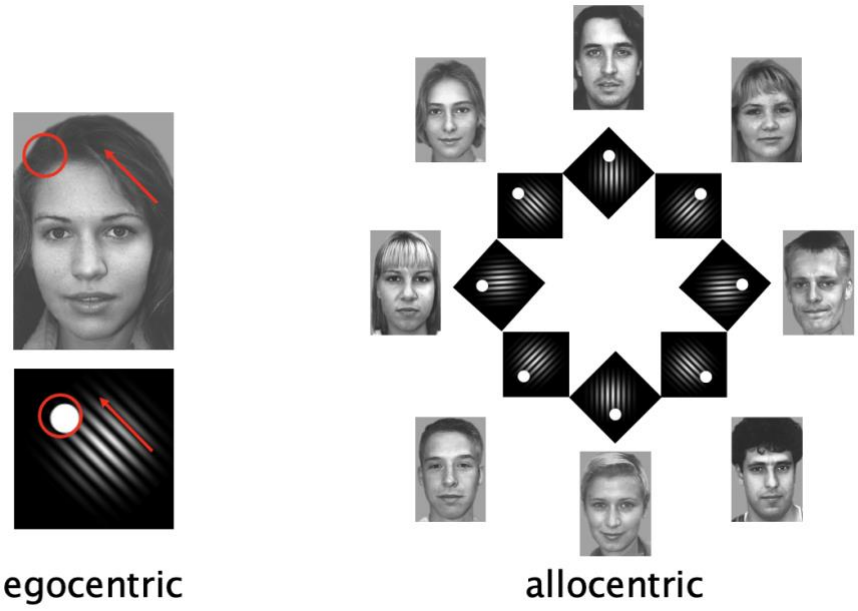

Figure 28. Two potential strategies. On the left side, retrieval cues may be built by determining face features such as the angle in hairstyle resembles the diagonal direction of the gabor patch. On the right side, a participant may attempt to place respective faces around a table and consider their positions next to each other as potential orientations of the gabor patch.

6.1.3 Muscarinic acetylcholine blockage as ageing model

The selective muscarine-1-receptor antagonist biperiden has been proposed as pharmacological model to understand age-related memory deficits (Bakker et al., 2021; Blokland, 2022). In Study 3, 30 healthy male adults (18-30 years) received 4 mg biperiden (= 3.58 mg active substance) or a placebo in a randomized controlled cross-over design where participants joined the study on two sessions. While session 2 showed a general memory improvement compared to session 1, no interaction effects between biperiden and the session it was given was found for predicting memory accuracy. Behavioral results not only confirmed the biperiden model for memory deficits with robust memory impairments but also resembled signatures in task performance compatible with cross-sectional age effects found in Study 2. Besides memory differences, biperiden was also related to under-confidence and diminished high-confidence reaction time benefits. Further analyses of this pattern suggested that the response bias was related to decreased task performance which underlines that respective changes in speed and choice upon confidence selection may represent intact meta-memory function. This is in line with previous studies proposing that memory-related metacognitive efficiency is only slightly impacted in older age when task performance is properly controlled for (Palmer et al., 2014). Furthermore, another study on biperiden showed largely comparable performance monitoring related hemodynamic responses in pMFC (Danielmeier et al., 2015). This suggests that cholinergic effects on memory performance may be located further down the hierarchy following pMFC related performance monitoring which detected memory formation demands. But biperiden also showed differences compared to cross-sectional age effects. For example, under biperiden participants were not generally slower compared to the placebo session. The main effect of biperiden on reaction times was that reaction time advantages of high-confidence trials attenuated. Furthermore, later blocks and runs showed higher reaction time advantages as effect of older age in Study 2, but these effects were not present under biperiden. This

suggests that cross-sectional age effects and biperiden-induced muscarinic cholinergic deficits overlap on impaired memory formation and increased retrieval uncertainty, while response speed differences show more diverse effects in older adults and the biperiden ageing model.

6.2 General limitations and outlook

The current dissertation bridges perspectives from neurophysiology, cross-sectional age effects and a cholinergic model for memory impairments. Although the cognitive paradigms used to investigate neurophysiological and behavioral processes had slight adaptations in Study 3, this may emphasize the generalizability of the results. Several findings were replicated – such as memory decline, biased confidence ratings and changes in confidence-related reaction time advantages. For the understanding of interactions between performance monitoring and memory formation, there are some further specifications required to be addressed for understanding what underlies demand dependent memory formation improvements.

6.2.1 Sources of memory error evidence

If pMFC, cholinergic basal forebrain and executive control network interactions are central for selective attention enhancement after memory errors are detected, in which time frame do these processes interact? In a previous EEG study, it has been suggested that negative feedback related EEG signals are predictive for following re-encoding success, although EEG signals during re-encoding themselves have not been systematically related to post-error improved memory formation (de Bruijn et al., 2020). In general, the timing between memory error detection and following learning situations has been speculated to underlie differences on whether memory errors lead to more errors or whether they lead to improved learning (Decker et al., 2020). For the literature on post-error slowing, it has also been proposed that timing after error detection matters for its adaptiveness (Ullsperger & Danielmeier, 2016). So how much

time went by in the FALT paradigm between error detection and re-encoding periods? This is not a simple question and the answer may not only vary from participant to participant, but also from trial to trial. In the primary idea of the paradigm, memory errors should at latest be detected by the presentation of negative feedback as means of accumulated external memory error evidence. Feedback may, however, have differential effects depending on its expectedness. Therefore, a binary confidence rating helped to determine internal models of error expectations but also supported specifications in the contrasts of the subsequent memory effect. The confidence rating provided another opportunity to detect memory errors. However, choice selection or already the presentation of only the face in the very beginning of a FALT trial (see Figure 1) may have been sufficient for a participant to recognize that memory retrieval failed. So even if feedback presentation may be the last opportunity to detect a memory error before re-encoding, it could also be the last bit to already accumulated evidence on mistaken memory recall. This temporal uncertainty on the moment of error detection may have an impact on the interpretation of the results, such that is seems important to understand during which time of unsuccessful retrieval error detection has become evident. Do older adults rely on external performance feedback, as has been proposed due to deficits in task representations (Hämmerer et al., 2019)? From a first point of view, negative feedback in older adults was the only contrast yielding hemodynamic responses in pMFC. Based on this result it is tempting to speculate that only negative feedback presentations in older adults provided sufficient evidence for the performance monitoring system to implement adaptive upregulation of the cholinergic system. The low temporal resolution of hemodynamic responses complicates to determine at which moment error detection occurs. Methods with higher temporal resolution such as EEG may be useful to evaluate at which time memory error evidence peaks and how long after-effects may be required to improved memory formation on following re-encoding and potentially also fixation/rehearsal periods between trials. Respective analyses could be

performed with drift diffusion models (Ratcliff et al., 2016) to better capture the temporal dynamics of memory error evidence accumulation and post-error memory formation. It may, however, also be advisable to adapt the FALT paradigm regarding that on some trials feedback presentation is omitted and on other trials confidence selection does not take place. Such approaches on the experimental design may help to understand how strong older adults rely on external performance feedback and how good they perform if they just have learning opportunities without informative feedback on what has already been learned.

6.2.2 Neuromodulatory specificity

In Study 3, the muscarine-1-acetylcholine receptor antagonist biperiden was used to investigate how a degraded basal forebrain cholinergic system may impact post-error memory formation. These data generally confirmed a biperiden model for age-related memory deficits (Bakker et al., 2021; Blokland, 2022). Although it has been proposed that basal forebrain integrity impacts memory performance upon ageing (Düzel et al., 2010), it should be noted that basal forebrain is not the only brain structure containing neurons which release acetylcholine. For example, there are cholinergic neurons in pedunculopontine nucleus, laterodorsal tegmentum, in a subset of thalamic nuclei, and there are striatal cholinergic interneurons, while basal forebrain cholinergic neurons provide the main projections to cortical and medial temporal lobe regions (Ballinger et al., 2016; Mesulam et al., 1983). Because pharmacological blockage of muscarine-1-acetylcholine receptors is not tract-specific, it cannot be excluded that other than basal forebrain cholinergic projections are involved in effects observed in Study 3. However, based on the regions typically found to be involved in successful memory formation, it seems most likely that basal forebrain cholinergic projections from medial septum to hippocampus and amygdala, and from nucleus basalis of Meynert to cortical regions and medial temporal lobe are the projections via which biperiden may have affected memory performance.

6.2.3 Subjective memory decline

As discussed earlier in this dissertation, previous studies found that some individuals noted cognitive and memory performances decreases before objective tests were able to capture these deficits and these individuals may have a higher probability on developing a neurodegenerative pathology (Kuhn et al., 2021). In this regard, it may be interesting to note that cholinergic deficits – as investigated in Study 3 – may still allow memory impairments to be recognized. If only cholinergic integrity declined with higher age, strategies compensating for respective deficits may still able to be implemented. However, it has also been suggested that with increased levels of neurodegeneration impaired memory may fail to be recognized due to increasing anosognosia (Kuhn et al., 2021). Increased anosognosia was related to stronger structural decline in default mode network regions, leading the authors to suggest that decreased awareness and worse self-related processing explain why subjective memory decline disappears (Kuhn et al., 2021). This explanation does, however, lack a mechanistic understanding on how subjective memory decline transitions to anosognosia. Further studies on respective target populations in the transition period between subjective memory decline and anosognosia may help to understand under which conditions performance monitoring fails to recognize declining memory functions. If the stage of anosognosia on memory deficits is sooner or later reached, error-less learning strategies – potentially bypassing pMFC and cholinergic basal forebrain – may find their application for compensating the loss of post-error selective attention increases.

6.3 Conclusions

Based on the results of young healthy adults, dementia-free aged individuals and younger adults with pharmacological cholinergic impairment, the current dissertation investigated

interactions between performance monitoring and memory formation as they are reflected in behavior and neurophysiology. Overall, the results of the three studies support a model in which pMFC and salience network associated performance monitoring processes detect memory errors. Detected memory errors may then lead to upregulation of cholinergic basal forebrain and executive control network associated selective attention enhancement towards memory relevant stimulus features such as face recognition in FFA as part of the ventral visual stream. The three studies, however, also suggested that the interaction between performance monitoring and memory formation is not a one-way street in which detected memory errors contribute to improved memory formation. Age-related and cholinergic-blockage mediated memory impairments can likewise be recognized via the performance monitoring system. This may lead to lower performance expectations such that successful retrieval is surprising and reaction time advantages for high confidence selection diminish – and low-confidence expectation may be more in line with general task expectations. Besides overlaps of age effects and the biperiden model of memory impairment, there were also differences between cross-sectional and biperiden effects. For example, age effects showed general response slowing but also higher reaction time advantages for later trials in the experimental session. Biperiden-related reaction times during confidence selection were not generally diminished, but rather showed loss of reaction time advantages selectively for high confidence by half of its size compared to placebo. This suggests that biperiden is a good model for investigating acetylcholine-related memory impairments with intact error detection, but it does not explain all of the behavioral changes observed in older adults. For a more complete understanding of interactions between performance monitoring and memory formation, future studies may omit opportunities for accumulating memory error evidence – such as feedback presentation or confidence ratings – to test whether older adults and cholinergically-impaired individuals rely on external feedback to increase the success of post-error learning opportunities.

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