Universidade do Minho
Escola de Psicologia

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Neural Correlates of Proactive Interference and Attentional Control Over Working Memory in Healthy Aging

maio de 2020

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Neural Correlates of Proactive Interference and Attentional Control Over Working Memory in Healthy Aging

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Doutoramento em Psicologia Básica

Trabalho efetuado sob a orientação da
Professora Doutora Adriana da Conceição Soares Sampaio

e sob a orientação do
Doutor Diego Pinal Fernandez

maio de 2020

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STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

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University of Minho, 29th of May 2020

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Resumo

Teorias do envelhecimento cognitivo sugerem que o declínio de funções cognitivas no envelhecimento saudável está associado a um controlo inibitório reduzido. Na presente dissertação, estudou-se como a resolução da interferência proativa (PI) se altera no envelhecimento saudável, usando-se uma abordagem multimodal. Desta forma, analisamos efeitos da PI no sinal do eletroencefalograma (EEG) e imagens de ressonância magnética funcional (IRMf) durante uma tarefa de 'Recent Probes' em grupos saudáveis de adultos jovens (18-39 anos) e adultos mais velhos (53-76 anos). Os estudos apresentados nos capítulos III, IV e V mostraram que os adultos jovens exibiram maiores efeitos de PI do que os adultos mais velhos, o que provavelmente se deve à dificuldade geral que os adultos mais velhos demonstraram na tarefa. No capítulo III, foi realizada uma análise de componentes principais dos dados de EEG obtidos durante a tarefa, que mostraram alterações ligadas à idade no processamento da familiaridade e um aumento da monitorização do desempenho no grupo de adultos mais velhos. Além disso, os resultados sugerem que o recrutamento de recursos neurais para a recuperação de informação contextual se encontra preservado no envelhecimento saudável. No capítulo IV é apresentada a análise de dados de EEG no domínio tempo-frequência. Os resultados evidenciaram maior potência na frequência theta (4-8 Hz) na condição de alta-PI do que na de baixa-PI nos adultos jovens, sugerindo um papel do controlo inibitório na resolução da PI. Adicionalmente encontramos evidência de uma modulação reduzida de potência de theta em adultos mais velhos, devido a ineficiência dos mecanismos oscilatórios que apoiam o controlo cognitivo. A análise ao nível das fontes da atividade de EEG documentou que os adultos mais velhos recrutaram áreas cerebrais adicionais para compensar a dificuldade que experimentaram na tarefa. No capítulo V apresentam-se os principais resultados derivados da análise de dados de IRMf durante a tarefa, onde se evidenciou uma maior ativação na condição de alta-PI nas regiões cerebrais frontais e parietais, sugerindo diferenças relacionadas com a idade na seleção de respostas e na monitorização de erros durante a resolução da PI. Também encontramos evidências que sugerem que, dependendo da capacidade da memória de trabalho, o envelhecimento afeita a recuperação de informação visual durante a resolução da PI. Com esta dissertação, pretendemos ampliar o conhecimento sobre a atividade neural necessária para compensar a diminuição da eficiência neural que se observa no envelhecimento, e desta forma contribuir para as teorias de envelhecimento cognitivo.

Palavras chave: EEG, Envelhecimento Saudável, Interferência Proativa, IRMf, Memória de Trabalho

Abstract

Theories of cognitive aging suggest that declines in cognitive functions such as working memory (WM) in healthy aging are due to decreased inhibitory control. The present thesis used a multimodal approach to study how the resolution of proactive interference (PI) changes in healthy aging. To carry out this aim, we analysed PI effects with electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) during a Recent Probes task in groups of young (18-39 years) and old (53-76 years) healthy adults. The studies presented in chapters III, IV and V found young adults to show greater PI effects than old adults in reaction time and accuracy, which was likely due to a general difficulty that old adults had performing the task. Chapter III presents temporo-spatial principal component analysis of EEG data recorded during the Recent Probes task and found age differences in PI effects that suggest alterations of the neural correlates of familiarity processing and performance monitoring in old adults, while the neural correlates of retrieving contextual information was preserved in old adults. Chapter IV describes analyses of EEG data in the time-frequency domain. The results showed young adults to produce greater power in the theta frequency band (4-8 Hz) in conditions of high-PI compared to low-PI, suggesting the possible role of inhibitory control in PI resolution. We also found evidence of reduced modulation of theta power activity in old adults, suggesting reduced efficiency of the oscillatory mechanisms supporting cognitive control. Source level analysis of the EEG time-frequency data found evidence to suggest old adults recruited additional brain areas to attempt to compensate for the difficulty observed during the task. Chapter V portrays an analysis of fMRI data during the Recent Probes task, which showed a network of frontal and parietal brain regions to be sensitive to PI, all of which showed greater activation in conditions of high-PI compared to low-PI. Age differences in PI effects at the neural level suggested age differences in biasing response selection and error monitoring when overcoming PI, and that these effects were not due to WM ability. We also found evidence to suggest that, depending on WM ability, aging affects the retrieval of visual information during PI resolution. With this dissertation, we aimed to improve our understanding on the recruitment of neural activity as compensation for reduced cognitive control and neural efficiency in healthy aging, in order to contribute to theories of cognitive aging.

Key words: EEG, fMRI, Healthy Aging; Proactive Interference; Working Memory.

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Abbreviations, Acronyms and Symbols

WM - Working memory

STM - Short-term memory

RT - Reaction time

ROI - Region of interest

CRUNCH - Compensation-related utilization of neural circuits hypothesis

STAC - Scaffolding Theory of Aging and Cognition

EEG - Electroencephalogram

ERP - Event-related potential

P3 - Positive 300 ms

N450 - Negative 450 ms

FFA - Fusiform face area

PPA - Parahippocampal place area

PI - Proactive Interference

LPC - Late Positive Component

ms - Miliseconds

MFN - Medial Frontal Negativity

fMRI - Functional Magnetic Resonance Imaging

IFG - Inferior frontal gyrus

VLPFC - Ventrolateral prefrontal cortex

MFG - Middle frontal gyrus

SMG - Superior medial gyrus

SMA - Supplementary motor area

RN - Recent negative

tsPCA - Temporo-spatial principal component analysis

PCA - Principal component analysis

Hz - Hertz

BOLD - Blood oxygen level-dependent

SD - Standard deviation

SMIC - Serviço Médico de Imagem Computorizada

MoCA - Montreal cognitive assessment

MCI - Mild cognitive impairment

BDI-II - Beck Depression Inventory-II

KDEF - Karolinska directed emotional faces

IAPS - International affective picture system

ITI - Inter-trial interval

RP - Recent positive

CMS - Common Mode Sense

DRL - Driven Right Leg

mV/μV - Microvolts

3T - 3 tesla

MRI - Magnetic resonance imaging

MPRAGE - Magnetized prepared rapid acquisition gradient echo

TR - Repetition time

TE - Echo time

FoV - Field of view

N - Number of participants

SECVS - Subcomissão de Ética para as Ciências da Vida e da Saúde

GDS - Geriatric Depression Scale

P - Positive

N - Negative

R - Recent

RM-ANOVA - Repeated Measures Analysis of Variance

IIR - Infinite impulse response

dB - Decibel

ICA - Independent component analysis

tPCA - Temporal principal component analysis

sPCA - Spatial principal component analysis

sLORETA - Standardised low-resolution brain electromagnetic tomography

MNI - Montreal Neurological Institute

mm - Milimetre

M - Mean

p - Probability value

η_p^2 - Partial eta-squared

SEM - Standard error of the mean

F - F-ratio

t - t-value

r - Correlation coefficient

N2 - Negative 200 ms

LRP - Lateralised readiness potential

P700-P800 - Positive 700-800 ms

N200-P200 - Negative 200 ms - Positive 200 ms

TFR - Time-frequency representation

PLS - Partial Least Squares

SVD - Singular value decomposition

FWE - Familywise error rate

BEM - Boundary element method

S/m - Siemens per metre

BA - Brodmann Area

WFU - Wake Forest University

k - Cluster size

EDI - Edinburgh Handedness Inventory

GLM - General linear model

vFDR - Voxel-wise false discovery rate

SVC - Small volume correction

IPL - Inferior parietal lobule

DLPFC - Dorsolateral prefrontal cortex

SMD - Standard mean difference

K-S - Kolmogorov-Smirnov

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Chapter I

Introduction

Healthy aging implies growing older in the absence of pathology, although it still involves changes in psychological and cognitive processes (Reese, Cherry, & Copeland, 2000). The improvement in healthcare systems and living standards, among other factors, led the portion of the general population in Europe older than 50 years to reach 20.8% by 2019 (Eurostat, 2019). This increase is especially relevant for countries such as Portugal, as over 21.8% of the population was over 65 years of age in 2019, and by 2050 the ratio of working adults to people over 65 years is expected to reach 65.8% (Eurostat, 2019), meaning that for every adult over 65 years there will be just less than two working adults. Therefore, as the ratio of old to young people in the general population increases, it is in everyone's interest to maximise healthy aging in order to reduce the potential stress on society due to an aging population. Therefore, a great challenge in the psychological and neuroscientific sciences is to understand the changes that occur in healthy aging.

Healthy aging has been found to be associated with declines in certain aspects of cognitive functioning. These declines in healthy aging have been reported in many cognitive functions, such as episodic memory (Park et al., 2002), working memory (WM; Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005) and executive functioning (Kramer, Hahn, & Gopher, 1999), although this is not true for other cognitive functions such as vocabulary (Park et al., 2002). Although memory has been found to decline in healthy aging, this is not true for all types of memory processes. For example, Park and colleagues (2002) observed a steady linear decline in visuospatial and verbal WM as well as on speed of processing measures, visuospatial and verbal episodic memory and visuospatial and verbal STM. Nyberg and colleagues (2003) also found episodic memory to linearly decline with age, with episodic recall being more sensitive to the aging process than episodic recognition. However, Nyberg and colleagues also found that semantic memory does not follow a linear decline in healthy aging. Specifically, semantic memory improved from young adulthood-middle age (35-50 years) to middle age-old adulthood (55-65 years), while the oldest age group (70-80 years) did not differ from the young adult-middle age group in semantic memory performance.

Working memory (WM) is one of the memory processes that has been found to decline in healthy aging. WM is the ability to hold and manipulate information in mind over a short period of time (Baddeley, 2010). Declines in WM have profound implications for healthy aging given its centrality in other cognitive processes such as problem solving, language, fluid intelligence and reasoning (Engle, Laughlin, Tuholski, & Conway, 1999), arithmetic (Bull, 2009) and episodic memory (Cabeza, Dolcos, Graham, & Nyberg, 2002). WM has been argued to comprise a system of coordinated component parts. The multi-

component model (Baddeley, 2000; Baddeley & Hitch, 1974) of WM posits that WM consists of a central executive that is served by subsidiary slave systems: the phonological loop, the visuospatial sketchpad and the episodic buffer. The phonological loop is responsible for the storage of verbal information, the visuospatial sketchpad is responsible for the storage of visual and spatial information, and the episodic buffer is responsible for binding the contents of WM into episodes. According to this model, the central executive is responsible for inhibitory control of the contents of WM by attending to relevant stimuli in WM and inhibiting the disruptive effect of irrelevant stimuli (Baddeley, 1996).

Previous research has found evidence that reduced WM in healthy aging is associated with changes at the neural level. Nagel and colleagues (2009) found a group of young (20-30 years) and old (60-70 years) adults to differ in both behavioural performance and brain activity during a spatial delayed match to sample WM task. In this task participants were asked to memorise the locations of either one, three or seven dots and when presented with a probe stimulus had to decide whether it matched the location of any of the memorised dots. The difference in the number of dots to be remembered was considered a manipulation of WM load, with a greater number of dots creating greater WM load. The results showed that old adults were less accurate and slower than young adults, and they were more susceptible to increases in WM load than young adults, which was observable in their accuracy and RT. At the neural level, however, old adults showed greater increases in activation in the right inferior frontal gyrus from low to high load conditions compared to young adults, whereas young adults showed greater increases in activation in posterior parietal regions from low to high load conditions compared to old adults. Interestingly, however, when age groups were analysed separately and according to whether they were classed as high or low performers on the WM task (based on their performance at medium and high WM loads), the results showed a different pattern: young high performing adults showed modulation of brain activity with increasing levels of WM load in bilateral prefrontal, premotor and posterior parietal areas, whereas old low performers showed declines in activity with increasing WM load in these same ROIs. This suggests that age-related declines in WM may be driven by changes at the neural level.

The present thesis aims to further our understanding on the neural correlates of changes in WM processes in healthy aging, with the aim of contributing to the literature on cognitive theories of aging.

1. Working Memory and the Aging Brain

Cognitive theories of aging aim to explain the cognitive deficits that occur in healthy aging, in the absence of pathology. These theories take behavioural, neural and biological evidence of changes in healthy aging in order to create complete, coherent accounts of cognitive decline in the aging brain. The

present thesis focuses on understanding changes in WM in healthy aging, and the subprocesses that predict WM capacity. Cognitive theories of aging posit that declines in WM capacity in healthy aging are due to functional and structural changes in the brain, albeit for different reasons depending on the theory in question. The speed of processing theory of cognitive aging posits that as we get older our processing speed decreases, which leads to declines in other cognitive functions such as WM (Salthouse, 1994; 1996; 2000). Park et al. (2002) found speed of processing to mediate age-related variance on WM tasks, and to also be strongly related to long-term memory ability. The processing speed account of cognitive aging suggests that a single mechanism commonly causes declines on a range of cognitive functions, and this mechanism may be reduced integrity of neural structures (Park et al., 2002), such as white matter (Rabbitt et al., 2007; Turken et al., 2008), which slows neural computations and communication.

Reduced WM capacity in healthy aging has also been argued to be caused by reduced efficiency of neural structures that support WM, which is subsequently compensated for by increases in neural activity in the same regions or in additional regions. In some cases, old adults produce greater neural activity than younger adults to achieve a similar level of performance. This pattern of results supports the compensation-related utilisation of neural circuits hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008), which posits that old adults recruit more neural resources at lower levels of cognitive load compared to young adults to compensate for less efficient neural processing. Interestingly, at high levels of cognitive load old adults do not show greater neural activity than young adults as this compensation is no longer effective. This has been demonstrated by Schneider-Garces and colleagues (2010) using a Sternberg item recognition task with various levels of WM load, in which participants had to hold either two, three, four, five or six items in WM. These authors found young adults (18-27 years) to increase activation in frontal, parietal and occipital brain areas from medium to large set sizes. Old adults (65-80 years) peaked in terms of WM capacity at the behavioural level at medium set sizes, and they also showed increased brain activity in frontal, parietal and occipital areas from small to medium set sizes, and much lesser increases in brain activation from medium to large set sizes. This suggests that brain activity in both young and old adults increased up to where their respective memory capacity reached, although this limit in WM capacity was different for both age groups, being smaller for old adults. This pattern of results suggests that older adults were unable to recruit frontal, parietal and occipital regions at higher levels of WM load due to less efficient processing.

The Scaffolding Theory of Aging and Cognition (STAC; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) also predicts compensatory changes in the aging brain to overcome structural

"challenges", such as brain shrinkage, reduced white matter integrity, cortical thinning, dopamine changes in white matter integrity, and functional "challenges", such as dedifferentiation of the recruitment of visual brain areas during cognitive tasks, reduced medial temporal recruitment in memory processes and increased activity of the default mode network during the execution of cognitive tasks. The STAC predicts that these neural challenges are overcome by the recruitment of supplementary neural circuitry to support cognitive functioning. Evidence supporting this is provided by Vallesi and colleagues (2011), who had young (20-34 years) and old adults (60-80 years) complete a simple and complex Go/No-Go task. The simple Go/No-Go task required participants to inhibit responses based on a simple rule (i.e. whether the stimulus is a specific colour and letter) while the complex task required the inhibition of responses based on a more complex rule (i.e. whether the stimulus is a specific colour and either a vowel or consonant). The complex task was more cognitively taxing than the simple task, as demonstrated by longer RTs. Furthermore, old adults recruited additional regions in the prefrontal cortex in the simple task compared to young adults, suggesting the adaptive recruitment of additional brain areas in conditions of low cognitive demand, and that this extra recruitment of brain areas was not possible in conditions of high cognitive demand as it was no longer beneficial.

As described before, the concept of the central executive in WM is also pertinent to cognitive aging, as the inhibitory deficit hypothesis posits that healthy aging is characterised by a decline in the ability to filter out irrelevant information and select relevant information, which has a detrimental effect on cognitive functions such as WM (Hasher & Zacks, 1988). Evidence of reduced inhibitory control in healthy aging has been found at the behavioural and the neural level. West (2004) found old adults (average age of 72 years) to show larger Stroop effects in their response accuracy and RT compared to young adults (average age of 21 years), and these Stroop effects were exaggerated further still in old adults with increasing task demands. Task demands were manipulated by cueing the relevant dimension of the stimulus before each trial, or just once at the beginning of each block, with trial-by-trial cueing placing greater demands on attentional control than block-by-block cueing. As performance in old adults was modulated by both congruency and task demands it is unlikely that worse task performance in old adults was due to general age-related slowing, but rather due to age-related declines in subprocesses that support inhibitory control such as context processing and conflict detection. This was supported by electroencephalogram (EEG) data that showed event-related potential (ERP) components previously associated with encoding and maintenance of task context (i.e. P3 and cue slow wave) and conflict processing (i.e. N450, sustained potential and event-related negativity) to be modulated in different ways in young and old adults in the Stroop task. Given that old adults also performed the task worse than

young adults, this suggests that healthy aging may be characterised by reduced efficiency of the neural mechanisms that support inhibitory control.

There is also evidence that reduced ability to inhibit processing of irrelevant material in old age is related to reduced WM ability. Gazzaley and colleagues (2005) had participants complete a WM task in which they had to either encode or ignore face and scene stimuli depending on their relevance to the task. Young adults (19-30 years) were significantly more accurate in the task compared to old adults (60-77 years). At the neural level, when participants encoded faces there was enhanced activity in a brain area associated with processing faces (fusiform face area; FFA) compared to a baseline condition in which participants passively viewed face stimuli. This was also the case when participants encoded scene stimuli, which results in enhanced activity in a brain area associated with processing scenery (parahippocampal place area; PPA) compared to a baseline condition in which scenes were passively viewed. Interestingly, when participants had to ignore irrelevant face stimuli, young adults showed decreased activity in the FFA compared to the passive baseline condition, suggesting that they successfully suppressed neural activity associated with processing face stimuli. Young adults also showed suppression of activity in the PPA when scene stimuli had to be ignored compared to the respective baseline condition. Although old adults were able to enhance activity in the FFA when face stimuli were relevant and were likewise able to enhance activity in the PPA when scene stimuli were relevant, they were unable to suppress activity in these areas when face and scene stimuli were irrelevant. Furthermore, the ability to suppress brain activity associated with irrelevant stimuli was correlated with accuracy in the WM task, suggesting that a reduced ability to inhibit the processing of irrelevant information may underlie reduced WM ability in old age.

In addition to the inhibitory deficit hypothesis, the frontal aging hypothesis (West, 1996) also posits reduced inhibitory control in aging but that this decline is due to reduced efficiency of frontal brain structures that support inhibitory control. Unlike the speed of processing account of cognitive aging, which posits that reduced efficiency occurs similarly over the whole brain at the same rate (Zanto & Gazzaley, 2019), the frontal aging hypothesis (West, 1996) posits that reduced efficiency in the frontal cortex occurs before reductions in efficiency in other regions in the brain in healthy aging, and that reduced cognitive functioning in healthy aging is due to reduced efficiency of frontal cortex structures. Zhu and colleagues (2010) present findings that support the frontal aging hypothesis in a study in which they found age differences in flanker interference effects at the behavioural and neural level. Old adults (average age of 74 years) were generally slower than young adults (average age of 20 years) in the task.

Further, the difference in RT between incongruent and congruent conditions was greater in old compared to young adults, suggesting that age differences were not due to a general age-related slowing of processing speed. Additionally, old adults showed similar neural activity to young adults in areas previously associated with flanker interference (i.e. inferior frontal gyrus and middle frontal gyrus), although to a lesser extent. This suggests older adults showed reduced efficiency in frontal brain structures that support inhibitory control. This evidence also supports the inhibitory deficit hypothesis of cognitive aging.

Cognitive theories of aging are not mutually exclusive, and the inhibitory deficit and frontal aging hypotheses of cognitive aging are not inconsistent with other accounts of aging that imply increased activity as a compensation mechanism, as they do not necessarily imply reduced activity in healthy aging (Schneider-Garces et al., 2010). Different accounts of cognitive aging are often complementary as they intend to provide a global account of brain functionality in healthy aging (Zanto & Gazzaley, 2019). For example, it may be the case that compensatory neural mechanisms are employed in old adults due to a decreased ability to inhibit the disruption caused by irrelevant contents of WM.

One such effect caused by irrelevant information in WM is proactive interference (PI), which is the disruptive effect of no longer relevant information on current processing in WM (Jonides & Nee, 2006).

2. Proactive Interference as a Means of Studying Cognitive Aging

PI can be separated into item-nonspecific and item-specific PI. Item-nonspecific PI is the disruptive effect of a build-up of no longer relevant material in WM rather than the disproportionately disruptive effect of a single item and can be typically seen to increase throughout WM tasks (Postle & Brush, 2004). On the other hand, item-specific PI is caused by a specific item that was recently relevant and is currently irrelevant to task demands.

Although resistance to PI in WM has been suggested to be an inhibition-related function, it has been found to be distinct from other types of inhibitory control such as resistance to distractor interference and response inhibition (Friedman & Miyake, 2004). Furthermore, there is evidence to suggest that PI is the result of a conflict between item familiarity and context recollection (Oberauer, 2005). According to this account, resistance to PI involves resolving this conflict by inhibiting the high familiarity of the stimulus producing PI or by retrieving the context in which it was seen or heard rather than solely inhibiting representations in WM that are no longer relevant. Therefore, as the resolution of PI in WM has been argued to involve some level of executive control, it can be argued that studying how

PI effects change in healthy aging will provide a vehicle that will allow us to understand how cognitive control is affected by healthy aging at both the behavioural and neural level, and what are the compensatory neural mechanisms that the aging brain employs to overcome declines in cognitive control.

The Recent Probes task is commonly used to study the effects of item-specific PI in WM (e.g., Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998). In this task, participants must memorise an array of stimuli (the target set), and a few seconds later when shown an individual stimulus (the probe stimulus), they must decide whether it was present in the target set or not. The trials producing PI have a probe stimulus that was absent in the target set of the current trial but present in the previous trial's target set. PI effects in the Recent Probes task are generally observed in young adults as longer reaction times (RTs) on high-PI compared to low-PI trials (D'Esposito, Postle, Jonides, & Smith, 1999), although studies have reported PI effects in both RTs and response accuracy (Badre & Wagner, 2005; Jonides et al., 1998; Loosli, Rahm, Unterrainer, Weiller, & Kaller, 2014; Loosli et al., 2016; Mecklinger, Weber, Gunter, & Engle, 2003; Nee, Jonides, & Berman, 2007; Nelson, Reuter-lorenz, Sylvester, Jonides, & Smith, 2003).

These behavioural effects of PI have been found to be modulated by healthy aging. In a pair of complementary studies using the Recent Probes task. Jonides and colleagues (1998; 2000) found old adults to be more affected by PI than young adults in terms of behavioural performance, which was measured as a z-score variable that combined accuracy and RT. However, Loosli and colleagues (2014; 2016) only found greater PI effects in old adults compared to young adults in accuracy in a Recent Probes task. Contrarily, Yi and Friedman (2014) found greater PI effects in RT in old than young adults in a modified Sternberg task. In this task, participants are presented with an array of stimuli to memorise and are subsequently presented with a visual cue that indicates which stimuli in the array are now irrelevant to the task. Immediately after, participants are presented with a probe stimulus. The probe stimuli that produce the higher PI match a stimulus in the memorised array that was subsequently signalled as irrelevant. In sum, age differences in PI effects at the behavioural level are inconsistent between studies, which might be due to methodological differences.

3. Proactive Interference and Brain Activity

3.1 EEG evidence

PI effects in the Recent Probes task have also been observed at the electrophysiological level using EEG. Zhang and colleagues (2010) combined the Recent Probes task with event-related potentials

(ERPs) - the average EEG signal time-locked to the presentation of the probe stimulus - in a study on young adults and found a Late Positive Component (LPC) to have greater amplitude in low-PI compared to high-PI trials at central and centro-parietal electrodes between 400-600 ms after probe stimulus presentation. Zhang and colleagues argue that the PI effect observed on LPC amplitude was evidence of the competition between familiarity and contextual information processing during high-PI trials, as previous research has shown the LPC to differentiate correctly recognised items and correctly rejected new items in a short-term memory task (Danker et al., 2008).

Effects of PI on ERP data have also been found to be modulated by healthy aging. Tays and colleagues (2008) found PI effects in response accuracy and RTs in both young (18-26 years) and old (65-87 years) adults, and observed PI effects on a Medial Frontal Negativity (MFN) component that occurred between 400-500 ms after probe stimulus presentation. However, MFN amplitude was greater in high-PI trials compared to low-PI trials in young adults, while no such effect was observed in old adults. The authors suggest that the MFN indicates the extent to which cognitive control functions are recruited in order to overcome interference or conflict. Therefore, Tays and colleagues' interpretation of the MFN suggests that young adults recruit cognitive resources in a selective way when responding to either high- or low-PI trials, whereas old adults recruit resources in an unselective way. It is noteworthy that Tays and colleagues (2008) did not find LPC to be modulated by PI in young adults, which was the case in Zhang and colleagues' (2010) aforementioned study. This may be due to methodological differences as Tays and colleagues used a higher percentage of PI-inducing trials, which may have increased the likelihood that participants were aware of the PI manipulation. Therefore, ERP PI effects in Recent Probes tasks that have an equal amount of high- and low-PI trials have only been observed in young adults, which means the temporal evolution of such PI effects in old adults in the Recent Probes task remains relatively unclear.

Nevertheless, age differences in PI effects in ERP activity have been observed in a study using a different paradigm to manipulate PI. For instance, Yi and Friedman (2014) also found differences in PI effects between young (20-28 years) and old adults (60-82 years) using the aforementioned modified Sternberg task. The authors found the difference in RTs between high- and low-PI trials (i.e. PI cost) to be greater in old than young adults. Furthermore, young adults elicited a positive component at fronto-central electrodes between 300-500 ms post probe stimulus presentation, while in old adults a similar component was observed between 600-800 ms post probe stimulus presentation, suggesting that old adults showed reduced speed of processing. However, as Yi and Friedman (2014) did not find neural

effects to be correlated with behaviour, it was not possible to determine to what extent reduced speed of processing in old adults at the neural level contributes to the greater PI costs observed in old adults at the behavioural level. Nevertheless, the authors found the positive component to present higher amplitude for low- compared to high-PI trials in both age groups. This positive component has similar characteristics to the LPC found by Zhang and colleagues (2010) in young adults using the Recent Probes task.

Consequently, based on ERP studies on the effects of PI in healthy aging it is unclear whether age-related changes in PI resolution reflect reduced efficiency of the neural mechanisms underlying cognitive control or reduced speed of processing. Tays and colleagues (2008) findings suggest a reduced efficiency in processing at the neural level as old adults failed to show the modulation of amplitude of the MFN, whereas Yi and Friedman's (2014) results suggest reduced speed of processing in healthy aging as shown by the modulation of amplitude of a late positive component occurring roughly 300 ms later in old adults compared to young adults. Furthermore, from these studies the neural mechanisms that old adults employ to compensate for declines in cognitive control are still unclear.

However, studying ERPs only offer information about how cognitive processes occur across space (i.e. the scalp) and time. EEG data also possesses other dimensions such as frequency (i.e., number of cycles of a neuronal oscillation per second), and the study of which can offer further insight into the electrophysiological correlates of cognitive functions. Nonetheless, PI effects in EEG data in the time-frequency domain remain unknown. The rhythmic activity measured in a given area of the brain can occur simultaneously at different frequency bands and previous research has found rhythmic activity in the theta frequency band (4-8 Hz) to be related to inhibitory control. For instance, in a study by Nigbur et al. (2011), participants completed three tasks that required different types of cognitive control: resistance to perceptual interference (Flanker task), response inhibition (Go/No-Go task) and conflict resolution (Simon task). In each of these tasks, participants responded slower in trials that required high cognitive control, and these same trials were also characterised by increases in theta power (i.e., the squared amplitude of the oscillation), with the Go/No-Go task producing the largest effects in the theta power. Furthermore, greater theta activity at frontal midline electrodes has also been found in conditions of high conflict compared to low conflict in a Stroop task (Hanslmayr et al., 2008). Previous research has also found theta activity to be related to executive control in WM. For example, Griesmayr and colleagues (2010) found that when participants had to retain and manipulate information in WM, compared to when they only had to retain information in WM, they showed greater theta power at frontal

and central electrodes. Additionally, increases in theta power at frontal midline electrodes have been found with increases in WM load in an *n*-back task (Gevins, Smith, McEvoy, & Yu, 1997).

Further research is needed to understand whether PI effects in WM are associated with frontal midline theta power given that this activity has been found in tasks requiring inhibitory control. As previous research has found inhibitory control to be related to EEG activity in the theta frequency band (4-8 Hz), it may be that PI effects are also detectable at this frequency. Furthermore, the putative relationship between inhibitory control and frontal midline theta power suggests that studying theta power in EEG signals recorded during PI resolution would offer insight into the underlying neuronal mechanisms that support executive control in WM.

In addition, there is currently no research on how time-frequency EEG data related to PI is altered in healthy aging, although there is previous research showing how differences in WM ability are expressed in EEG time-frequency data. One such piece of evidence is provided by Dong and colleagues (2015), who divided participants into groups of high and low WM capacity according to performance on a digit span task, and then had them carry out an n-back task that had conditions of low (1-back) and high (4-back) cognitive load. As expected, low WM participants were generally slower than high WM participants in the n-back task. They also showed reduced frontal theta synchronisation in both conditions of low and high load, suggesting that participants with lower WM capacity are less able to recruit midline frontal theta activity during WM processing. As old adults have been found to have reduced WM capacity compared to young adults, it may be the case that they also show reduced frontal midline theta when processing in WM. Furthermore, as frontal midline theta activity has been associated with inhibitory control, analysing time-frequency EEG data during a PI task will allow us to better understand the neural mechanisms underlying cognitive control and how they are altered in healthy aging.

3.2 Functional Magnetic Resonance Imaging Evidence

PI effects have also been observed at the neural level using functional magnetic resonance imaging (fMRI). Neuroimaging studies have consistently observed the left inferior frontal gyrus (IFG) and left ventrolateral prefrontal cortex (VLPFC) to show greater activation during the retrieval phase of high-PI trials compared to low-PI trials in the Recent Probes task (e.g., Badre and Wagner, 2005; Nee et al., 2007). It has been suggested that the left IFG aids the resolution of PI by selecting among competing responses (Jonides & Nee, 2006). However, Nee and co-workers (2007) found the left IFG to distinguish between recent and non-recent positive trials in this paradigm, neither of which involve conflict among competing responses. These authors therefore argue that the left IFG supports the selection of contextual

features during memory retrieval. Other studies have also reported sensitivity to PI effects in other frontal and parietal regions such as the right frontopolar cortex, right VLPFC (Badre & Wagner, 2005), right middle frontal gyrus (MFG), right anterior intraparietal sulcus, right precuneus (Mecklinger et al., 2003), insula, left frontal superior medial gyrus (SMG) and left pre-supplementary motor area (pre-SMA; Loosli et al., 2016).

Age differences in PI effects have been found in other neuroimaging studies. Previous work has found PI effects in the left IFG in old adults, although to a lesser extent than in young adults (Jonides et al., 2000; Loosli et al., 2016). Loosli and colleagues (2016) found evidence of decreased PI effects in healthy aging in other brain areas, with old adults (66-74 years) showing smaller differences between high- and low-PI conditions in the right IFG, left insula, and left frontal SMG when compared to young adults (19-28 years). No other studies have found age differences in PI effects in these brain areas. Additionally, Loosli and co-workers (2016) pair-wise matched young and old adults according to WM ability in order to separate differences in brain activity related to reduced WM capacity from differences in brain activity related to healthy aging. These authors found that when young and old adults were matched on WM ability, the latter still showed greater PI effects than young adults at the behavioural level, but reduced PI effects at the neural level. These studies on the functional organisation of brain areas that support resolution of PI suggest that reduced modulation of haemodynamic activity occurs in healthy aging principally in the left IFG and also in other cortical areas. This suggests reduced efficiency of the brain regions that support cognitive control in healthy aging, and also that this reduced efficiency was not due to age differences in WM capacity.

However, the Recent Probes task employed in Loosli and colleagues' (2016) study may have created high item non-specific PI throughout the task due to the relatively small pool of stimuli used. In the Recent Probes task, probe stimuli that create relatively high-PI (termed *recent negative* probes) do not match any memorised item on the current trial but do match a memorised item from the previous trial. Performance on recent negative (RN) trials is compared with that of trials that produce relatively low-PI (termed *non-recent negative* probes), which contain probe stimuli that do not match a memorised item on the current trial nor any memorised item from the previous trial. In the Recent Probes task employed in Loosli and colleagues' study (2016), the array of items that participants had to memorise in each trial consisted of four black and white line drawings. Furthermore, the total stimulus pool for the task consisted of only 12 unique line drawings, meaning that the stimuli had to be re-presented with high frequency across trials. It can be argued that studies that have a small stimulus pool inadvertently create

high item non-specific PI across all trials due to the high frequency with which they repeat the presentation of stimuli across trials. It can be further argued that in such studies low-PI trials also create a nonnegligible degree of PI because the size of the stimulus pool only permits the stimulus matching the probe of a low-PI trial to be presented a few trials back, or in some cases only two trials back. Therefore, as participants in Loosli and colleagues' work were matched based on their performance in low-PI trials, it may be the case that they were matched based on WM ability as well as the ability to overcome item non-specific PI. Therefore, further research is needed to fully understand how PI effects change in healthy aging and how these changes are influenced by WM ability.

This limitation also applies to other studies that investigate PI in healthy aging, which employ the Recent Probes task. Experimental studies that use letters as stimuli in the Recent Probes task necessarily have a small pool of stimuli to use in order to create the PI manipulations (e.g. D'Esposito et al., 1999; Jonides et al., 2000; Nee et al., 2007). Therefore, in order to confirm that the reduced neural efficiency of brain areas supporting cognitive control in old age groups observed in previous studies was not due to a general build-up of item non-specific PI, we argue that further research is needed in which a healthy aging sample complete a Recent Probes task based on a larger pool of stimuli.

In summary, evidence from ERP studies suggest that PI resolution in healthy aging is characterised by reduced neural efficiency and speed of processing, although further research is needed to separate potentially overlapping ERP components into latent variables associated with inhibitory control and how they are affected by the aging process. The electrophysiological correlates of age-related changes in PI resolution in the time-frequency domain remain unknown, although due to the putative relationship between inhibitory control and frontal midline theta power, studying PI effects in EEG oscillatory activity will increase our understanding of how the neuronal mechanisms supporting cognitive control are altered in healthy aging. Furthermore, evidence from fMRI studies suggest that age-related changes in overcoming PI are associated with reduced efficiency of frontal brain areas, and that these changes are not driven by declines in WM capacity. However, further research is needed to discount the possibility that this observed reduced efficiency in brain areas supporting cognitive control is due to age-differences in the ability to overcome item non-specific PI.

4. Objectives, Hypotheses and Overview of the Literature

The objective of the present thesis is to advance knowledge on how PI effects change in healthy aging at the behavioural, electrophysiological and neural level in order to contribute to theories of cognitive aging. In order to do so we analysed PI effects in both EEG and fMRI data in young and old

adults during the Recent Probes task. We argue that combining electrophysiological and neuroimaging data will enhance our knowledge on cognitive aging by providing a global view of the time course and spatial organisation of age-related changes in brain activity supporting cognitive control. By doing so we will also achieve a broad and in-depth view of the changes in the efficiency of brain regions due to the aging process, and the neural mechanisms recruited to compensate for these declines. Additionally, we aimed to disentangle the role of age-related changes in WM capacity from the effects of healthy aging on PI resolution. Three parallel analyses were carried out to achieve this objective; each of them employed the same Recent Probes task based on a large pool of stimuli on a group of young and old healthy adults.

Chapter II aims to introduce and describe the methodology employed throughout this thesis in order to answer the research questions and test the hypotheses. The characteristics of the sample of participants is described and how they differ between studies presented in the various chapters. Chapter II also explains the experimental materials and tasks used throughout this thesis and the data analyses and inferential statistics employed.

Chapter III aims to characterise PI effects in a group of young and old healthy adults in EEG data in the time domain. Studying EEG data in the time domain is a valuable way of studying cognitive processes due to its high temporal resolution. This allows us to observe changes in the EEG signal time-locked to cognitive processes that occur over milliseconds. Therefore, the present analysis used temporo-spatial principal component analysis (tsPCA) to study the temporal and spatial characteristics of neural activity associated with PI resolution in the Recent Probes task, and how these characteristics change with age. As there is a lack of studies that have investigated the source of EEG activity related to age differences in PI effects, we subsequently aimed to localise the sources of differences between age groups and PI conditions in the temporo-spatial PCA factors, helping to fill the gap between evidence generated in EEG studies and that stemming from magnetic resonance work. Based on previous research, we expected to observe PI effects in participants' electrophysiological data between 300-800 ms at central electrodes, with greater positivity in conditions of low-PI compared to high-PI. We predicted that young adults would show such increases in amplitude on low-PI compared to high-PI trials, and that this modulatory activity would be reduced in old adults, providing evidence of reduced efficiency of the neural mechanisms supporting cognitive control in WM and supporting previous research that has found old adults to be less able to modulate ERP activity between conditions of PI (Tays et al., 2008).

Chapter IV aims to understand how age-related changes in PI effects are expressed in EEG data in the time-frequency domain. We argue that by studying the oscillatory activity associated with age-

related changes in resistance to PI we will be able to directly observe how oscillatory activity that supports cognitive control in WM changes with age. Furthermore, we aimed to localise the source of oscillatory activity associated with PI. Although the EEG time-frequency correlates of PI are unknown, we hypothesised that conditions of high-PI would be associated with increased theta power at frontal midline electrodes, given the putative relationship between activity in this frequency band and inhibitory control. Furthermore, we argued that this increase in frontal midline theta synchronisation in response to PI would be altered in old adults, reflecting reduced efficiency of the neuronal mechanism supporting cognitive control in WM.

Chapter V aims to further understanding of the functional organisation of PI effects and how it changes in healthy aging, by using fMRI. Chapter V will therefore shed light on the functional organisation of haemodynamic activity related to PI resolution, and how it is altered in healthy aging. To achieve this, we conducted an fMRI study while participants performed a Recent Probes task. This analysis also aimed to build on Loosli and colleagues' (2016) findings in order to understand how age-related changes in PI effects are influenced by WM ability. By disentangling WM ability from the effects of aging, we aimed to differentiate brain regions sensitive to age-related changes in PI effects from regions sensitive to WM-related changes in PI effects. Based on previous research (Loosli et al., 2016) we expected old adults to show reduced PI effects in brain activity in frontal brain areas (i.e. bilateral IFG, left frontal SMG) and the left insula, thereby reflecting reduced neural efficiency in the brain areas supporting cognitive control of the contents of WM.

As all three studies were based on different electrophysiological and neuroimaging measures acquired during the completion of the same Recent Probes task, in all three analyses we expected that effects of PI would be found in both young and old adults' accuracy and RTs, but that PI effects would be larger in old compared to young adults, providing support for the inhibitory deficit hypothesis of healthy aging.

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Chapter II

General Methods

1. Overview of the Methods

Changes in cognitive functions due to healthy aging presumably occur on many levels (Cabeza et al., 2018), some of which may be the timing of neural responses that support cognitive functions, the recruitment of rhythmic oscillatory neural activity that supports cognitive functions and the functional organisation of neural responses that support cognitive function. Therefore, in an effort to achieve the most complete picture possible of the changes in the brain that occur due to cognitive aging, the present thesis combined electrophysiological and neuroimaging techniques to measure these changes.

It can be argued that the complementary use of EEG and fMRI techniques can provide a global view of the neural basis of the inhibitory control involved in overcoming PI in WM, and therefore how the neural mechanisms underlying inhibitory control are disrupted in healthy aging. The high spatial resolution of the fMRI technique plus the high temporal resolution of the EEG technique allows the observation of the spatial distribution of brain regions recruited to exert cognitive control when resolving PI as well as the time course of the neural processes recruited to employ this cognitive control.

EEG data reflects the electrical activity measured at the scalp that results from local field potentials in the cortex. These local field potentials are created by summated dipoles in extracellular space in the cortex as a result of the synchronous occurrence of post-synaptic potentials of pyramidal cells (Luck, 2005). Therefore, the analysis of EEG data allows us to study the synchronous activity of populations of neurons occurring over milliseconds that support a given cognitive process. One technique of analysing EEG data is by using ERPs. As previously mentioned, ERPs are the averaged EEG signals time-locked to a physical or mental event such as the presentation of a stimulus or a motor response. ERP signals contain various positive and negative peaks (or components), each of which reflect a specific part of the neural response to an event. Therefore, analysing how each ERP component covaries with the demands of an experimental task offers us a way of observing how neural activity associated with a cognitive process behaves in time and space in relation to an experimental manipulation. By studying ERPs related to PI effects in WM in healthy aging, we will have the opportunity to observe how the spatial distribution and the time course of neuronal activity that supports executive control in WM is altered by cognitive aging.

Several studies have used the ERP technique to investigate PI, but some limitations have been discussed. Due to volume conduction through the different organic materials in the human head, the electrical signal detected at the scalp may come from many neuronal generators and produce overlapping ERP components that are difficult to distinguish. Furthermore, the dipolar nature of neuronal generators

of the EEG signal mean that negative and positive signal detected at opposite parts of the scalp might be mistaken for separate ERP components rather than signal arising from opposite ends of the same dipole. One technique that overcomes the problem of overlapping components is principal component analysis (PCA). PCA is a factor analytic procedure that extracts linear combinations of latent variables using eigenvalue decomposition (Dien & Frishkoff, 2005). PCA is a data-driven approach to extracting variance in the EEG signal in a precise, unbiased and parsimonious way by offering solutions to separate variance in ERPs that may be otherwise confounded when identifying ERP components with the naked eye (Dien, 2010). Therefore, it can be argued that applying PCA to EEG data recorded during the resolution of PI to extract latent variables associated with inhibitory control would enhance our knowledge on the neural mechanisms supporting cognitive control and how they are affected by healthy aging.

In addition to studying EEG data in the time domain (such as applying PCA to ERPs), it can be argued that studying EEG data in the time-frequency domain offers additional insights into the neural underpinnings of cognitive functions. Time-frequency analysis of EEG data allows the observation of neural oscillations in EEG data, which reflect the rhythmic activity of the synchronous firing in large populations of neurons. Oscillatory EEG activity can be measured along various dimensions, such as time, frequency, phase and power. As already briefly mentioned, frequency refers to the number of cycles that an oscillation achieves in a second and is measured in the units of hertz (Hz), whereas phase is measured in radians or degrees and refers to the point along the sine wave at a given moment. Power is the square amplitude of an oscillation and reflects the amount of energy in a frequency band.

Analysing EEG data in the time-frequency domain can reveal the behaviour of neurons that underlie a cognitive process, given that oscillatory activity detected at the scalp is a direct reflection of the neural oscillations occurring in the brain (Cohen, 2014). This is important given that neuronal oscillations have been argued to be a fundamental neural mechanism that supports the integration of brain functions that occur in distant areas of the brain and on different time scales (Varela, Lachaux, Rodriguez, & Martinerie, 2001). Furthermore, analysing EEG data in the time-frequency domain can reveal variance that would be irretrievable using analysis techniques in the time domain alone, such as when analysing ERPs. It can therefore be argued that by studying EEG data in the time-frequency domain as well as the time-domain, we will increase our understanding of the rhythmic activity of the neural mechanisms that support executive control in WM, and how this activity is affected by healthy aging.

In addition to electrophysiological methods such as EEG, it can be argued that neuroimaging methods such as fMRI can offer insights into the functional organisation of PI resolution in WM and how

it changes in old age. fMRI is a neuroimaging technique that can be exploited to measure haemodynamic activity in the brain associated with cognitive processes. This is done via measurement of the blood oxygenation level-dependent (BOLD) effect, which reflects changes in blood flow, blood volume and oxygenation in the brain. In contrast to electrophysiological methods such as EEG, the BOLD effect is an indirect measure of neural activity in the brain, which is caused by changes in energy consumption and blood flow in areas of the brain due to changes in local neural activity (see Soares et al., 2016). However, due to its exceptionally high spatial resolution, fMRI allows the study of how haemodynamic changes correlate with a cognitive process, and how this is functionally organised in the brain with high spatial precision. Therefore, in addition to exploiting electrophysiological methods, by taking advantage of fMRI analyses we can understand the functional organisation of brain regions that are recruited to exact cognitive control when confronted with PI, and how this functional organisation changes in healthy aging.

The analyses presented in Chapters III, IV and V were conducted in parallel, and therefore share many commonalities which are outlined here. Specific methodological details to each analysis are described in their corresponding chapter.

2. Participants

Chapters III and IV recruited the same pool of participants, although identical samples were not included in both analyses. This is because differences between the EEG analyses meant that some participants met exclusion criteria in one of the analyses and not in the other. Chapter V recruited a largely separate pool of participants from Chapters III and IV.

Ninety-six people were originally recruited to participate across the studies reported in Chapters III, IV and V. Participants were included in the analyses if they did not meet the following criteria: a) were currently receiving psychotherapeutic or pharmacological treatment for a psychiatric disorder, or had a history of a psychiatric disorder, and b) had a major medical or neurological disorder. In addition, participants over 50 years of age were excluded if they had a score lower than 2 SDs from the normal score for their age group given their years of education on a screening measure of mild cognitive impairment (see *General Materials* section). Additionally, participants who showed depressive symptoms according to a self-report measure of depression (see *Materials* section) were excluded from the study. In Chapters III and IV, two participants were excluded due to the presence of depressive symptoms. In Chapter V, three participants were excluded due to their score on the screening measure of mild cognitive impairment and one participant was excluded due to the presence of depressive symptoms. Participants included in the analysis presented in Chapter V fulfilled safety criteria regarding magnetic resonance

imaging scanning as specified by the *Serviço Médico de Imagem Computorizada* (SMIC) at the *Casa de Saúde de Boavista*, Portugal.

In the present thesis young participants were recruited in return for course credits or via invitation and old participants were recruited from other projects concerning healthy aging at the University of Minho via invitation. Participants gave full written informed consent and were treated in accordance with the Code of Ethics of the World Medical Association (as stated by the Declaration of Helsinki) regarding experimentation on humans.

3. Cognitive and Psycho-emotional Assessment

The *Montreal Cognitive Assessment* (MoCA (Nasreddine et al., 2005); Portuguese version: (Freitas, Simões, Alves, & Santana, 2011); Spanish version: (Pereiro et al., 2017)) screened participants for mild cognitive impairment (MCI). The MoCA is a brief test that assesses short-term memory, visuo-spatial abilities, executive functions, attention, concentration, working memory, language and orientation to time and place. The maximum score of the MoCA is 30, and participants were excluded if their score exceeded 2 SDs of the normative score given their age and education level.

The *Beck Depression Inventory-II* (BDI-II (Beck, Steer & Brown, 1996); Portuguese version: (Campos & Gonçalves, 2011); Spanish version: (Sanz, Perdigón, & Vázquez, 2003)) measured depression symptoms in young adults. The BDI-II is a self-report questionnaire that consists of 21 multiple choice items that measure depression symptomatology (e.g., "I feel unhappy", "I am somewhat less active than usual"). For each item there are four possible responses (from 0 to 3), and the individual must select the response that best reflects how they have felt during the past two weeks including the present day. The BDI-II cut-off score for young Portuguese participants was 13, while the cut-off score for young Spanish participants was 9.

The *Geriatric Depression Scale* (GDS (Yesavage et al., 1982); Portuguese version: (Pocinho, Farate, Dias, Lee, & Yesavage, 2009); Spanish version: (Fernández-San Martín et al., 2002)) measured depressive symptoms in old adults. The GDS is a self-report questionnaire that consists of 30 questions (e.g., "Do you feel that your life is empty?"), which must each be responded to using a yes/no format. The GDS cut-off score for Portuguese-speaking and Spanish-speaking participants was 10.

A translated version of the *Edinburgh Handedness Inventory* (EDI; Oldfield, 1971) assessed handedness. The EDI is a questionnaire that measures the dominance of the participant's right and left hands in everyday activities. The participant must judge whether they would use their left, right or both

hands to carry out a specific activity (e.g., writing). A score of over .5 indicates right hand dominance, whereas a score less than .5 indicates left hand dominance. The proximity of the total score to either 1 (total right-hand dominance) or 0 (total left-hand dominance) indicates the dominance of handedness.

4. Experimental Task

4. 1. Stimuli

The Recent Probes task was programmed and carried out in PsychoPy (Peirce, 2007). We implemented the Recent Probes task using pictures as stimuli to be memorised in order to promote overall performance in old adults, as previous Recent Probes studies have found old adults to be generally less accurate and slower than young adults when using verbal stimuli. Furthermore, there is evidence to suggest that old adults show equivalent memory performance to young adults when pictures are used as stimuli (see Friedman, 2013, for a review). Additionally, we used pictures of faces and scenes as stimuli as old adults have been found to show good recollection of scene (Gutchess, Ieuji, & Federmeier, 2007) and face (Grady et al., 1995) stimuli in episodic memory tasks. We used both face and scene stimuli to ensure that any advantage was not specific to the type of stimulus. Face stimuli were 48 images of emotionally neutral faces (24 female and 24 male faces) from the Karolinska Directed Emotional Faces (KDEF; Lundvist, Flykt & Öhman, 2004). Scene stimuli were 48 emotionally neutral images of scenes from the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert, 2013).

4. 2. Task

The Recent Probes tasks employed in Chapters III and IV were identical to each other, however it was not so in Chapter V. The only difference between the experimental tasks of Chapters III and IV to that in Chapter V is the duration of the presentation of stimuli, the inter-stimulus intervals, and the inter-trial intervals (ITI). Specific durations of each part of the trial, and the inter-trial interval are explained in their respective chapters, although these differences are presented in Figure 1.

The stimuli in the Recent Probes task were presented on a screen monitor in colour on a black background. Each trial began with the presentation of an array of six images, termed the *target set*. The target set comprised three images of faces and three images of scenes. After a short delay period that consisted of the presentation of a white fixation cross in the centre of the screen, a single stimulus, which was an image of either a face or a scene, was presented in the centre of the screen and termed the *probe*. When participants saw the probe, they had to decide as quickly and as accurately as possible whether it matched any item in the target set of the current trial. Participants responded by pressing a

keyboard button for "yes" and a button for "no" using only their dominant hand. After the probe stimulus disappeared, a white fixation cross was presented in the centre of the screen until the beginning of the following trial.

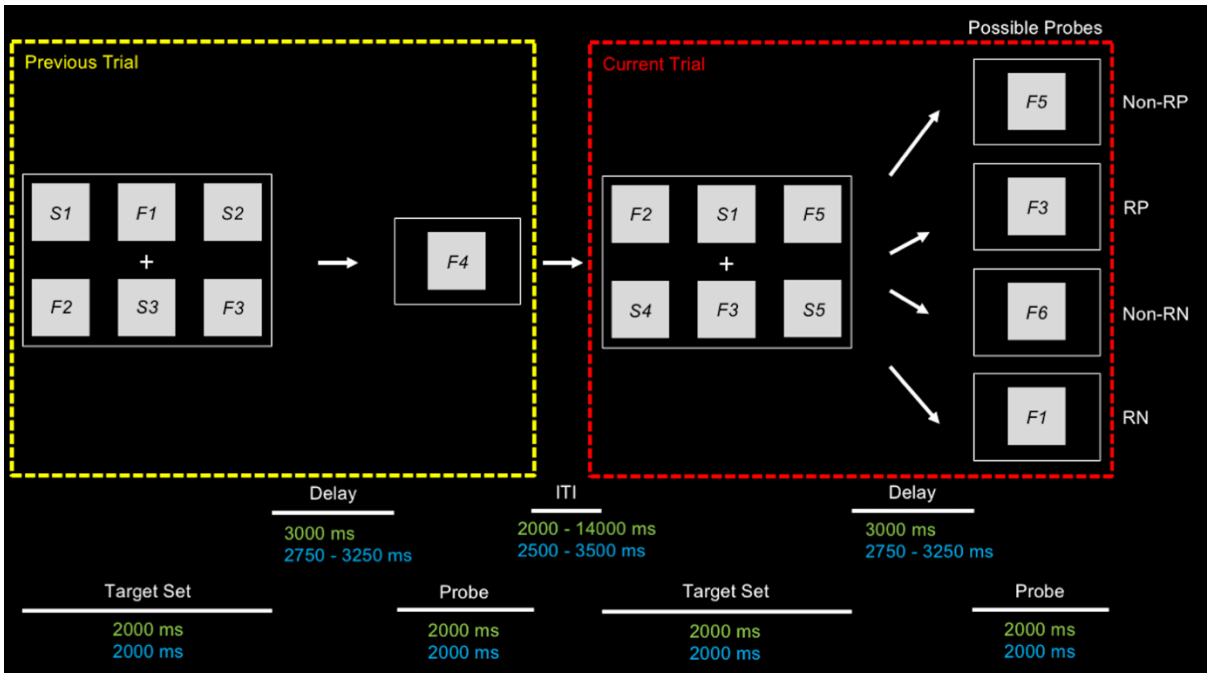


Figure 1. Trial scheme of the Recent Probes task. Durations of trial phases in the fMRI study (presented in Chapter V) are presented in green and durations of trials phases in the EEG studies (presented in Chapters III and IV) are presented in blue. ITI = Inter-trial interval.

The task was completed in two blocks of trials. In one of the blocks the probe was always a face, and participants had to memorise only face stimuli in the target set. In the other block, the probe was always a scene, and participants had to memorise only scene stimuli in the target set. Face and scene stimuli were presented together in the target set to increase the ecological validity of the task: in everyday settings it is likely that when trying to memorise something there are other irrelevant stimuli present. The order of block completion was randomised across participants.

Fifty percent of total trials had a probe that matched a stimulus in the target set of the current trial, and therefore the correct response was “yes” (positive trials). Half of the positive trials had a probe stimulus that also matched a stimulus in the target set of the previous trial (*recent positive* [RP] trials), and the other half of positive trials had a probe stimulus that did not match a stimulus in the target set

of any of the previous 6 trials, but may have appeared further back than 6 trials ago (*non-recent positive* [non-RP] trials). Conversely, fifty percent of total trials had a probe that was not present in the target set of the current trial, and therefore the correct response was "no" (negative trials). The negative trials were implemented in a similar vein to the positive trials. Half of the negative trials had recent negative (RN) probes, which matched a stimulus presented in the previous trial while the other half had non-recent negative (non-RN) probes, which did not match any stimulus in the target sets of the previous 6 trials, but may have been presented more than 6 trials ago. PI is measured as the difference between responses to RN trials and non-RN trials.

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Chapter III

Age differences in the principal temporo-spatial components of EEG activity during a proactive interference task.

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Abstract

Proactive interference (PI) is the disruptive effect of no longer relevant information on current processing. PI effects in EEG data have been previously found to be altered in healthy aging, although it remains unclear the extent to which such changes reflect alterations in inhibitory processes employed to control the content of WM at the neural level and how they are compensated for. To this end, twenty-six young (18-34 years) and sixteen old (53-68 years) healthy adults completed a PI task while EEG data was recorded. Although old adults were generally slower and less accurate than young adults, the effects of PI on reaction time were greater in young adults than old adults. Nevertheless, this was likely due to a general difficulty that old adults had in the task. Temporo-spatial principal component analysis of the EEG data showed PI effects in young and old adults at ~260 ms, although in opposite directions, which may suggest that old and young adults differ in how they recruit neural resources that support the processing of familiarity. Neural PI effects were also observed at ~670 ms although to the same extent in young and old adults, suggesting the preserved recruitment of neural resources that aid retrieval of contextual information. Age differences were also observed in conditions of low-PI at ~1300 ms, which may indicate performance monitoring in old adults in an attempt to compensate for the difficulty they experienced in the task.

1. Introduction

Working memory (WM) has been found to suffer a marked decline in healthy aging (Park et al., 2002). WM is the ability to maintain and manipulate information in the mind over a short period of time (Baddeley, 2010), and supports important cognitive functions such as fluid intelligence and reasoning (Engle, Laughlin, Tuholski, & Conway, 1999), language comprehension (Daneman & Merikle, 1996), and long-term memory (Park et al., 1996).

It may be the case that reduced WM capacity in old age is partly due to reduced inhibitory control. The inhibitory deficit hypothesis predicts that a decline in cognitive functions such as WM in healthy aging is due to a decreased ability to inhibit disruption from goal-irrelevant information (Hasher & Zacks, 1988). One such situation that requires inhibitory control is proactive interference (PI), which has also been found to predict WM capacity (May, Hasher, & Kane, 1999). PI is the disruptive effect of no longer relevant information on current WM processing (Jonides & Nee, 2006). As the resistance to PI has been found to be an inhibition-related function (Friedman & Miyake, 2004), it can be argued that the study of PI in aging may help us understand how inhibitory control of WM contents is altered in healthy aging, what the neural correlates of these alterations are, and how they are compensated for.

PI has been previously researched using the Recent Probes task (e.g. Jonides et al., 2000). In this task, participants must memorise an array of stimuli (the target set), and a few seconds later are shown an individual stimulus (the probe) and must decide whether it was present in the memorised array or not. The probe that produces relatively high PI in the Recent Probes task does not match any stimulus in the target set of the current trial but does match a stimulus in the target set of the previous trial. In other words, the stimulus that causes PI is no longer relevant in the context of the current trial, but it was indeed relevant in the previous trial. These probes that produce PI are called *recent negative* (RN) probes. PI has been suggested to arise from the conflict between the high familiarity caused by a stimulus that induces PI and the recollection of the context in which it was previously encountered (Oberauer, 2005). In the Recent Probes paradigm, RN probes are highly familiar because they were recently presented (i.e. the previous trial), although in order to correctly respond to them the context in which it was encoded must be retrieved. These PI effects in the Recent Probes task are generally observed as longer reaction times (RTs) on RN probes compared to *non-recent negative* (non-RN) probes (D'Esposito, Postle, Jonides, & Smith, 1999), which were not presented in the current trial or the previous trial and therefore produce relatively low PI. Other studies have also reported PI effects in both RTs and response accuracy (Badre

& Wagner, 2005; Jonides et al., 1998; Jonides et al., 2000; Loosli et al., 2014; Loosli et al., 2016; Mecklinger et al., 2003; Nee et al., 2007; Nelson et al., 2003).

PI effects in the Recent Probes task have also been observed at the brain activity level using electroencephalogram (EEG) data. Zhang and colleagues (2010) used the event-related potential (ERP) technique to analyse EEG data recorded during the Recent Probes task in young adults and found a Late Positive Component (LPC) to have greater amplitude in non-RN trials compared to RN trials at central and centro-parietal electrodes between 400-600 ms. Zhang and colleagues argue that the PI effect observed on LPC amplitude was to some extent evidence of the competition between familiarity and the recollection of contextual information during PI, as previous evidence has shown a LPC to differentiate correctly recognised items from correctly rejected items in a short-term memory task (Danker et al., 2008).

Previous research has found evidence of differences in PI effects between young and healthy old adults. For instance, in a pair of complementary studies, Jonides and colleagues (1998; 2000) found old adults to show larger PI effects than young adults when taking into account both accuracy and RT. Age differences in PI effects have also been found in ERP studies. Tays and colleagues (2008), for example, found PI effects to be present in RT in both young and old adults and in response accuracy of old adults. These authors also observed PI effects on a Medial Frontal Negativity (MFN) component that occurred between 400-500 ms whose amplitude was greater on high PI trials compared to low PI trials in young adults, while no such difference in amplitude between PI conditions was observed in old adults. The authors suggest that the MFN indicates the extent to which cognitive control is recruited in order to overcome interference or conflict. Therefore, Tays and colleagues' interpretation of the MFN suggests that young adults recruit cognitive resources in a selective way in response to conditions of high and low cognitive demand, whereas old adults are incapable of such selective recruitment. This pattern of results is consistent with theories of cognitive aging that suggest old adults show less efficient recruitment of neural resources across situations that require different levels of cognitive control (Reuter-Lorenz and Park, 2014; Grady, 2008).

Yi and Friedman (2014) also found differences in PI effects between young and old adults using a modified Sternberg WM task, which is similar to the Recent Probes task. In this task, participants are presented with an array of stimuli to memorise and are subsequently presented with a visual cue that indicates which stimuli in the array are now irrelevant to the task. Immediately after, participants are presented with a probe stimulus. Probe stimuli that produce high PI match a stimulus in the memorised

array that was subsequently signalled as irrelevant. The authors found the difference in RTs between high PI and low PI trials (i.e. PI cost) to be greater in old adults compared to young adults. Furthermore, young adults elicited a positive component at fronto-central electrodes between 300-500 ms, while old adults elicited a similar component, but between 600-800 ms. This suggests that old adults had reduced processing speed compared to young adults, as demonstrated by the increased latency of the ERP component. The processing speed theory of cognitive aging posits that not only does processing speed slow with age, but also that decreased speed of processing hinders cognitive functions such as WM (Salthouse, 1994). However, as Yi and Friedman (2014) did not find neural effects to be correlated with behaviour it was not possible to determine to what extent reduced processing speed in old adults at the neural level contributes to the greater PI effects in old adults at the behavioural level, or whether this delayed component signals that old and young adults differ in the structure of their brain activity and mental processing while completing a PI task. If old adults were eliciting a separate ERP component to the one elicited by young adults in response to high PI trials, it may be the case that they were recruiting neural resources in a different way in order to compensate for their worse behavioural performance compared to young adults. Nevertheless, the authors found the positive component to have higher amplitude for low interference trials compared to high interference trials in both age groups, and the elicited positive component has similar temporal and spatial characteristics to the LPC found by Zhang and colleagues (2010) in young adults using the Recent Probes task.

In sum, ERP studies on the age differences in PI effects at the electrophysiological level indicate a reduced efficiency of neural responses as well as potential reductions of processing speed of neural responses in healthy aging. The different patterns of results found in previous studies may be explained by methodological differences. Tays and colleagues (2008), for instance, used a higher percentage of PI-inducing trials, which may have increased the likelihood that participants were aware of the PI manipulation, whereas Yi and Friedman (2014) used a balanced proportion of PI-evoking trials. However, it can also be argued that it is unclear whether the age differences in ERP waveforms observed by Yi and Friedman (2014) represent increased latency in old adults of the same ERP component evoked in young adults, indicative of reduced speed of processing, or whether a separate ERP component was evoked in each of the two age groups. Therefore, the present study aimed to further knowledge on this topic by having a group of young and old healthy adults complete a Recent Probes task with a balanced distribution of conditions of trials and by applying an analytical technique that allowed us to separate potentially overlapping ERP components.

Principal component analysis (PCA) was therefore used to achieve these objectives. PCA is a factor analytic technique that extracts linear combinations of latent variables using eigenvalue decomposition (Dien & Frishkoff, 2005). It is a data-driven approach to extracting variance in the EEG signal in a precise, unbiased and parsimonious way by offering solutions to separate variance in ERPs that may be otherwise confounded by the naked eye (Dien, 2010). We therefore argue that applying PCA to EEG data recorded during the resolution of PI would help untangle potentially overlapping ERP components and therefore enhance our knowledge on how the neural correlates of cognitive control change in healthy aging. By doing so we hope to further understanding of whether age differences in PI effects represent reduced speed of processing or compensatory recruitment of neural resources, or reduced efficiency of neural activity in healthy aging. Consequently, the present work used temporo-spatial principal component analysis (tsPCA) to study the temporal and spatial characteristics of neural activity associated with PI resolution in the Recent Probes task, and how these characteristics change with age. We subsequently aimed to localise the sources of differences between age groups and PI conditions in the temporo-spatial PCA factors, as they remain unknown.

We expected that effects of PI would be found in both young and old adults' accuracy and RTs, but PI costs would be larger in old compared to young adults, providing support for the inhibitory deficit hypothesis of healthy aging (Hasher & Zacks, 1988). As the reviewed results seem to suggest that the period of time between 300 and 800 ms after probe stimulus onset is a crucial window for PI resolution, and that these effects occur somewhere between frontal and centro-parietal sensors at the scalp level, we expected to observe PI effects in EEG data between 300-800 ms in fronto-central electrodes with greater positivity in conditions of low-PI compared to high-PI. We expected these effects in EEG data to be altered in old adults.

2. Methods

2. 1. Participants

Participants met the following criteria: a) not currently receiving psychotherapeutic or pharmacological treatment for a psychiatric disorder, and no history of a psychiatric disorder, and b) no major medical or neurological disorder. Eleven participants were excluded due to not meeting these criteria (*N* = 1), missing data (*N* = 1), high number of EEG artefacts (*N* = 2), depression symptoms (*N* = 2) or outlying behavioural data (*N* = 5; see below for further details). Forty-two healthy adults were included in the study: 26 young adults between 18-34 years (16 females, *M* age = 25.96, *SD* age = 6.17, *M* years of education = 18.81, *SD* years of education = 2.45), and 16 old adults between 53-68 years (9 females, *M* age = 62.88, *SD* age = 3.40, *M* years of education = 15.94, *SD* years of education = 3.45).

Participants were recruited via the course credit system of the under-graduate Psychology course or via invitation in senior universities and leisure centres with specific activities to old adults. Participants gave full written informed consent and were treated in accordance with the Code of Ethics of the World Medical Association (as stated by the Declaration of Helsinki) regarding experimentation on humans. This study's protocols were approved by the Ethics Committee for Life and Health Sciences at the University of Minho (Ref. SECVS 108/2016).

2. 2. Materials

The *Montreal Cognitive Assessment* (MoCA; Nasreddine et al., 2005) screened old adult participants for mild cognitive impairment (MCI). Participants were excluded with a score above or below 2 standard deviations of the normative score for their age and education level. The *Beck Depression Inventory-II* (BDI-II; Beck, Steer & Brown, 1996) measured depression symptoms in young adults, and the *Geriatric Depression Scale* (GDS; Yesavage et al., 1982) measured depressive symptoms in old adults to verify the absence of undiagnosed depression. The *Edinburgh Handedness Inventory* measured participants' handedness (Oldfield, 1971).

The Recent Probes task was implemented using PsychoPy (Peirce, 2007). As previous studies using this paradigm with verbal stimuli have observed main effects of age on performance, we used pictures as memoranda to promote overall performance in old adults while preserving potential PI effects. Previous evidence has shown that old adults perform as well as young adults on memory tasks using pictorial stimuli (see Friedman, 2013 for a review). Further, as there is evidence to suggest that old adults

show advantages in episodic memory recollection of scenes (Gutchess, Ieuji, & Federmeier, 2007) and faces (Grady et al., 1995), we used both categories to ensure that any improvements in performance were not specific to the type of stimuli. Face stimuli were 48 images of emotionally neutral faces (24 female and 24 male faces) from the Karolinska Directed Emotional Faces (KDEF; Lundqvist et al., 2004). Scene stimuli were 48 emotionally neutral images of scenes from the International Affective Picture System (IAPS; Lang et al., 2013).

2. 3. Procedure

Participants completed the cognitive task in a soundproof cabin. The aim of the cognitive task was to manipulate PI such that a portion of trials produced relatively high PI, against which we would compare performance and EEG activity on trials that produced relatively low PI. Participants were presented with an array of six images (the target set), which they were instructed to memorise. After a short delay period, a probe stimulus was presented. Participants' task was to decide whether the probe stimulus matched any stimulus in the target set of the current trial. Stimuli were presented on a computer screen in colour on a black background. The target set comprised three images of faces and three images of scenes around a white fixation cross (two faces and one scene above the fixation cross and two scenes and one face below the fixation cross, or vice versa), which was present in the centre of the screen (see Figure 2). The target set was presented for 2000 ms. The delay period consisted of a white fixation cross in the centre of the screen and its duration was jittered between 2750-3250 ms across trials with an average duration of 3000 ms. The probe stimulus was presented in the centre of the screen for 2000 ms, which was an image of either a single face or a single scene. After the probe stimulus disappeared, a white fixation cross was presented in the centre of the screen for an average of 3000 ms (jittered between 2500-3500 ms across trials) until the beginning of the following trial. Participants had to decide whether the probe matched any stimulus in the target set of the current trial or not by pressing a keyboard button for "yes" and a keyboard button for "no". Participants responded with their dominant hand, and response keys were counter-balanced across participants (two young adults and one old adult were left-handed).

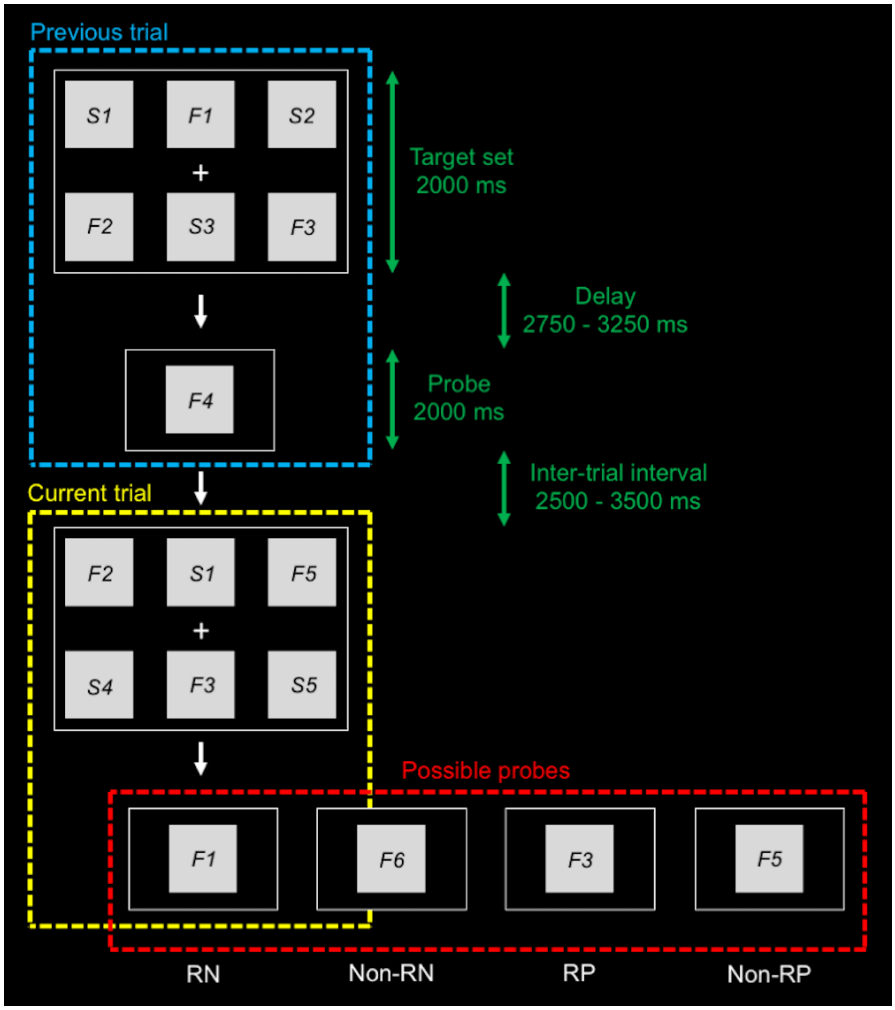


Figure 2. Trial scheme of the recent probes task. This scheme shows two trials from the face-relevant block of trials. The right side of the scheme indicates the duration of each phase of the trials. The bottom part of the figure shows what condition of PI (RN, non-RN, RP or non-RP) would be created if either of these stimuli were presented as the probe stimulus of the current trial. Different possible conditions of PI are achieved when the probe matches or does not match a stimulus in the target set of the current and previous trial. Labels of faces and scenes are used instead of the original stimuli used in the task for representation purposes. RN = Recent Negative. RP = Recent Positive. *F* = face stimulus, *S* = scene stimulus.

The task was completed in two blocks of 96 trials. In one of the blocks the probe was always a face, and participants had to memorise only face stimuli in the target set. In the other block, the probe was always a scene, and participants had to memorise only scene stimuli in the target set. Face and scene stimuli were presented together in the target set to increase the ecological validity of the task: in

everyday settings it is likely that when trying to memorise something there are other irrelevant stimuli present. The order of block completion was randomised across participants.

Trials were divided into four types according to type of response and recency of the probe: *recent positives (RP), non-recent positives (non-RP), recent negatives (RN)* and *non-recent negatives (non-RN)*. Thus, positive (P) trials required a "yes" response since the probe was present in the target set of current trial, while negative trials (N) required a "no" response given the probe stimulus was absent from the current trial target set. Similarly, recent (R) trials have a probe that appeared in the target set of the previous trial while the probe in non-recent (non-R) trials did not appear in the target set of, at least, the six previous trials. Each of these conditions represents 25% of trials and were presented in a pseudo-random order. In all trials the target set had three stimuli (two faces and one scene, or, vice versa) that were also presented in the target set of the previous trial, and three items that were not presented in the previous six trials, to avoid confounding familiarity with PI. PI was measured as the difference between RN trials and non-RN trials.

2. 4. Behavioural Data Analysis

Accuracy (% correct trials) and RTs (time from probe stimulus onset to button press) from non-RN and RN trials were analysed. Only RTs from correct trials were analysed. Repeated Measures Analyses of Variance (RM-ANOVAs) with the within subjects factors Block Type (face vs. scene) and PI Condition (non-RN vs. RN trials), and with the between subjects factor Age Group (young vs. old) were run on accuracy and RTs. Greenhouse-Geisser corrections and Bonferroni adjustments were applied where appropriate.

We ran independent samples *t*-tests on proportional PI cost for RT as well as accuracy (i.e. (RN – non-RN)/non-RN) calculated across both blocks of trials. The proportional PI costs was analysed instead of the subtracted differences between RN and non-RN trials in order to take into account between group differences on the baseline condition (i.e. non-RN trials). Proportional PI costs were also calculated separately for each block and compared using a paired samples t-test in order to see if PI costs are different in each block for each age group. In order to analyse the relationship between PI costs in RT and accuracy, Pearson correlations were run on proportional PI RT costs and proportional PI accuracy costs separately in young and old adults, as well as across participants.

Participants were excluded from analysis if their behavioural data on any variable of interest had a z-score larger than ±3. Further, alpha level was set at 0.05 for all statistical tests.

2. 5. EEG Recording and Analyses

EEG signal was recorded using an ActiveTwo Biosemi system (Biosemi, Amsterdam, the Netherlands) with 64 active electrodes inserted in an elastic cap according to the international 10-10 system. A Common Mode Sense (CMS) and Driven Right Leg (DRL) montage of two electrodes located over the vertex was used as a reference. Electrode offset was kept below 30 mV. EEG data was filtered online between 0.01-100 Hz and digitized at a sampling rate of 512 Hz.

Only correctly answered negative trials (i.e. non-RN and RN trials) entered EEG analysis as our hypotheses concerned PI effects and how they differ between age groups. EEG data was filtered offline using a phase-shift free IIR Butterworth bandpass filter between 0.1-30 Hz with 12 dB roll-off in ERPLab (Lopez-Calderon & Luck, 2014). Bad channels were eliminated and artefacts were corrected in EEGLab using Artefact Subspace Reconstruction (see Mullen et al., 2015). The EEG signal was re-referenced to the average. EEG data was epoched from 200 ms prior to 1500 ms after probe stimulus onset. The pre-stimulus interval was used as the reference period for baseline correction, which consist of the subtraction from each data point in the pre- and post-stimulus period for any given electrode of the mean of all data points in the pre-stimulus interval for that electrode. Independent component analysis (ICA) was carried out in EEGLab (Delorme & Makeig, 2004) to remove ocular and muscular components (components removed in young adults $M = 7.25$, $SD = 2.96$; components removed in old adults = $M = 8.84$, $SD = 5.76$). Eliminated channels were interpolated using the superfast spherical interpolation method (Ferree, 2000; Perrin et al., 1989) as implemented in EEGlab. Automated artefact detection routines in ERPLab rejected epochs with data points exceeding ±150 μV or two consecutive data points that differed by more than 50 μV. In total, an average of 0.11 (SD = 0.49) negative trial epochs across both blocks were removed in young adults due to artefacts, while an average of 0.30 (SD = 0.70) negative trial epochs across both blocks were removed in old adults due to artefacts (amount of removed epochs did not differ between age groups, $t(40) = -1.04$, $p = .30$, Cohen's $d = 0.31$). Epoched data was averaged at each electrode according to experimental conditions: block type (face-relevant and scene-relevant) and PI condition (non-RN and RN), resulting in 4 bins of averaged ERP waveforms for each participant (average number of trials per condition: non-RN, in Face-relevant block 23.19 ($SD = 1.23$) for young adults and 21.69 ($SD = 3.24$) for old adults and in Scene-relevant block 22.92 ($SD = 1.79$) for young and 22.75 ($SD = 1.91$) for old adults; RN, in Face-relevant block 21.08 ($SD = 2.21$) for young and 19.63 ($SD = 3.30$) for old adults and in Scene-relevant block 21.08 ($SD = 3.03$) for young and 20.44 ($SD = 1.93$) for old adults). There were no between group differences in number of epochs entered in analysis

in either condition of each block. The grand averaged ERP waveforms per condition across participants for each age group are present in the Supplementary Material (Supplementary Figure 1).

We used PCA Toolkit (Dien, 2010) to apply temporal (tPCA) and spatial (sPCA) principal component analysis to the ERPs. The matrix of ERP waveforms entered into tPCA had the following structure: observations (participants by block by condition/bin by electrode) × timepoints. tPCA was done on the covariance matrix with Kaiser loading weighting with no factor rotation. Based on the result, we retained all temporal factors that explained at least 5% of the total variance. The temporal factors that met this criterion were submitted to a Promax factor rotation. The resultant temporal factor scores were submitted to sPCA, meaning a separate sPCA was carried out on each temporal factor, which results in a separate eigen-decomposition (i.e. vector of eigenvalues) per temporal factor. For example, conducting sPCA on the factor scores of three temporal factors results in three vectors of eigenvalues, each with as many elements as there are electrodes in the EEG dataset (i.e., 64). Each element of these vectors represents an unrotated spatial factor. Therefore, to know how much of the total variance each unrotated spatial factor explained on average across the temporal factors, we averaged the eigenvalues across the vectors (as in Foti et al., 2011), which resulted in a single vector of average eigenvalues. We retained all of these spatial factors whose average eigenvalue across temporal factors explained at least 5% of the total variance. The spatial factors that met this criterion were submitted to an Infomax factor rotation.

In order to determine whether age groups showed differences in the time courses of principal components, we first carried out tPCA separately on each age group. tPCA in young adults resulted in three temporal factors that each explained at least 5% of the total variance (total variance explained = 77.21%). The peak latency of these temporal factors was 669.92 ms, 251.95 ms and 1304.69 ms respectively (see Supplementary Figure 2). tPCA in old adults also resulted in three temporal factors that each explained at least 5% of the total variance (total variance explained = 73.78%). The peak latency of these temporal factors was 685.55 ms, 1375.00 ms and 281.25 ms respectively (see Supplementary Figure 3).

As the temporal components in both age groups were highly similar, we then carried out tPCA on the whole sample, and then conducted sPCA on the resultant temporal factor scores from the whole sample. tPCA on the whole sample also resulted in three temporal factors (see Figure 3) that each explained at least 5% of the total variance (total variance explained = 75.71%). The peak latency of these temporal factors is presented in Table 1. When the factor scores of these temporal factors from the whole sample were submitted to sPCA, four spatial factors explained at least 5% of the total variance. Factor

scores of each temporal factor were each subjected to a separate sPCA to each retain 4 spatial factors, which resulted in a total of 12 temporo-spatial factors (see Figure 3), which together explain 27.77 % of variance in the data. The total variance explained by each resultant temporo-spatial factor (TSF) is presented in Table 1.

Factor	Peak Latency	Unique Variance Explained
TSF1.1	673.83 ms	5.29%
TSF1.2	673.83 ms	2.58%
TSF1.3	673.83 ms	0.86%
TSF1.4	673.83 ms	0.78%
TSF2.1	257.81 ms	8.01%
TSF2.2	257.81 ms	1.38%
TSF2.3	257.81 ms	0.80%
TSF2.4	257.81 ms	0.76%
TSF3.1	1302.73 ms	3.45%
TSF3.2	1302.73 ms	1.99%
TSF3.3	1302.73 ms	1.06%
TSF3.4	1302.73 ms	0.81%

Table 1. Peak latencies of each temporo-spatial factor for the whole sample during the retrieval phase of the Recent Probes task (note that each spatial factor pertaining to the same temporal factor have identical peak latencies as they each share the same time course as dictated by the factor loadings of that temporal factor); unique variance explained (the percentage of variance a factor accounts for that is not accounted for by any other factor).

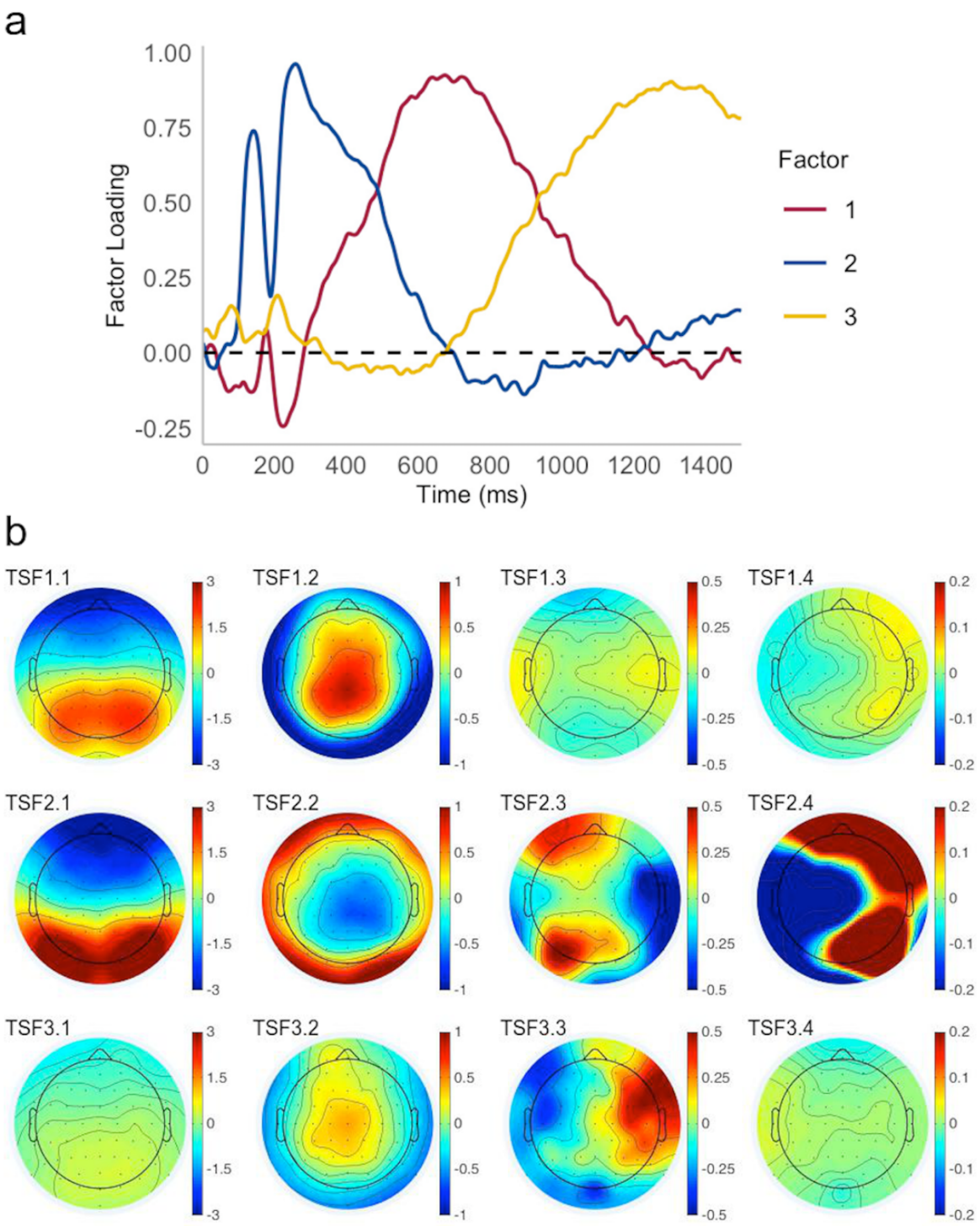


Figure 3. Temporal and spatial factors of EEG activity during the retrieval phase of the Recent Probes task for the whole sample. Panel *a* contains factor loadings of each temporal factor. Panel *b* contains reconstructed voltage topographies of the temporo-spatial factors. Voltages were reconstructed using the equation in Dien and Frishkoff (2005). Note that each row of topographies in panel *b* represents the four spatial factors that belong to a temporal factor.

TSF scores were submitted to a RM-ANOVA, with Block Type (face-relevant vs. scene-relevant) and PI Condition (non-RN vs. RN) as within subjects factors, and Age Group (young vs. old) as the between subjects factor. Greenhouse-Geisser corrections and Bonferroni adjustments were applied where appropriate. Pearson correlations between the TSF score differences (RN – non-RN) and proportional PI costs (i.e. (RN – non-RN)/non-RN) for RT and accuracy collapsed across blocks analysed the relationship between brain activity and behaviour. We initially ran these correlations on all participants, and in the case of significant correlations used Fisher z transformations of the Pearson coefficients calculated for each group separately to analyse between groups differences in those correlations. For all statistical analyses alpha level was set at 0.05.

As there is evidence of age differences at the electrophysiological level during the encoding phase of similar WM tasks (Gazzaley et al., 2005; Pinal et al., 2015), we also analysed the EEG data during the encoding phase (i.e. memorisation of the target set) of the Recent Probes task. We argue that analysing the encoding phase of the Recent Probes task will help us better understand whether potential age differences in performance are due to differences in EEG activity during the retrieval phase or whether they are also influenced by EEG activity during the encoding phase. Encoding phase EEG data was pre-processed in the same manner as retrieval phase data and only the encoding phase epochs belonging to correct non-RN and RN trials for each task block were included in further analyses. Given that in theory the encoding phase should not be affected by PI condition, epoched data was averaged according to block type, resulting in 2 bins of averaged ERP waveforms: face-relevant or scene-relevant trials. In total, an average of 1.67 (SD = 2.52) trial epochs across both blocks were removed in young adults due to artefacts, while an average of 1.25 (SD = 1.86) trial epochs across both blocks were removed in old adults due to artefacts (amount of removed epochs did not differ between age groups, $t(40) = 0.58$, $p = .57$, Cohen's $d = .19$). Epoched data was averaged at each electrode according to block type (face-relevant and scene-relevant), resulting in 2 bins of averaged ERP waveforms for each participant (average number of trials per conditions: Face-relevant block, 42.04 ($SD = 4.37$) for young and 41.13 ($SD = 6.40$) for old adults; Scene-relevant block, 42.12 ($SD = 5.39$) for young and 42.44 ($SD = 4.99$) for old adults). There were no between groups differences in number of epochs entered into analysis in either block (face-relevant block: t(40) = 0.55, SE = 1.66, p = .59; scene-relevant block t(40) = -0.19, SE = 1.67, p = .85).

Temporo-spatial PCA was also applied to the encoding phase EEG data using the same methods applied to the retrieval phase. Three temporal factors explained more than 5% of variance in the data

(total variance explained = 83.42%) and were therefore subjected to a Promax factor rotation (see Figure 4). The resultant temporal factor scores were submitted to sPCA. We aimed to retained spatial factors that explained at least 5% of the total variance when their eigenvalue decompositions were averaged across temporal factors, although as one spatial factor explained 4.89% of total variance, we lowered the criteria to 4.89%. Four spatial factors met this criterion and were submitted to an Infomax factor rotation (see Table 2). This resulted in 12 TSFs explaining a total of 35.25% of data variance (see Figure 4).

Factor	Peak Latency	Unique Variance Explained
TSF1.1.E	646.48 ms	8.30%
TSF1.2.E	646.48 ms	3.94%
TSF1.3.E	646.48 ms	1.66%
TSF1.4.E	646.48 ms	1.35%
TSF2.1.E	1419.92 ms	7.08%
TSF2.2.E	1419.92 ms	4.94%
TSF2.3.E	1419.92 ms	1.50%
TSF2.4.E	1419.92 ms	1.33%
TSF3.1.E	250.00 ms	3.16%
TSF3.2.E	250.00 ms	0.84%
TSF3.3.E	250.00 ms	0.76%
TSF3.4.E	250.00 ms	0.39%

Table 2. Peak latencies of each temporo-spatial factor for the whole sample during the encoding phase of the Recent Probes task (note that each spatial factor pertaining to the same temporal factor have identical peak latencies as they each share the same time course as dictated by the factor loadings of that temporal factor); unique variance explained (the percentage of variance a factor accounts for that is not accounted for by any other factor).

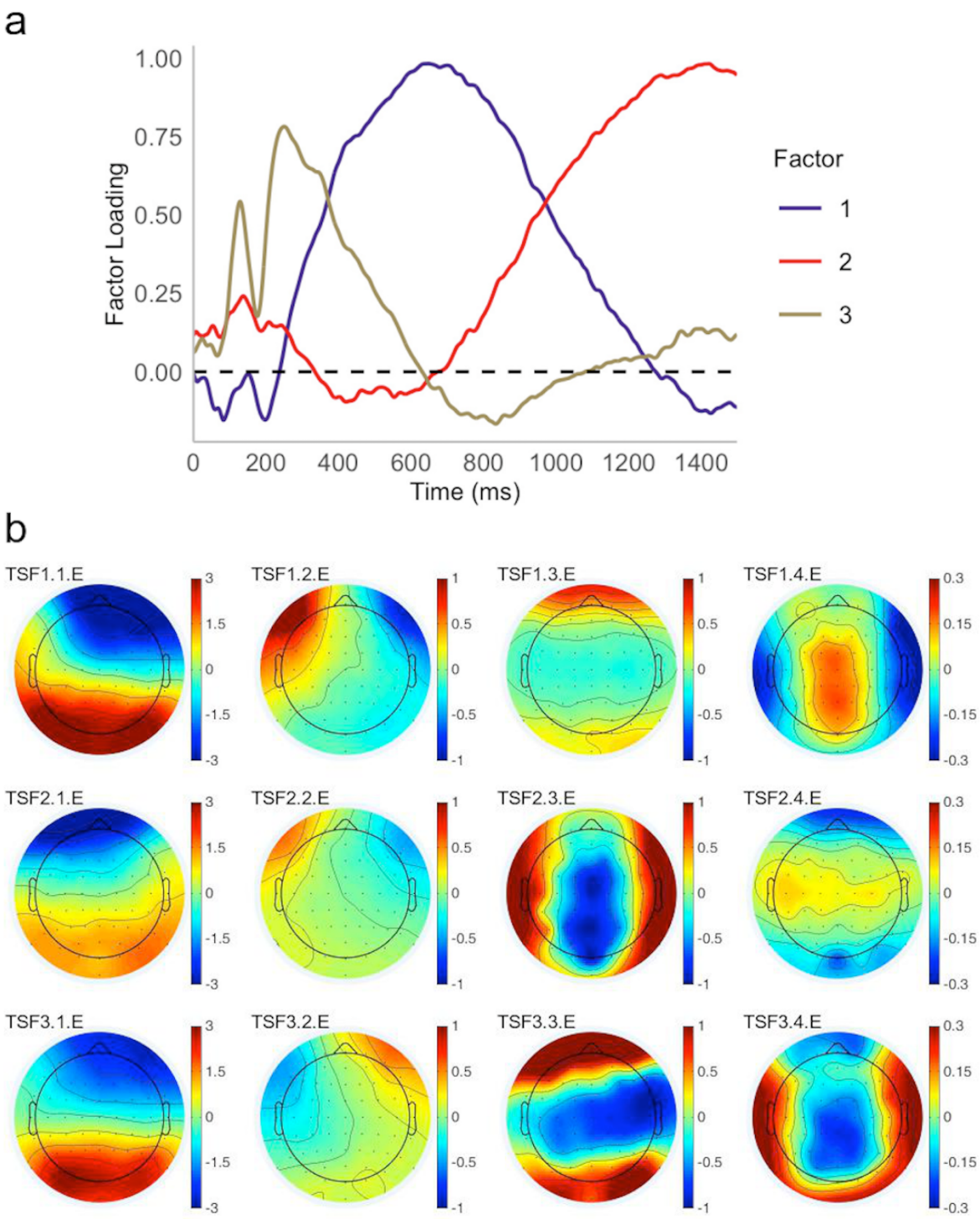


Figure 4. Temporal and spatial factors of EEG activity during the encoding phase of the Recent Probes task for the whole sample. Panel *a* contains factor loadings of each temporal factor. Panel *b* contains reconstructed voltage topographies of the temporo-spatial factors. Voltages were reconstructed using the equation in Dien and Frishkoff (2005). Note that each row of topographies in panel *b* represents the four spatial factors that belong to a temporal factor.

TSF scores from the encoding phase were entered into a RM-ANOVA, with Block Type (face-relevant vs. scene-relevant) as the within subjects factor, and Age Group (young vs. old) as the between subjects factor. Greenhouse-Geisser corrections and Bonferroni adjustments were applied where appropriate. Pearson correlations between the average TSF scores across block types and proportional PI costs (i.e. (RN – non-RN)/non-RN) for RT and accuracy collapsed across blocks, and Pearson correlations between the average TSFs scores across block types and RT and accuracy across all negative trials analysed the relationship between brain activity and behaviour. We initially ran these correlations on all participants, and in the case of significant correlations used Fisher z transformations of the Pearson coefficients calculated for each group separately to analyse between groups differences in those correlations. For all statistical tests, alpha level was set at 0.05.

2. 6. Source Localisation Analysis

Standardised low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) software was used to localise the source of the differences in temporo-spatial factor scores between conditions and age groups detected at the scalp. sLORETA offers a solution to the inverse problem by estimating the current source density distribution for the whole brain based on the EEG activity measured across all electrodes at the scalp. The weights used by sLORETA creates images of current source densities with highly accurate localisation although with low spatial resolution. This low spatial resolution is because sLORETA calculates the smoothest current source density estimate possible, which reflects the high correlation between neighbouring populations of neurons. sLORETA conducts source localisation by dividing the estimated current source density at each voxel by the square root of its estimated variance, meaning that the estimated current source density is provided in z-scores.

We first converted temporo-spatial factor scores to voltages using the equation described in Dien and Frishkoff (2005). We then create difference waves between conditions and age groups (depending on the comparison of interest), which were submitted to source localisation in sLORETA. The difference waves submitted to sLORETA contained the whole epoch of interest (0 - 1500 ms), as the spatial distribution of temporo-spatial factor scores converted to voltages does not vary over time. Source localisation was done using a realistic head model based on the Montreal Neurological Institute (MNI152) template (Mazziotta et al., 2001). The anatomical space in which the solution was estimated was restricted to cortical grey matter, and the intracerebral volume was partitioned in 6239 voxels of 5 x 5 x 5 mm. Results are reported in MNI coordinates.

3. Results

3. 1. Accuracy

A significant main effect of Block Type was found on accuracy, $F(1,40) = 6.15$, $p = .017$, $\eta_p^2 = .13$, with trials in the scene-relevant block ($M = 93.60$, $SEM = .69$) having higher accuracy than in the face-relevant block ($M = 90.49$, $SEM = 1.30$). There was a significant main effect of PI Condition on accuracy (see Figure 5), $F(1,40) = 100.09$, $p < .001$, $\eta_p^2 = .71$, with non-RN trials ($M = 95.97$, $SEM = .73$) having higher accuracy than RN trials ($M = 88.11$, $SEM = 1.07$). A main effect of Age Group on accuracy only approached significance, $F(1,40) = 3.21$, $p = .081$, $\eta_p^2 = .07$, showing young adults ($M = 93.52$, $SEM = 1.02$) to have marginally higher accuracy than old adults ($M = 90.56$, $SEM = 1.30$). No interaction effects were found between Block Type, PI Condition or Age Group.

Age groups did not significantly differ in proportional PI accuracy costs when trials were combined across both block types, $t(40) = -0.62$, $SE = 0.02$, $p = .54$, Cohen's $d = 0.19$.

3. 2. Reaction Time

A significant main effect of PI Condition was found on RTs (see Figure 5), $F(1,40) = 81.59$, $p < .001$, $\eta_p^2 = .67$, with non-RN trials ($M = 1010.00$, $SEM = 22.85$) having shorter RTs than RN trials ($M = 1133.57$, $SEM = 24.39$). There was a significant main effect of Age Group on RTs, $F(1,40) = 22.78$, $p < .001$, $\eta_p^2 = .36$, with young adults ($M = 963.81$, $SEM = 27.93$) having shorter RTs than old adults ($M = 1179.76$, $SEM = 35.60$). There was a significant interaction effect found between Block Type and PI Condition, $F(1,40) = 20.53$, $p < .001$, $\eta_p^2 = .34$: non-RN trials in the scene block ($M = 973.79$, $SEM = 21.23$) had shorter RTs than non-RNs in the face block ($M = 1046.21$, $SEM = 29.81$) ($p = .005$), while non-RN trials had shorter RTs than RN trials for both the face block (RN trials in face block $M = 1121.37$, $SEM = 29.33$) ($p < .001$) and the scene block (RN trials in scene block $M = 1145.78$, $SEM = 27.07$) ($p < .001$). No other significant main or interaction effects were found.

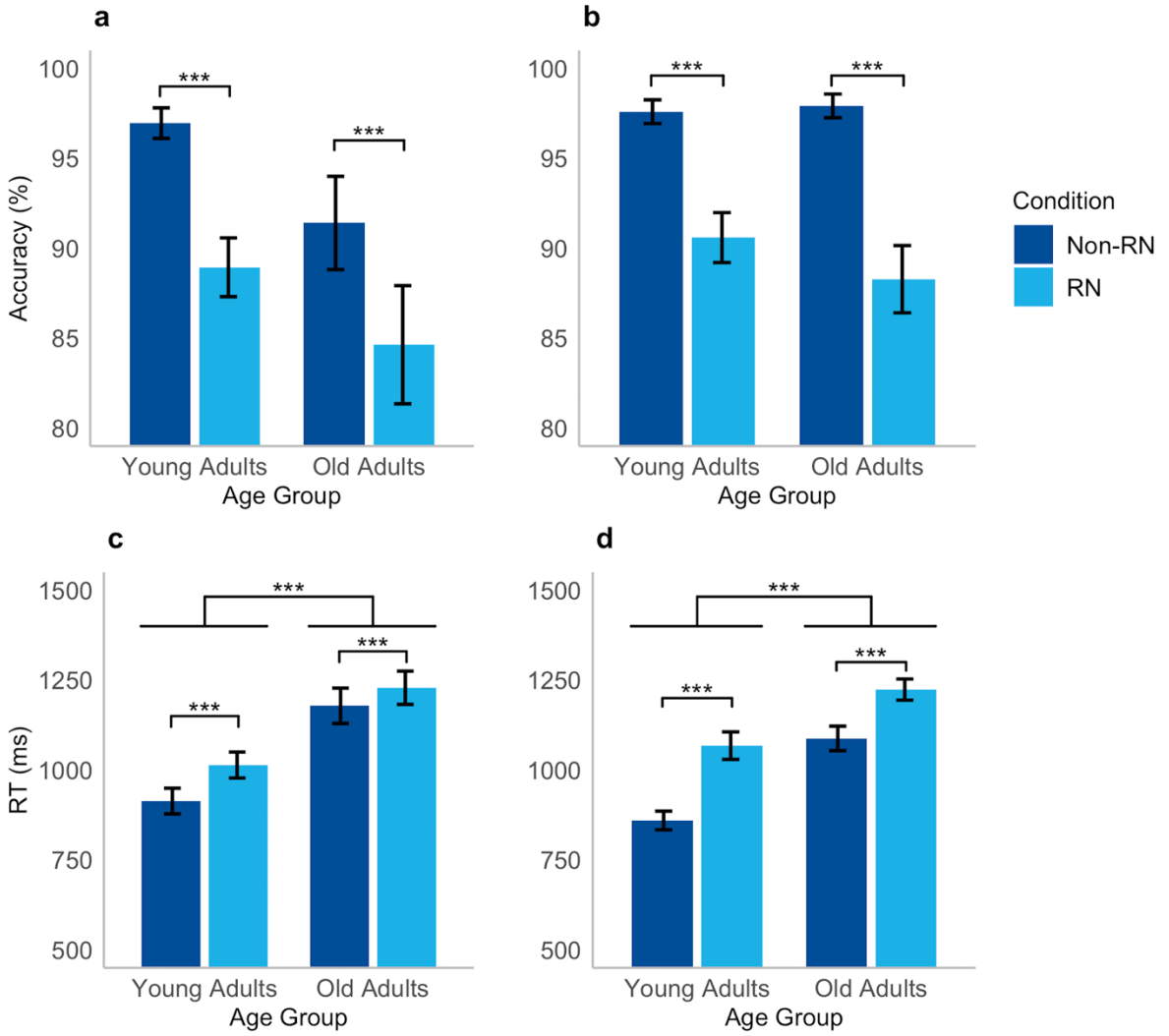


Figure 5. Accuracy and RT for young and old adults in each PI Condition (non-RN and RN) separated by Block Type. Panel *a* is accuracy in the face-relevant block, panel *b* is accuracy in the scene-relevant block, panel *c* is RT in the face-relevant block and panel *d* is RT in the scene-relevant block. *** = $p <$ .001

Age groups were found to significantly differ in proportional PI RT costs when trials were combined across both block types, $t(40) = 3.01$, $SE = .03$, $p = .005$, Cohen's $d = 0.99$, with young adults ($M = 0.18$, $SD = 0.10$) having greater PI costs than old adults ($M = 0.09$, $SD = 0.08$). Proportional PI costs in all participants were found to be lower in the face-relevant block ($M = 0.09$, $SD = 0.10$) compared to the scene-relevant block ($M = 0.20$, $SD = 0.15$), $t(41) = -4.84$, $p = .000$. This effect was also significant when analysed separately in young $t(25) = -3.73$, $p = .001$ and old adults $t(15) = -3.55$, $p = .003$. Proportional PI RT costs did not significantly correlate with proportional PI accuracy costs when calculated in all

participants r = -.01, p = .96 or separately in each age group (young adults, r = .15, p = .46; old adults, r = .16, p = .56).

3. 3. Retrieval Phase EEG Activity

A significant main effect of PI Condition was found on the TSF1.2 factor scores, $F(1,40) = 6.36$, p = .016, η_p^2 = .14, with non-RN trials (M = .65, SEM = .14) having higher factor scores than RN trials (M = .48, SEM = .12). The maximally activated source of the difference between PI conditions was localised to the left postcentral gyrus (X = -5, Y = -55, Z = 70).

A significant main effect of Age Group was found on TSF2.1 factor scores, $F(1,40) = 8.13$, p = .007, η_p^2 = .17, with old adults (M = -.65, SEM = .21) having less negative factor scores than young adults (M = -1.42, SEM = .17). The maximally activated source of the difference was the right medial frontal gyrus (X = 10, Y = 65, Z = -15).

A significant main effect of Age Group was found on TSF2.2 factor scores, $F(1,40) = 6.23$, p = .017, η_p^2 = .14, as well as a significant interaction between PI Condition and Age Group, $F(1,40) = 12.88$, p = .001, η_p^2 = .24: old adults (M = .05, SEM = .22) had less negative factor scores on non-RN trials than young adults (M = -.84, SEM = .17) (p = .003; maximally activated source of the difference = right inferior frontal gyrus [X = 50, Y = 45, Z = -10]). Additionally, young adults had less negative factor scores on RN trials (M = -.65, SEM = .16) than non-RN trials (M = -.84, SEM = .17) (p = .026; maximally activated source of the difference = left middle temporal gyrus [X = -60, Y = 0, Z = -25]), while old adults had less negative factor scores on non-RN trials (M = .05, SEM = .22) compared to RN trials (M = -.24, SEM = .20) (p = .009; maximally activated source of the difference = right superior parietal lobule [X = 20, Y = -65, Z = 65]). TSF2.2 results are presented in Figure 6.

A significant interaction between PI Condition and Age Group was found on TSF3.4 factor scores, $F(1,40) = 6.58$, p = .014, η_p^2 = .14, with old adults (M = .45, SEM = .20) showing positive factor scores on non-RN trials while young adults presented negative factor scores on non-RN trials (M = -.28, SEM = .16) (p = .008; maximally activated source of the difference = left cuneus [X = -15, Y = -100, Z = 5]). TSF3.4 results are presented in Figure 7.

A significant main effect of Block Type was found on the factor scores of TSF1.2, TSF2.2 and TSF3.2, while Block Type also interacted significantly with Age Group on TSF3.2 factor scores. These results are presented in the Supplementary Results and Discussion.

No significant correlations were found between temporo-spatial factor scores for EEG data during the retrieval phase and behavioural data.

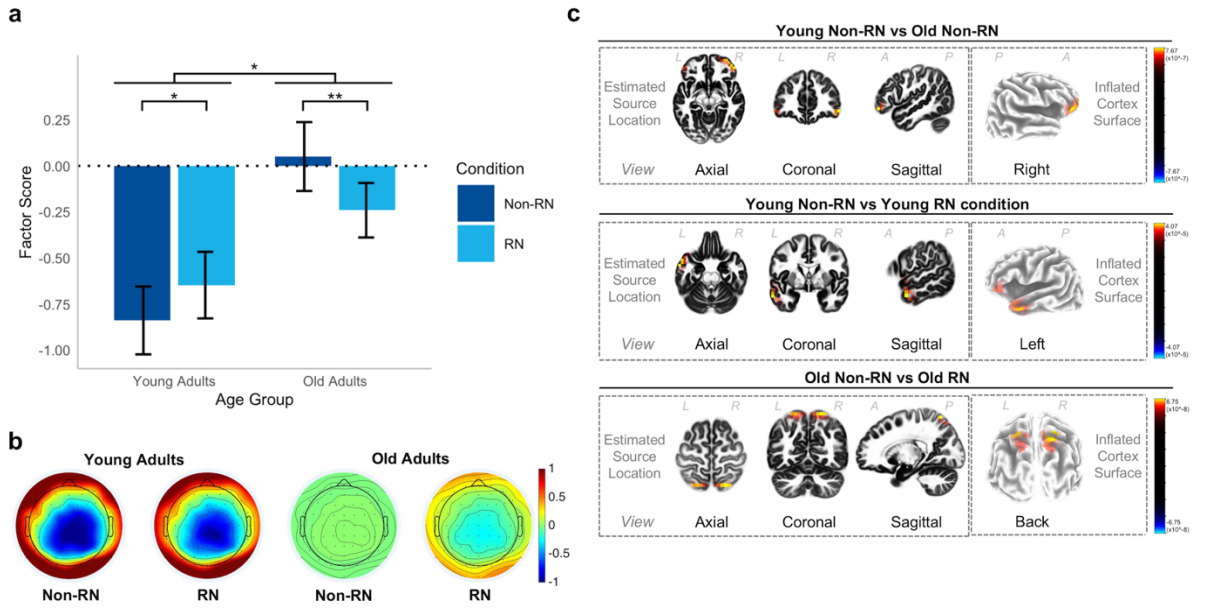


Figure 6. Factor scores of temporo-spatial factor 2.2 and source localisation results. Panel ***a*** shows temporo-spatial factors scores in young and old adults for each PI condition (* = $p < .05$, ** = $p < .01$), panel ***b*** shows topographical maps of reconstructed voltages of temporo-spatial scores for each age group and PI condition using the equation in Dien and Frishkoff (2005), panel ***c*** shows the localised source of maximal activation of the difference between age groups and PI conditions.

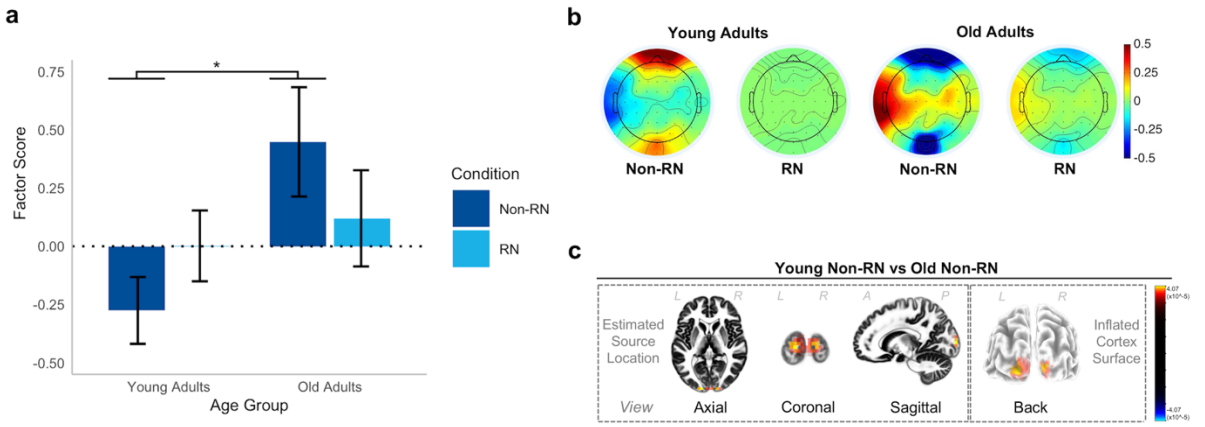


Figure 7. Factor scores of temporo-spatial factor 3.4 and source localisation results. Panel ***a*** shows temporo-spatial factors scores in young and old adults for each PI condition (* = $p < .05$), panel ***b*** shows topographical maps of reconstructed voltages of temporo-spatial scores for each age group and PI

condition using the equation in Dien and Frishkoff (2005), panel ***c*** shows the localised source of maximal activation of the difference between age groups for non-RN trials.

3. 4. Encoding Phase EEG Activity

A significant main effect of Age Group was found on the factor scores of TSF1.1.E, $F(1,40) = 5.05$, $p = .03$, $\eta_p^2 = 0.11$, with young adults ($M = 1.15$, $SD = 0.15$) having greater factor scores than old adults ($M = 0.61$, $SD = 0.19$). The factor scores of TSF1.1.E, when collapsed across both bock types, negatively correlated with RT across all negative trials in all adults, $r = -.34$, $p = .026$, suggesting that greater factor scores were associated with shorter RTs. This correlation was not significant when run separately on each age group.

The same pattern of results was also found on TSF3.1.E. A main effect of Age Group was found, $F(1,40) = 6.06$, $p = .018$, $\eta_p^2 = 0.13$, with young adults ($M = 1.25$, $SD = 0.16$) showing greater factor scores compared to old adults ($M = 0.63$, $SD = 0.20$), and factor scores across both block types negatively correlated with RT across all negative trials $r = -.46$, $p = .002$. This correlation was not significant when run separately on each age group.

A significant main effect of Block Type was also found on the factor scores of TSF1.4.E and TSF2.3.E, which are presented in the Supplementary Results and Discussion.

4. Discussion

We observed evidence of age differences in PI effects in participants' performance in our Recent Probes task, as well as age differences in PI effects in the EEG signal. Participants responded less accurately and slower to RN trials than non-RN trials. We hypothesised that old adults would show larger PI effects than young adults in both accuracy and RT, and in contrast to this we found evidence of greater PI costs in young than old adults in RT. However, old adults were generally less accurate and slower than young adults, suggesting a general difficulty when performing the task independently of PI condition. Stimulus type also affected performance: face-relevant trials were responded to less accurately and more slowly than scene-relevant trials. Although trials in the face-relevant block were responded to more slowly than in the scene-relevant block only in conditions of low interference, when we calculated PI RT costs in each block, PI costs were significantly greater in the scene-relevant block compared to the face-relevant block. This effect did not differ between age groups. In sum, this suggests that responding to trials in the face-relevant block was difficult even in conditions of low PI, given that RT on non-RNs was almost as long as RT on RN trials in the face-relevant block.

Unlike previous studies (Jonides et al., 2000; Yi & Friedman, 2014; Loosli et al., 2014; Loosli et al., 2016; Oberauer, 2001), our behavioural results show evidence of greater PI effects in young adults compared to old adults. At face value, our data seems to contradict the inhibitory deficit hypothesis (Hasher & Zacks, 1988), which predicts that as we get older we experience more interference from irrelevant information. However, our data appear to indicate that PI effects were masked in old adults as they were equally slow in both non-RN and RN trials. In contrast to this, young adults showed more pronounced PI effects than old adults as RT on RN trials was disproportionally longer than on non-RN trials. It can therefore be argued that old adults may not have shown PI effects to the same extent as young adults due to a general difficulty they found on the cognitive task that caused them to be relatively slow on all trials. This also raises the possibility that greater PI costs in RT do not necessarily indicate reduced cognitive control capacity. It may be the case that PI costs in RT represent the extra time taken on RN trials in order to produce a correct response to these trials. This is supported by the fact that PI costs in RT were not correlated with PI costs in accuracy.

We argue that this general difficulty observed in old adults may have been caused by the presence of distracting stimuli during the encoding phase, rather than a general reduction in processing speed. Reuter-Lorenz and Sylvester (2005) argue that in the absence of interference it is unlikely that old adults show deficits in WM ability compared to young adults on a simple maintenance task such as the

Recent Probes task, as such deficits would likely be found on tasks that involve greater cognitive control or contain some level of interference. In the present task, participants had to ignore irrelevant stimuli (i.e. either faces or scenes) during the encoding phase of the task in order to successfully encode relevant stimuli. The EEG data recorded during the encoding phase showed age groups to differ on two TSFs, with young adults having greater factor scores for both factors. Furthermore, the factor scores of both of these TSFs negatively correlated with RT in both RN and non-RN trials, suggesting that participants who showed greater factor scores on these TSFs generally had shorter RT in the cognitive task. This relationship between TSFs and behaviour during the encoding phase, and the reduced activity found in old adults, may indicate that a decreased ability to recruit neural resources in order to suppress distraction from irrelevant stimuli hindered performance on the task in old adults. Similar results have been previously found in a study by Gazzaley and colleagues (2005), who found old adults to be less able to suppress brain activity associated with encoding irrelevant stimuli in a WM task, and the ability to suppress this activity was correlated with performance on the task. Therefore, it may be the case that in the present study the irrelevant stimuli in the encoding phase disproportionately disrupted old adults to the extent that low-interference trials were nearly as difficult as high-interference trials or at least difficult enough to mask a larger effect of PI in old adults.

Age differences in PI effects were observed at the scalp level, as reflected by TSF2.2 (peak latency ~260 ms). Both age groups showed PI effects on TSF2.2 although in opposite directions: young adults had more negative factors scores on non-RN trials than RN trials (this difference was localised to the left middle temporal gyrus) while old adults had more negative factor scores on RNs than on non-RNs (localised to the right superior parietal lobule). This pattern of results may indicate that one of the neural mechanisms supporting resistance to PI is altered in old adults, suggesting perhaps that the neural mechanism underlying TSF2.2 is less efficient in healthy aging. Reduced efficiency of neural resources in healthy aging is normally characterised as over-recruitment of neural resources or recruitment of additional brain areas in old adults (Grady, 2008). Therefore, further research is needed to confirm whether age differences on TSF2.2 reflect reduced efficiency of the neural mechanisms supporting cognitive control in aging or compensatory brain activity.

TSF2.2 has similar characteristics to a negative ERP component found in Zhang and colleagues' study (2010) that employed the Recent Probes task with verbal stimuli on young adults. Zhang and colleagues observed an N2 at frontal and fronto-central sensors between 250-350 ms, although this N2 component was not sensitive to PI condition. However, Du and colleagues (2008) used a modified

Sternberg task to manipulate PI in young adults and observed an N2 component between 200-350 ms at frontal and fronto-central sensors that showed greater negativity in low-PI trials compared to high-PI trials, which is the same pattern as what we have observed in young adults on TSF2.2. Du and colleagues interpret the N2 as indexing the extent to which a stimulus evokes familiarity and appropriate or inappropriate "context codes". For example, they found N2 amplitude to be lowest in trials of high familiarity and when the probe had a context code (i.e. the context in which it was encoded) that matched the current trial (i.e. positive trials). They also found negative non-lure trials to produce the highest N2 amplitude, which is a condition that produced low familiarity and context codes that did not match the current trial. Lure trials, however, produced medium amplitude N2, and the authors interpret this as demonstrating a mixture of positive and negative non-lure trials, specifically, a condition that produces high familiarity and a context code that does not match the current trial. This suggests that TSF2.2 may index familiarity processing when resolving PI, and that familiarity processing is somehow altered in healthy aging. Despite the similarity between TSF2.2 and the N2 component found by Du and colleagues, these authors localised the N2 to the left superior frontal gyrus, whereas we localised the difference between PI conditions in young adults to the left middle temporal gyrus, suggesting distinct neuronal generators.

Age was also found to interact with PI condition on the factor scores of TSF3.4 (peak latency ~1300 ms). Age differences were only apparent on non-RN trials for which old adults had higher factor scores than young adults and the source of this difference was localised to the left cuneus. This suggests that old adults recruited neural resources to a greater extent than young adults, although only in conditions of relatively low cognitive load. This pattern of results is consistent with the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008), which posits that old adults recruit neural resources to a greater extent than young adults in conditions of low cognitive load, as such high levels of neural recruitment in conditions of low cognitive demand is not necessary in young adults. This over-recruitment of neural resources at low levels of cognitive load may be to compensate for reduced efficiency of the neural resources supporting cognitive control. However, at high levels of cognitive load this compensatory mechanism is no longer effective, leading to equivalent or less activation in old adults compared to young adults. There is an open debate about whether performance in both age groups should be more or less equivalent in order to consider this pattern of activation in old adults as compensatory (Grady, 2008). Zarahn and colleagues (2007) argue that this condition may not be necessary for a neural response to be deemed compensatory in nature, as it may be the case that old adults would perform *even worse* than they were observed to were it not for compensatory neural

activity. Consequently, even if performance was not equivalent between groups in the present study, the pattern of results observed for TSF 3.4 may still reflect compensatory mechanisms.

Although TSF3.4 peaked around the latency at which old adults responded, suggestive of a factor related to motor movement, it is unlikely that it reflects the lateralised readiness potential (LRP) involved in preparation of motor responses, as the LRP is typically expressed as a negative-going component (Eimer, 1998) in both young and old adults (Falkenstein, Yordanova, & Kolev, 2006). Furthermore, the difference between age groups on TSF3.4 factor scores on non-RN trials was localised to the Left Cuneus, making it unlikely that this variance represents preparation of a motor response. Alternatively, TSF3.4 may be related to response monitoring and trial execution. In other cognitive control tasks such as the Stroop paradigm, a centro-parietal P700-P800 or Slow Positivity has been shown to have higher amplitude in high interference trials compared to low interference trials (Shen et al., 2013; Larson et al., 2009). These studies measured the P700-P800 and Slow Positivity roughly around the time of the mean RT, which may explain why the P700-800 and Slow Positivity occur earlier in these studies compared to the present study. This component has been suggested to reflect performance monitoring and conflict adaptation to upcoming trials (Larson et al., 2009). Therefore, age differences on this temporo-spatial factor may demonstrate that old adults recruited greater neural resources associated with conflict adaptation in non-RN trials compared to young adults, as they found these trials more difficult than young adults. Furthermore, the over-recruitment of this neural activity may have been an attempt to compensate for this general difficulty in old adults.

Further PI effects were found on the factor scores of TSF1.2 (peak latency ~670 ms; see Supplementary Figure 4). In both age groups, non-RN trials produced greater factor scores than RN trials (this difference was localised to the left postcentral gyrus). This suggests that the neural mechanism reflected by TSF1.2 is unaffected by healthy aging. During a Recent Probes task, Zhang and colleagues (2010) found an LPC with similar temporal and spatial characteristics as TSF1.2 to peak between 400-600 ms. This component was prominent at central and parieto-central electrodes. Similar to our findings, Zhang and colleagues found greater LPC amplitude in non-RN than RN trials and suggested that this effect was a neural index of PI. Similarly, Yi and Friedman (2014) found a late positive ERP component to have higher amplitude for low- compared to high-PI probes in a modified Sternberg task, and this modulation of amplitude occurred to the same extent in both young and old adults. Interestingly, the PI effect observed in Yi and Friedman's study was prominent across fronto-central, central and parietal sensors, suggesting a similar topography to the PI effect observed on TSF1.2. However, this positive

component in Yi and Friedman's study was elicited 300 ms later in old than young adults, suggesting that old adults showed a general reduced speed of processing. When temporal PCA was applied to the data of the present study separately in young and old adults (see Supplementary Figures 2 and 3), both age groups showed very similar temporal distributions of the temporal factor corresponding with TSF1.2. Therefore, our results are not in line with those of Yi and Friedman that found increased latency in old adults on an ERP component with similar characteristics to TSF1.2, and therefore we provide no evidence of reduced processing speed in old adults.

The LPC has been previously found to be related to conflict resolution in Stroop tasks as this component has been found to have more positive amplitude in conditions of high conflict than in conditions of low conflict between 550-900 ms at centro-parietal distributions (Coderre et al., 2011; Li et al., 2013; Liotti et al., 2000). However, there is evidence to suggest that the LPC may not necessarily reflect conflict resolution. For instance, West and colleagues (2005) also found an LPC between 600-700 ms at parietal electrodes to be modulated by conditions of high and low conflict in a Stroop task. However, the methodology they employed (partial least-squares analysis) allowed them to see that the magnitude of the positive correlations between the LPC and RTs was the same for conditions of both high and low conflict. Because the ERP component correlated equally with RTs in trials of both conditions, it is unlikely that the LPC indexes the ability to overcome response conflict. West and colleagues therefore argue that the LPC indexes response selection, which would be required for both conditions of high and low conflict.

The LPC has also been previously found to be related to the recollection of contextual information, we argue that TSF1.2 may reflect the employment of this process in order to influence response selection in the face of PI. Danker and colleagues (2008) found an LPC prominent at central electrodes between 500-700 ms to have greater amplitude on correctly recognised old items than on correctly rejected new items in a short-term memory (STM) task, suggesting that the LPC was sensitive to successful recollection. Further, Danker and colleagues suggested that the old/new effect on the LPC in STM is related to the parietal old/new effect found in episodic LTM, which has been suggested to index recollection processes (Curran, 2000). However, the LPC related to the parietal old/new effect in LTM typically has greater amplitude at centro-parietal electrodes for correctly remembered items compared to correctly rejected items (Curran, 2000; Stróżak et al., 2016). However, in the present study, the LPC-like TSF1.2 differentiated trials of high- and low-PI, which are both conditions that require rejection (i.e. a ‘no’ response). Nevertheless, it has previously been suggested that the high familiarity produced by PI-

provoking stimuli produces a response tendency that must be overcome by recollection contextual information (Oberauer, 2005). It may be the case that TSF1.2 represents the recollection of contextual information in order to influence response selection, and if this is the case, this process appears to be preserved in old adults.

It is also noteworthy that Tays and colleagues (2008) found an MFN component with a similar time course (peak between 400-500 ms) to TSF1.2 to be modulated by PI. However, the MFN observed in Tays and colleagues' study produced a negativity at frontal midline electrodes, which was more negative for high PI trials than for low PI trials. Furthermore, in Tays and colleagues' study no such modulation of MFN was found in old adults, suggestive of reduced efficiency of neural activity in healthy aging. Therefore, it is likely that TSF1.2 does not capture the same MFN observed in Tays and colleagues' study, which may be due to methodological differences regarding the percentage of PI-eliciting trials, to which we alluded in the introduction.

Aside from PI effects, there were also age differences regardless of PI condition found on the factor scores of TSF2.1 (peak latency ~260 ms; see Supplementary Figure 5). TSF2.1 differentiated age groups at fronto-central sensors with young adults having more negative factor scores than old adults. This difference was localised to the right medial frontal gyrus, which is a region that has been found to differentiate young and old adults on an item-recognition WM task similar to the one used in the present study, in which old adults performed slower and less accurately than young adults (Rypma, Prabhakaran, Desmond, & Gabrieli, 2001). Taken together with the fact that old participants were generally slower than young adults, TSF2.1 result may support the general difficulty that old adults experienced in the task and reflect a reduced capacity to recruit neural resources for WM processing in this group.

In conclusion, despite not finding greater PI effects in old adults compared to young adults at the behavioural level, we found evidence of a general difficulty in WM processing in old adults that may have been caused by distracting information during encoding of the stimuli. We found evidence at the scalp level that old adults may show reduced efficiency of neural resources that support processing of familiarity during PI resolution. We also found evidence in the TSFs of attempted compensatory recruitment of neural resources in old adults to support performance monitoring and conflict adaption. Furthermore, we found evidence to suggest that the neural mechanisms underlying the recollection of contextual information in order to influence response selection in the face of PI is preserved in healthy aging. Additionally, we failed to find evidence to support previous studies on PI in healthy aging that suggest old adults show reduced processing speed when confronted with PI.

5. Supplementary Results and Discussion

5. 1. Retrieval Phase EEG Activity

5. 1. 1. Block Type Effects and Interactions

A significant main effect of Block Type was found on the factor scores of TSF1.2, $F(1,40) = 46.29$, $p < .001$, $\eta_p^2 = .54$, with higher factor scores in the face block ($M = 0.96$, $SEM = 0.14$) than the scene block ($M = 0.17$, $SEM = 0.14$). The maximally activated source for the difference wave between block types was localised to the left superior frontal gyrus (X = -20, Y = 65, Z = 0). As mentioned in the main text, we argue that we provide evidence to suggest that TSF1.2 is related to the recollection of contextual information during retrieval processes, and that TSF1.2 shares similarities with the LPC observed in other studies. The LPC has also been associated with the recollection of contextual information during the retrieval of faces. Guillaume and Etienne (2015) found an LPC to be modulated by viewing already seen faces and novel faces in an episodic memory task, and therefore suggested that this component reflects the controlled recollection of contextual information related to face stimuli. Although we are unaware of any study reporting the LPC to be modulated by scene stimuli, our data suggests that TSF1.2 reflects the recollection of contextual information, and that its amplitude is modulated by the type of stimulus being retrieved. In the present study, this is demonstrated by face stimuli provoking greater factor scores than scene stimuli.

A significant main effect of Block Type was found on the factor scores of TSF2.2, $F(1,40) = 4.54$, $p = .039$, $\eta_p^2 = .10$, with trials in the face block ($M = -0.29$, $SEM = 0.14$) having less negative factor scores than the scene block ($M = -0.55$, $SEM = 0.15$). The difference wave between blocks has the maximally activated source localised to the Left Inferior Frontal Gyrus (X = -50, Y = 45 Z = -10). Carretie and Iglesias (1995) found differences between neutral faces and landscapes on an N200-P200 complex between 150-250 ms recorded at fronto-central electrodes, and both the N200 and P200 amplitudes were less negative for faces than for scene stimuli, which is consistent with the direction of our results. As we have provided evidence to suggest that TSF2.2 likely reflects processing the familiarity of the probe stimuli, it may be the case that the effect of block type on TSF2.2's factor scores reflect that the familiarity produced by faces is greater than the familiarity produced by scenes.

A significant main effect of Block Type was found on the factor scores of TSF3.2, $F(1,40) = 5.86$, $p = .02$, $\eta_p^2 = .13$, as well as a significant interaction between Block Type and Age Group on the factor scores of TSF3.2, $F(1,40) = 4.30$, $p = .045$, $\eta_p^2 = .10$, with young adults having higher factor scores in

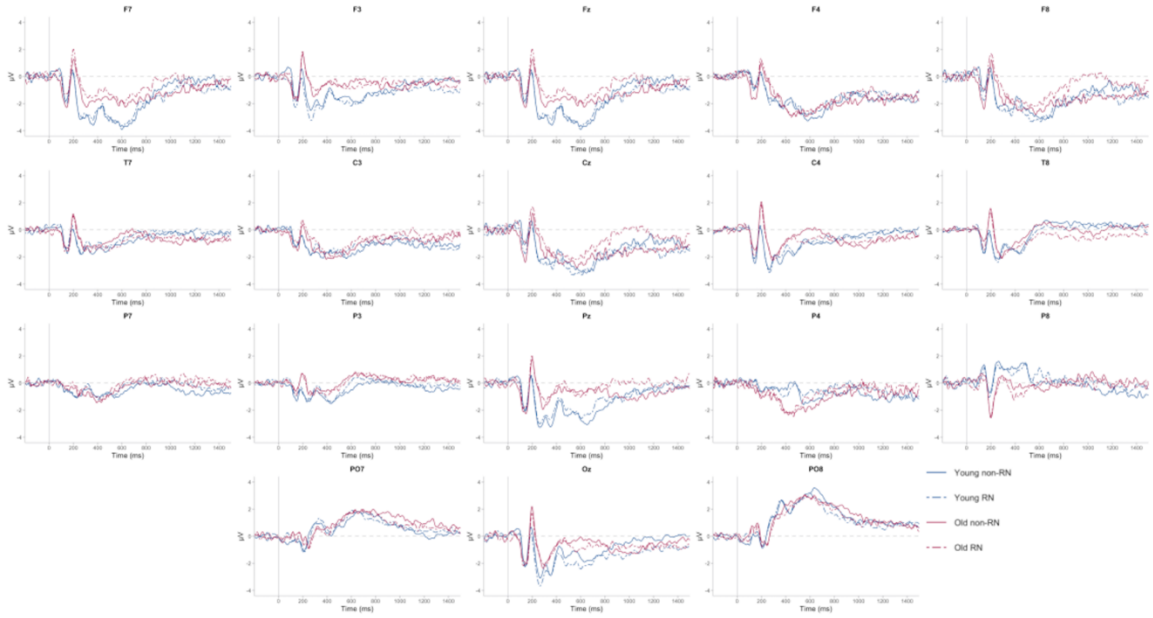
the face block (*M* = .68, *SEM* = .20) compared to the scene block (*M* = .01, *SEM* = .16) (*p* = .001; source of maximal activation localised to the Left Superior Frontal Gyrus [X = -30, Y = 50, Z = -15]); while no sensitivity to the type of stimulus was observed in old adults. It may be the case that TSF3.2 reflects the increased recruitment of neural resources to process face stimuli, suggesting that old adults recruit these neural resources to the same extent for both scene and face stimuli. For instance, in a study with young adults, Eimer and Holmes (2002) found the presentation of neutral faces to elicit a late positive component from 250 to 1000 ms at fronto-central electrodes, with a very similar effect also being produced at fronto-central sensors elsewhere (Wheatley, Weinberg, Looser, Moran, & Hajcak, 2011). However, as far as we know there are no studies showing age differences on this very late positive component. Therefore, future studies are needed in order to shed light on the potential age-related differences in this face processing related component, as highlighted in the current study

5. 2. Encoding Phase EEG Activity

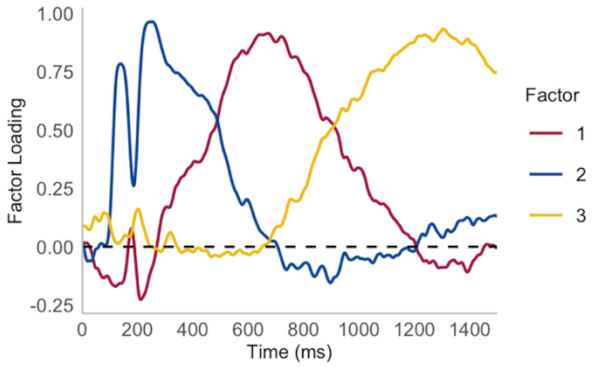
5. 2. 1. Block Type Effects and Interactions

A significant main effect of Block Type was found on TSF1.4.E factor scores, $F(1,40) = 4.94$, $p = .032$, $\eta_p^2 = 0.11$, with factor scores in the face-relevant block (*M* = 0.25, *SD* = 0.16) being greater than in the scene-relevant block (*M* = 0.05, *SD* = 0.15). A significant main effect of Block Type was also found on TSF2.3.E factor scores, $F(1,40) = 8.41$, $p = .006$, $\eta_p^2 = 0.17$, with factor scores in the face block (*M* = -0.37, *SD* = 0.14) being greater than in the scene block (*M* = -0.76, *SD* = 0.16).

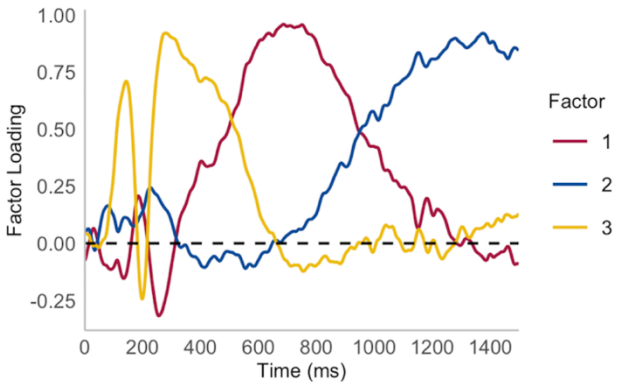
6. Supplementary Figures



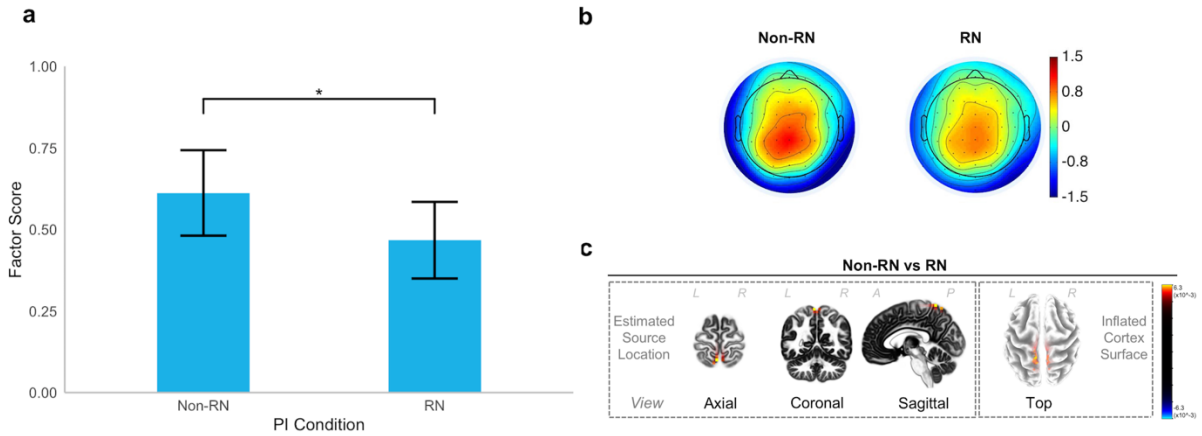
Supplementary Figure 1. Averaged ERP waveforms according to age group (young or old adults) and PI condition (non-RN or RN). ERP waveforms are averaged across face- and scene-relevant blocks at selected electrodes.



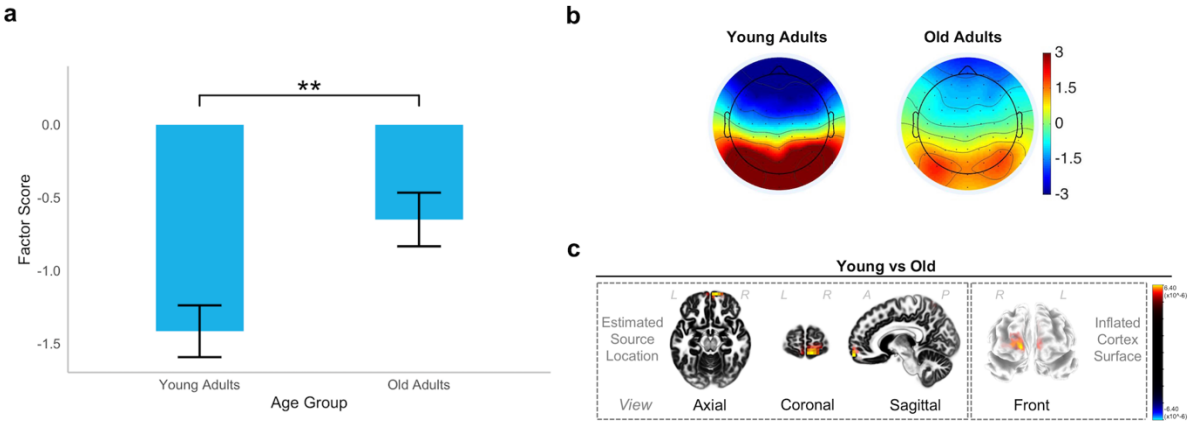
Supplementary Figure 2. Factor loadings of each temporal factor during the retrieval phase of the Recent Probes task in young adults.



Supplementary Figure 3. Factor loadings of each temporal factor during the retrieval phase of the Recent Probes task in old adults.



Supplementary Figure 4. Factor scores across all subjects of temporo-spatial factor 1.2 for each PI condition and source localisation results. Panel ***a*** shows temporo-spatial factor scores for each PI condition (* = $p < .05$), panel ***b*** shows topographical maps of reconstructed voltages of temporo-spatial scores for each PI condition using the equation in Dien and Frishkoff (2005), panel ***c*** shows the localised source of maximal activation of the difference between PI conditions.



Supplementary Figure 5. Factor scores across experimental conditions of temporo-spatial factor 2.1 for each age group and source localisation results. Panel ***a*** shows temporo-spatial factor scores for each age group (** = $p < .01$), panel ***b*** shows topographical maps of reconstructed voltages of temporo-spatial scores for each age group using the equation in Dien and Frishkoff (2005), panel ***c*** shows the localised source of maximal activation of the difference between age groups.

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Chapter IV

Effects of Healthy Aging on Proactive Interference Resolution and the Role of Theta Synchronisation.

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Abstract

Resistance to proactive interference (PI) in working memory declines in healthy aging, although the oscillatory activity associated with these declines is unknown. To advance understanding of this topic, thirty young (18-39 years old) and sixteen old (53-68 years old) adults completed a Recent Probes task while EEG data was recorded. Although old adults were generally slower and less accurate than young adults, the effects of PI on reaction time were greater in young adults than old adults, however this was likely due to a general difficulty that old adults had in the task. Analysis of EEG time-frequency data at the electrode level found young adults to produce greater power in the theta frequency band (4-8 Hz) in conditions of high-PI compared to low-PI, suggesting the possible role of inhibitory control in PI resolution. This is further supported by the greater theta power in high-PI than low-PI trials in parietal and posterior frontal brain regions that was found for young adults in the source level analyses. Old adults did not show such modulation of theta activity, suggesting reduced efficiency of the oscillatory mechanisms supporting cognitive control in healthy aging. Analysis at the electrode and source level also found old adults to produce theta power at frontal and temporal areas to a greater extent than young adults across all PI conditions, suggesting the recruitment of additional brain areas to attempt to compensate for the difficulty they had in the task.

1. Introduction

Healthy aging has been associated with a decline in tasks that require cognitive control. For example, old adults have been previously found to be more susceptible to distractor interference in the Flanker task compared to young adults (Zhu, Zacks, & Slade, 2010). Sweeney et al. (2001) also found reduced ability to inhibit eye movements in old adults in an anti-saccade task. Old adults have also been found to show larger interference effects in the Stroop task compared to young adults (West, 2004). West and Alain (2000) found greater Stroop effects in old adults compared to young adults in reaction time (RT). These authors also found old adults to show reduced amplitude of a positive event-related potential (ERP) component around 300 ms post-stimulus in high conflict trials compared to low conflict trials, suggesting that effects of healthy aging on inhibitory control are also observable at the electrophysiological level.

Another cognitive function that has been found to decline in healthy aging is working memory (WM). WM is the ability to hold and manipulate information in the mind over a short period of time (Baddeley, 2010). It can be argued that it is important to study how WM changes in healthy aging given that it supports other higher order cognitive functions such as fluid intelligence and reasoning (Engle, Laughlin, Tuholski, & Conway, 1999), language comprehension (Daneman & Merikle, 1996), and long-term memory (Park et al., 1996). Park and colleagues (Park et al., 2002) found evidence that WM ability shows a steady linear decline in healthy aging, and that this was observable in both visuospatial and verbal modalities.

It may be the case that the decline of WM ability in healthy aging is in part due to reduced inhibitory control. The multi-component model (Baddeley, 2000; Baddeley & Hitch, 1974) of WM posits that WM consists of a central executive that is served by subsidiary slave systems: the phonological loop, the visuospatial sketchpad and the episodic buffer. According to this model, the central executive is responsible for attending to relevant stimuli in WM and inhibiting the disruptive effect of irrelevant stimuli (Baddeley, 1996). The concept of the central executive in WM is pertinent to cognitive aging, as the inhibitory deficit hypothesis posits that healthy aging is characterised by a decline in the ability to filter out irrelevant information and select relevant information, which has a detrimental effect on cognitive functions such as WM (Hasher & Zacks, 1988).

Gazzaley and colleagues (2005) found evidence to support this hypothesis in a neuroimaging study by observing old adults to be less able to inhibit the processing of irrelevant information in WM compared to young adults. Participants had to either memorise face stimuli and ignore scene stimuli, or

vice versa, during the encoding phase of a WM task. When participants memorised face stimuli there was enhanced activity in a brain area associated with processing faces (i.e. fusiform face area; FFA) compared to a baseline condition. Likewise, when participants memorised scene stimuli there was enhanced activity in a brain area associated with processing scenes (i.e. parahippocampal place area; PPA) compared to the baseline condition. However, despite old adults being equally able as young adults at enhancing activity related to processing relevant stimuli, they were less able to suppress activity related to processing irrelevant stimuli compared to young adults. Furthermore, young adults were significantly more accurate in the task compared to old adults, and the ability to suppress activity was correlated with accuracy in the WM task, suggesting that a reduced ability to inhibit the processing of irrelevant information may underlie reduced WM ability in old age.

Another aspect of cognitive function that has an influence on WM and that requires inhibitory control, is resistance to proactive interference (PI). PI is the disruptive effect of no longer relevant information on current processing in WM (Jonides & Nee, 2006). The Recent Probes task is commonly used to study the effects of item-specific PI in WM (e.g. Jonides et al., 1998). Participants must memorise an array of stimuli (the target set), and a few seconds later are shown an individual stimulus (the probe stimulus) and must decide whether it was present in the target set or not. Trials that produce PI have a probe stimulus that was absent in the target set of the current trial but present in the target set of the previous trial.

Although resistance to PI in WM has been suggested to be an inhibition-related function, it has been found to be distinct from other types of inhibitory control such as resistance to distractor interference and response inhibition (Friedman & Miyake, 2004). Furthermore, there is evidence to suggest that PI is the result of a conflict between item familiarity and context recollection (Oberauer, 2005). According to this account, resistance to PI involves resolving this conflict by inhibiting the high familiarity of the stimulus producing PI or by retrieving the context in which it was seen or heard rather than solely inhibiting representations in WM that are no longer relevant.

Previous research using the Recent Probes task has mainly observed PI effects in young adult samples as longer RT on high-PI trials compared to low-PI trials (D'Esposito, Postle, Jonides, & Smith, 1999), although some studies have found such effects in both RT and accuracy (e.g., Nee, Jonides, & Berman, 2007). PI effects have also been found in young adults' electroencephalogram (EEG) data using the ERP technique. For instance, Zhang and colleagues (2010) observed a Late Positive Component

(LPC) between 400-600 ms to have greater amplitude in low-PI trials compared to high-PI trials at central and centro-parietal electrodes.

PI effects in the Recent Probes task have also been found to be modulated by healthy aging. Jonides and colleagues (1998; 2000) found old adults to show greater PI effects than young adults when taking into account both RT and accuracy. Similarly, Tays and colleagues (2008) also found PI effects on accuracy and RTs in young and old adults. Additionally, these authors also found greater amplitude of a Medial Frontal Negativity (MFN) component between 400-500 ms in high-PI trials compared to low-PI trials in young adults, while this effect was absent in old adults. The lack of modulation of the LPC in young adults, which contrasts with the results of the study by Zhang and colleagues' (2010), together with the absence of MFN modulation in old adults, may be due to methodological differences between studies. In this regard, Tays and colleagues used a higher percentage of PI-inducing trials than previous studies, which may have made participants more aware of the PI manipulation and therefore biased their responses.

Yi and Friedman (2014) also found PI effects in ERP data to change in healthy aging using a directed-forgetting procedure. The authors found the difference in RT between high- and low-PI trials to be greater in old than young adults, and furthermore young adults elicited a positive component between 300-500 ms at fronto-central electrodes, while in old adults a similar component was observed later, between 600-800 ms. Additionally, the authors found the positive component to present higher amplitude for low- compared to high-PI trials in both age groups. This positive component has similar time and spatial characteristics as the LPC found in young adults in the aforementioned study by Zhang and colleagues (2010) that used the Recent Probes task.

However, the nature of PI effects in EEG data in the time-frequency domain remains unknown. As previous research has found inhibitory control to be related to EEG activity in the theta frequency band (4-8 Hz), it may be that PI effects are also detectable at this frequency. For example, rhythmic activity in the theta frequency band at frontal midline electrodes has been suggested to reflect cognitive control (see Cavanagh & Frank, 2014 for a review). This is further supported by a study by Nigbur et al. (2011), in which participants completed three tasks that required different types of cognitive control: resistance to perceptual interference (Flanker task), response inhibition (Go/No-Go task) and conflict resolution (Simon task). In each of these tasks, participants responded slower in trials that required high cognitive control, and these same trials were also characterised by increases in theta synchronisation, with the Go/No-Go task producing the largest effects in the theta synchronisation. Furthermore, greater frontal

midline theta power has also been found in conditions of high conflict compared to low conflict in a Stroop task (Hanslmayr et al., 2008).

Previous research has also found theta activity to be related to cognitive control in WM. For instance, Griesmayr and colleagues (2010) found that when participants had to retain and manipulate information in WM, compared to when they only had to retain information in WM, they showed greater theta synchronisation at frontal and central electrodes. Additionally, increases in theta power at frontal midline electrodes have been found with increases in WM load in an *n*-back task (Gevins, Smith, McEvoy, & Yu, 1997). Hence, it has also been demonstrated that frontal midline theta activity is modulated by WM capacity. Further evidence is provided in a study by Dong and colleagues (2015), in which participants were divided into groups of high and low WM capacity according to performance on a digit span task, and then carried out an n-back task that had conditions of low (1-back) and high (4-back) cognitive load. As expected, low WM participants were generally slower than high WM participants in the n-back task. They also showed reduced frontal theta synchronisation in both conditions of low and high load, suggesting that participants with lower WM capacity are less able to recruit the midline frontal theta activity during WM processing. As old adults have been found to have reduced WM capacity compared to young adults, it may be the case that they also show reduced frontal midline theta activity when processing in WM.

In light of the presented research, we aimed to shed light on how PI effects are expressed in EEG data in the time-frequency domain. Analysing EEG data in the time-frequency domain can reveal the behaviour of neurons that underlie a cognitive process, given that oscillatory activity detected at the scalp is a direct reflection of the neural oscillations occurring in the cortex (Cohen, 2014). Furthermore, we aimed to understand how these effects change in healthy aging and thereby contribute to the literature concerning the neural mechanisms underlying cognitive control in WM in healthy aging. We studied these effects at the behavioural, scalp and cortical level.

At the behavioural level, we expected old adults to show greater PI effects than young adults in performance on a Recent Probes task. At the scalp level we expected conditions of high-PI to be associated with increased frontal midline theta synchronisation, reflecting greater demands of cognitive control in order to overcome PI. We also hypothesised that in conditions of high-PI old adults would recruit less midline frontal theta activity than young adults, reflecting reduced efficiency in the neuronal mechanisms that support cognitive control in healthy aging. Finally, we hypothesised that we would find PI effects in frontal midline theta activity in the anterior cingulate and premotor cortex, given that previous

studies on inhibitory control have localised this activity to these regions (e.g. Hanslmayr et al., 2008; Zhu et al., 2010).

2. Methods

2. 1. Participants

Participants were included in the study if a) they were not currently receiving psychotherapeutic or pharmacological treatment for a psychiatric disorder, and had no history of a psychiatric disorder, and b) they had no major medical or neurological disorder. Participants were also excluded if they had a score lower than 2 SDs from the normal score for their age group given their years of education on a screening measure of mild cognitive impairment (see *Materials* section). Additionally, participants who showed depressive symptoms according to a self-report measure of depression (see *Materials* section) were excluded from the study. Nine participants were excluded in total: two due to self-reported symptoms of depression, one due to taking medication, three due to low performance in the task, two due to artefacts in their EEG data, and one due to missing data. Forty-six participants were included in the present study, 30 of which were young adults between 18 and 39 years old and 16 were old adults between 53 and 68 years old (see Table 3).

	Young Adults	Old Adults
N females	21	9
Age	27.63 (± 7.00)	62.88 (± 3.40)
Years of education	18.87 (± 2.58)	15.94 (± 3.45)
MoCA score	26.69 (± 1.62)	28.28 (± 1.56)

Table 3. Characteristics of participants included in the sample according to age group. MoCA = Montreal Cognitive Assessment. Mean values are presented with standard deviations (within brackets).

Young participants were recruited in return for course credits or via invitation. Old participants were recruited from other projects concerning healthy aging at the University of Minho via invitation. Participants gave full written informed consent and were treated in accordance with the Code of Ethics of the World Medical Association (as stated by the Declaration of Helsinki) regarding experimentation on humans. This study was approved by the Ethics Committee for Life and Health Sciences at the University of Minho (Ref. SECVS 108/2016).

2. 2. Materials

The *Montreal Cognitive Assessment* (MoCA; Nasreddine et al., 2005) was used to screen participants for mild cognitive impairment. The *Beck Depression Inventory II* (BDI-II; Beck, Steer & Brown, 1996) was used to assess young adults' depression symptoms, and the *Geriatric Depression* Scale (GDS; Yesavage et al., 1982) was used to assess old adults' depression symptoms. Participants that had a score higher than the cut-off score on the corresponding depression test were considered to show depressive symptoms and excluded from the analyses. The *Edinburgh Handedness Inventory* assessed participants' handedness (Oldfield, 1971).

2. 3. Cognitive Task

Participants completed a computerised Recent Probes task that contained trials of different levels of PI in order to observe PI effects in response accuracy and RT. Furthermore, participants completed this task while we recorded EEG data in order to observe the electrophysiological correlates of PI. The Recent Probes task was created and run using PsychoPy2 (Peirce, 2007). Since previous research using the Recent Probes task using verbal stimuli have reported main effects of age on performance, we used pictures as memoranda in the Recent Probes task to promote performance in old adults while preserving potential PI effects. This is supported by previous research that has found old adults to perform as well as young adults on memory tasks using images as memoranda (Gutchess, Welsh, Hedden, & Minear, 2005). Furthermore, there is evidence that old adults show improvements in episodic memory recollection when images of scenes (Gutchess, Ieuji, & Federmeier, 2007) and faces (Grady et al., 1995) are used as memoranda. This led us to use both scene and face stimuli as memoranda in the Recent Probes task to ensure that any improvements in performance in the task were not specific to a single type of stimuli. Forty-eight emotionally neutral images of faces were taken from the Karolinska Directed Emotional Faces (KDEF; Lundqvist, Flykt & Öhman, 2004), and 48 emotionally neutral images of scenes were taken from the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert, 2013).

The Recent Probes task was completed in a soundproof cabin. Stimuli were presented on a computer screen in colour on a black background. Each trial started with an array of six images (target set) presented for 2000 ms on the computer screen around a white fixation cross. The target set contained three face stimuli and three scene stimuli. Next, a blank screen with a fixation cross was presented with a delay period that was jittered between 2750-3250 ms across trials (M = 3000 ms). After the delay period the probe stimulus, either a face or a scene stimulus, was presented for 2000 ms in the centre of the screen. A blank screen with a fixation cross was then presented in the centre of the

screen for a jittered duration of 2500-3500 ms (*M* = 3000 ms) until the start of the following trial. The participants were asked to decide whether the probe stimulus matched any stimulus in the target set of the current trial or not. Participants made this decision by pressing one of two keys (i.e. "yes" or "no") on a computer keyboard using their dominant hand.

2. 4. Procedure

Participants completed the task in two blocks of 96 trials. In one block (face-relevant block) the probe stimulus was always a face stimulus, and therefore participants had to only encode face stimuli in the target set. In the other block (scene-relevant block), the probe stimulus was always a scene, and therefore participants had to only encode scene stimuli in the target set. Face and scene stimuli were presented together in the target set to increase the ecological validity of the task. In everyday settings it is likely that when trying to encode memoranda there are other stimuli present that are irrelevant to the task objective. Block order was randomised across participants.

Fifty percent of total trials had a probe that matched a stimulus in the target set of the current trial, and therefore the correct response was "yes" (positive trials). Half of the positive trials had a probe stimulus that also matched a stimulus in the target set of the previous trial (*recent positive* [RP] trials), and the other half of positive trials had a probe stimulus that did not match a stimulus in the target set of any of the previous 6 trials, but may have appeared further back than 6 trials ago (*non-recent positive* [non-RP] trials). Conversely, fifty percent of total trials had a probe that was not present in the target set of the current trial, and therefore the correct response was "no" (negative trials). The negative trials were implemented in the same vein as the positive trials. Half of the negative trials had recent negative (RN) probes, which matched a stimulus presented in the previous trial while the other half had non-recent negative (non-RN) probes, which did not match any stimulus in the target sets of the previous 6 trials, but may have been presented more than 6 trials ago. In all trials the target set had three stimuli (two faces and one scene, or, vice versa) that were also presented in the target set of the previous trial, and three items that were not presented in the previous six trials, to avoid confounding familiarity with PI. PI is measured as the difference between responses to RN trials and non-RN trials.

2. 5. Behavioural Data Analysis

We analysed participants' accuracy (% correct trials) and RTs (time between probe stimulus onset and button press) on non-RN and RN trials as our hypotheses only concerned PI effects and how they are affected by age group. Only RTs from correct trials were analysed. Repeated measures (RM) ANOVAs with the within subjects factors Block Type (face-relevant vs. scene-relevant) and PI Condition (non-RN

vs. RN), and with the between subjects factor Age Group (young vs. old) were run on accuracy and RTs. Greenhouse-Geisser corrections and Bonferroni adjustments were applied where appropriate. We ran independent samples *t*-tests on proportional PI costs (i.e. (RN – non-RN)/non-RN) calculated for each group's RT and accuracy. Participants were excluded from analysis if their behavioural data on any variable of interest had an absolute z-score greater than 3. Alpha level for statistical significance was set at 0.05.

2. 6. Processing of EEG data

EEG data was recorded using an ActiveTwo Biosemi system (Biosemi, Amsterdam, the Netherlands) with 64 active electrodes inserted in an elastic cap according to the international 10-10 system. A Common Mode Sense (CMS) and Driven Right Leg (DRL) montage of two electrodes located over the vertex was used as a reference. Electrode offset was kept below 30 mV. EEG data was filtered online between 0.01-100 Hz and digitized at a sampling rate of 512 Hz. As we were principally interested in investigating the electrophysiological effects of PI and how they change with age, only correctly answered non-RN and RN trials entered EEG analysis.

EEG data was filtered offline using a notch filter at 50 Hz and a phase-shift free IIR Butterworth bandpass filter between 0.1-100 Hz with 12 dB roll-off in ERPLab (Lopez-Calderon & Luck, 2014). Noisy channels were identified and eliminated in EEGLab using the clean raw data plug-in (see Mullen et al., 2015), and immediately after were interpolated using spherical splines. Independent component analysis (ICA) was carried out in EEGLab (Delorme & Makeig, 2004) to remove ocular and muscular components after data rank correction. EEG data was then epoched from -3000 ms pre probe stimulus onset to 2600 ms post probe stimulus onset in order to avoid edge artifacts when calculating time frequency representations (TFRs). Epoched data was separated into four bins according to experimental conditions: block type (face-relevant and scene-relevant) and PI condition (non-RN and RN), resulting in 4 bins of trial epochs. All trials epochs were manually inspected for artefacts and trials containing artefacts were removed from analysis. The average number of trials included in the EEG analysis per participant in the young adult age group averaged across blocks was 43.43 non-RNs (SD = 3.58) and 40.03 RNs (SD = 3.43). The average number of trials included per participant in the old adult age group averaged across blocks was 42.88 non-RNs (SD = 5.74) and 39.81 RNs (SD = 4.89). There was no difference in number of trials between age groups for non-RN trials (t = 0.41, p = .69) or RN trials (t = 0.18, p = .86). The EEG signal was re-referenced to the average of all electrodes. Baseline correction was carried out on each trial epoch using -950 ms to -450 ms before probe stimulus onset as a reference period by subtracting

the mean of baseline period from each time-point in the baseline period and the trial epoch (i.e. 0 to 1000 ms), and then dividing each time-point in the baseline period and the trial epoch by the mean of the baseline period.

Correct negative trial epochs were converted from the time domain to the time-frequency domain. TFRs for each trial were calculated for each participant using Fieldtrip toolbox (http://fieldtrip.fcdonders.nl/) by calculating time-frequency information from 2 to 25 Hz in steps of 0.25 Hz using a Morlet wavelet of 6 cycles. The resultant TFRs were baseline corrected using -950 ms to -450 ms pre probe stimulus onset as the reference. This was done by subtracting the mean of baseline period from each sample (i.e. the EEG data at a given electrode at a given time-point) in the period of interest (i.e. 0 to 1000 ms), and then dividing each sample in the period of interest by the mean of the baseline period. This means that the resultant TFRs contained normalised power values.

2. 7. Analysis of EEG Oscillations at Electrode Level

Partial Least Squares (PLS) analysis was applied to the TFRs to identify the strongest task-related covariance in time, frequency and space in the EEG data using PLScmd toolbox (https://www.rotman-baycrest.on.ca/pls/source). The input matrix for PLS was organised as subject and conditions in the first dimension (i.e. rows) x time points of the trial epoch at each frequency for each electrode in the second dimension (i.e. columns). This input matrix was mean-centered, meaning that the grand-average of each column of the matrix was subtracted from each value in that column. The singular value decomposition (SVD) was then applied to the matrix of means of the input matrix, which is created by calculating the column-wise means of the input matrix. The SVD extracts as many latent variables equal to the rank of the matrix of means, which in this case is four. The SVD results in three types of value that explain the structure of latent variables in the EEG data: singular values, design saliences and electrode saliences. Singular values are a vector of values that each indicate the amount of covariance in the data attributable to a latent variable. Design saliences indicate how a latent variable behaves across task conditions and/or groups. Electrode saliences explain where in time, frequency and space the effects associated with a latent variable are expressed.

Latent variables were considered significant if they showed a significant singular value. Singular values were tested for significance using 10000 permutation tests, which provided the probability of observing the singular value by chance (at an alpha level of 0.05). In other words, singular values were considered significant if less than 5% of the permutation tests produced singular values greater than the observed singular value. In the case of a latent variable with a significant singular value, we first identified

the specific electrodes that showed stable electrode saliences. To that end we used 2000 bootstrap samples of electrode saliences associated with a significant latent variable. Electrode saliences with values greater or lower than 2 standard errors of the bootstrap distribution were considered to be stable. These electrodes were retained to further analyse the nature of the effect expressed by the significant latent variable at the electrode level.

A significant latent variable may show effects of condition or group or their interaction, which are discernible in the design salience values. In the case of significant group effects, independent samples t-tests were carried out that compared the electrode saliences averaged across all retained electrodes at each time-frequency data point between groups, resulting in a t-statistic for each post-stimulus time-frequency data point. In the case of significant condition effects, paired samples t-tests were carried out in the same fashion. In the case of significant interaction effects, paired samples t-tests and independent samples t-tests were used to test for simple effects. The familywise error rate (FWE) of these t-tests was corrected using the maximum statistic approach (Maris, 2004), which was done by carrying out 5000 randomisations of the t-test, and the maximum t-statistic from each randomisation was retained. The 95th quantile of the distribution of the maximum t-statistics gave us a threshold to control for FWE. All observed t-values that surpassed this threshold were considered significant under the null hypothesis.

2. 8. Source Localisation of EEG Oscillations

We subsequently aimed to localise the neuronal generator underlying significant latent variable effects observed at the electrode level. To do so, we identified the contribution of activity throughout the whole cortex to the effects detected at the scalp. Thus, we analysed data at all electrodes and timepoints in the frequency at which the significant effect of a latent variable was observed at the electrode level. As we aimed to estimate the neuronal generator underlying the strongest effects of condition or age group at the sensor level, we localised the cortical source of EEG oscillations at the frequency and time point at which the maximal effect was found at the electrode level. Specifically, we took the maximal t-statistic from the t-tests comparing condition or age effects at the electrode level that survived correction for FWE rate, and the time point and frequency band at which this t-statistic was observed was the subject of source localisation. Furthermore, we only localised effects of condition or group observed at the electrode level if the frequency and time point at which the maximal effect was observed showed a significant difference in power from the baseline period (i.e. -950 to -450 ms pre-stimulus onset) to the post-stimulus period in each age group at the retained electrodes from analysis of the significant latent variable. Specifically, we carried out independent samples t-tests with 5000 randomisations separately for each

age group to compare average baseline power against each post-stimulus sample (i.e. time-frequency data point). We also controlled for FWE in these t-tests using the aforementioned maximum statistic approach.

In order to localise the source of the neural generator underlying effects observed at the scalp, the phase of the EEG data for each participant across all trials was aligned to the phase of the EEG sample (i.e. time-frequency data point) that showed the greatest effect (i.e. the maximal observed t-statistic) at the scalp level. To carry out this phase alignment, phase and amplitude information was extracted from each individual trial for each time point for all electrodes in the frequency at which the maximal effect was observed at the electrode level (Guderian & Düzel, 2005). This was done for each participant by calculating the difference in phase and amplitude between each electrode and the electrode that showed the greatest power across all trials at the time point at which the maximal effect was observed at the electrode level. This was done as there is evidence to suggest that the recollection of memories (Tallon-Baudry & Bertrand, 1999) and cognitive control (Cohen & Donner, 2013) are processes that produce induced oscillatory EEG. As induced activity is not precisely synchronised in time with the onset of a stimulus, it is likely that its phase at a given time point varies across trials. Therefore, when averaging oscillatory activity across trials, the induced part of this activity is attenuated due to trials with jittered phase activity cancelling each other out (Düzel, Neufang, & Heinze, 2005). This cancellation can be overcome by aligning the phase of each trial so that the data of each trial can be better averaged across trials (Guderian & Düzel, 2005). The covariance matrix was then calculated separately for the baseline period and for the post-stimulus period of each trial in the frequency at which the maximal effect was observed at the electrode level. This covariance matrix was then subsequently used to estimate the power of the neuronal generator at each voxel of the cortex. A regularisation parameter of 0.001% was applied to the first singular value obtained from the singular value decomposition of the covariance matrix.

A beamforming approach was adopted to estimate the sources of neural activity. A key assumption of beamforming is that sources of neural activity are not highly correlated in time (Sekihara, Nagarajan, Poeppel, Marantz, & Miyashita, 2002). If this assumption is not met the strength of the sources of activity will be underestimated and the localisation of the source of activity will be somewhere in between the two correlated sources, which would be inaccurate. To overcome this, we applied a dual-core beamforming technique (Diwakar et al., 2011) using the beamforming functions in Fieldtrip to identify the location of pairs of correlated sources of activity in order to suppress them. To identify the

pairs of sources of activity that showed the greatest correlations we ran 1000 searches for pairs of correlated sources of activity in each subject, with each search resulting in one pair of correlated sources. Over the 1000 searches, the pairs of correlated sources that were present in more than 1.5% of the searches and were at least 5 voxels apart were selected to be suppressed. The activity of these pairs of correlated sources of activity was suppressed using a multiple restriction beamformer (Sekihara & Nagarajan, 2006), which creates spatial filters for each voxel in the cortex by taking into account the leadfield matrix for each correlated source of activity in each participant. The leadfield matrix contains information about the conductivity and geometry of the tissues in the head (Weinstein, Zhukov, & Johnson, 2000). The leadfield matrix was made using a boundary element method (BEM) realistic head model of the brain (conductivity = 0.33 S/m), cranium (conductivity = 0.0041 S/m) and scalp (conductivity = 0.33 S/m). The head model was based on a high-resolution MRI image (Colin27) created by the McConnell Brain Imaging Centre at the Montreal Neurological Institute (MNI; Oostenveld, Praamstra, Stegeman, & Van Oosterom, 2001). The leadfield matrix describes the contribution of each voxel (5 x 5 x 5 mm) in the head model to the signal measured at each electrode. After applying the spatial filters to the covariance matrices of each trial we obtained normalised z-score maps of each trial (i.e. at each time point in each trial), which were carried on to statistical analysis.

2. 9. Statistical Analysis of Spatial Maps

To analyse differences in the z-score spatial maps between conditions and groups we carried out hierarchical contrasts to minimise inter-individual variability (Holmes & Friston, 1998). We first ran independent samples t-tests to contrast the z-score spatial maps of the baseline period and the post-stimulus period in each subject. The result of this contrast for each participant was used to contrast conditions or groups. To test for effects of condition we carried out paired samples t-tests, and to test for effects of group we carried out independent samples t-tests. Before carrying out these contrasts, the spatial maps were smoothed with an isotropic Gaussian kernel of 10 mm, as cluster analysis assumes dependency between clusters. The FWE of the p-values produced by these t-tests was controlled via 10000 permutation tests using the Monte Carlo method together with cluster analyses based on the maximum statistic (Nichols & Holmes, 2002). Specifically, each permutation test determines voxels with significant effects and these voxels are grouped into clusters according to proximity and similarity of p-values. Next, the t-values of all voxels included in each cluster are summed. The cluster with the greatest summed value in each permutation forms part of the distribution of values against which we test the significance of the originally observed contrast. The observed contrast is considered significant under the

null hypothesis if its value is greater than the 95th quantile of the distribution of maximum permutation values.

We transformed the coordinates of the voxel that showed the maximum t-statistic in each cluster from MNI to Talairach space (Talairach & Tournoux, 1988) using a nonlinear transformation in Matlab. Cluster voxels were labelled according to the Brodmann Area (BA) atlas included in the WFU Pick Atlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003).

3. Results

3. 1. Accuracy

Results of accuracy for each condition and group are shown in Figure 8. As expected, young adults (M = 93.58, SD = .94) were more accurate than older adults (M = 90.56, SD = 1.29), but the difference did not reach statistical significance $F(1,44) = 3.56$, $p = .07$, $\eta_p^2 = .08$. The repeated measures ANOVA showed a significant main effect of PI condition $F(1,44) = 102.03$, $p = .000$, $\eta_p^2 = .70$ and of block type $F(1,44) = 5.81$, $p = .02$, $\eta_p^2 = .12$. In particular, participants were more accurate in response to non-RN trials (M = 95.77, SD = 0.71) than RN trials (M = 88.37, SD = 1.02), as well as in the scene-relevant block (M = 93.60, SD = .66) than in the face-relevant block (M = 90.54, SD = 1.28). However, these effects were independent of age. No other main or interaction effects were found.

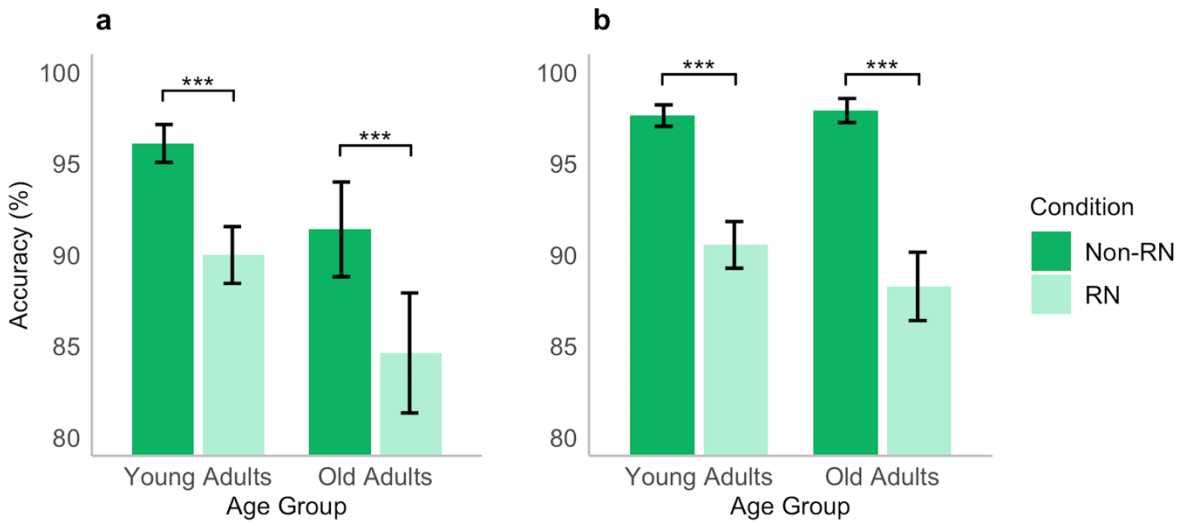


Figure 8. Accuracy per PI Condition (non-RN and RN), separated by Block Type in young and old adults. Panel ***a*** is accuracy in the face-relevant block, and panel ***b*** is accuracy in the scene-relevant block. *** = $p < .001$.

3. 2. Reaction Time

RT results in each condition and group are presented in Figure 9. As expected, non-RN trials (M = 1010.63, SD = 23.46) were responded to significantly faster than RN trials (M = 1135.39, SD = 24.26), $F(1,44) = 119.96$, $p = .000$, $\eta_p^2 = .73$. Young adults (M = 966.26, SD = 27.28) showed significantly shorter RT on all trials compared to old adults (M = 1179.76, SD = 37.35), $F(1,44) = 21.31$, $p = .000$,

η_p^2 = .33. Block Type was found to significantly interact with PI condition, $F(1,44) = 33.51$, $p < .001$, η_p^2 = .43, such that non-RN trials (*M* RT in face-relevant block = 1046.03, SD = 31.03; *M* RT in scene-relevant block = 975.23, SD = 20.13) had shorter RT than RN trials (*M* RT in face-relevant block = 1122.78, SD = 31.10; *M* RT in scene-relevant block = 1148.00, SD = 24.67) in both the face-relevant ($p < .001$) and scene-relevant ($p < .001$) blocks, while non-RN trials had longer RT in the face-relevant block compared to the scene-relevant block ($p = .004$). No other significant main or interaction effects were found.

Additionally, an independent samples t-test showed young adults to have greater proportional PI RT costs than old adults, $t(44) = 3.49$, $p = .001$, Cohen's $d = 1.10$.

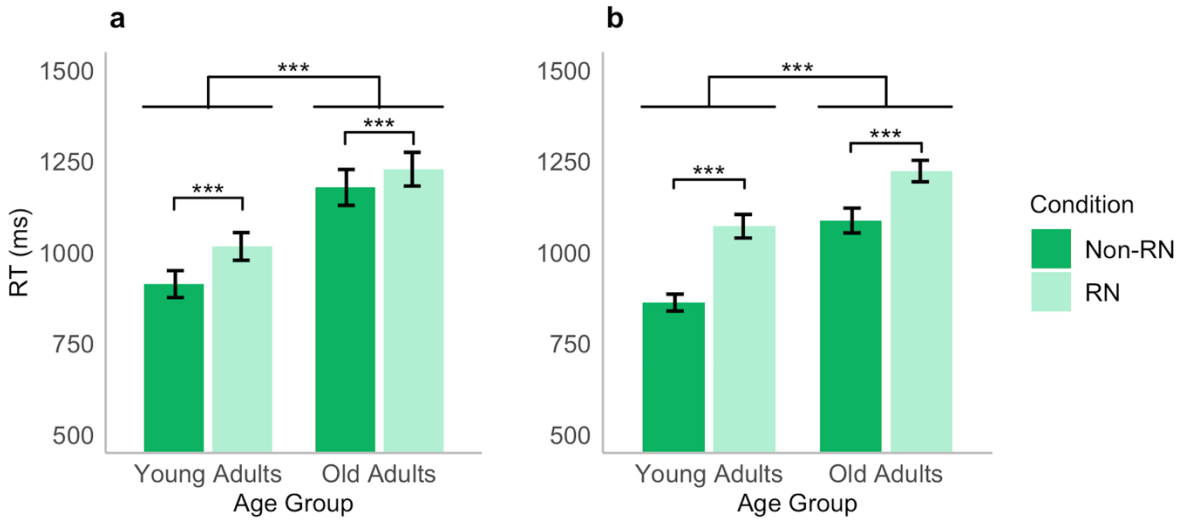


Figure 9. Reaction time (RT) per PI Condition (non-RN and RN), separated by Block Type in young and old adults. Panel ***a*** is RT in the face-relevant block, and panel ***b*** is RT in the scene-relevant block. *** = $p < .001$

3. 3. EEG Oscillations at Electrode Level

PLS analysis revealed one significant latent variable (p < .001) that explained 49.89% of task-related variance in the EEG data. The design and electrode saliences showed that this latent variable represented an interaction effect between Age Group and PI condition between 400-850 ms in the theta frequency band range (4-8 Hz) at frontal (AFz, AF4, Fz, F2) fronto-central (FCz, FC1, FC2, FC3, FC4), central (C2), parieto-occipital (PO3, PO4, PO8) parietal (P8) and occipital (O1) sites. Post-hoc t-tests

revealed greater theta (6.75 Hz) synchronisation on RN trials compared to non-RN trials only in the young adult group between 350-850 ms post-stimulus onset. Greater theta (~5 Hz) synchronisation was observed in older adults compared to young adults in the non-RN condition between 0 and 250 ms post-stimulus onset, although the maximum effects occurred later in the epoch between 600 and 1000 ms at a lower frequency of 3.75 Hz. Additionally, greater theta (5.5 Hz) synchronisation was observed in old adults compared to young adults in the RN condition at 0 to 250 ms post-stimulus onset. As the post-stimulus period showed significant increases of theta power compared to the baseline period at 5.5 Hz but not at 6.75 Hz, we localised the source of oscillatory activity at the frequency corresponding with the maximum effect of age on RN trials in the time window in which it occurred (i.e. 5.5 Hz between 0 and 500 ms post-stimulus; see Figure 10).

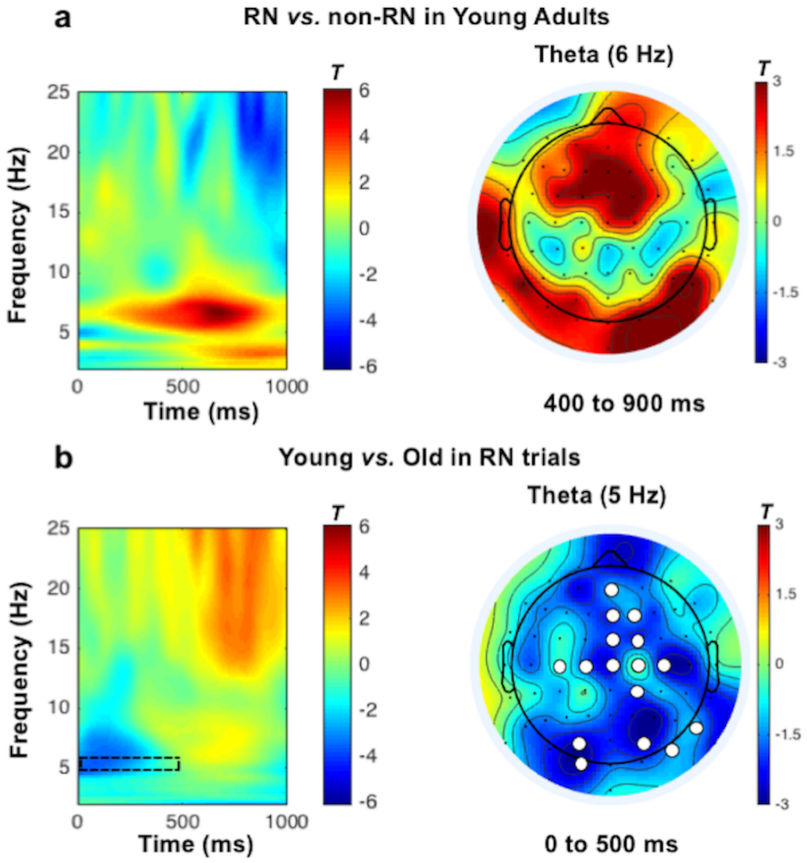


Figure 10. Differences in power between conditions and groups. Panel ***a*** shows differences in power between RN trials and non-RN trials in the young adult age group. The topographic map on the right side of the panel shows differences between conditions averaged across the window of 400 to 900 ms post-stimulus onset in the theta (6 Hz) frequency band. Panel ***b*** shows differences in power between young

and old adults on RN trials. The topographic map on the right side of the panel shows differences between groups averaged across the window of 0 to 500 ms post-stimulus onset in the theta (5 Hz) frequency band. The electrodes highlighted by white dots on the right side of the panel are the electrodes selected for source level analysis, while the black dashed box in the left side of the panel is the time-frequency window in which source level analysis was conducted.

3. 4. Oscillations at Source Level

Results derived from analyses at the source level are shown in Figure 11. Old adults showed greater theta power than young adults in a cluster in the right hemisphere that spanned temporal and frontal areas as well as the right insula and anterior cingulate across both conditions of PI (statistical results are shown in Table 4). Old adults were also found to show greater theta power on non-RN trials compared to RN trials in a cluster that spanned the bilateral cingulate gyrus and left middle and medial frontal regions. Young adults showed greater theta power on RN trials compared to non-RN trials in clusters in the left parietal lobe, right frontal lobe and left cingulate gyrus, although these effects did not survive correction for multiple comparisons. Young adults also showed greater theta power on non-RN trials compared to RN trials in a cluster in the right hemisphere spanning temporal and frontal areas as well as the anterior cingulate gyrus and the parahippocampal gyrus. However, these effects also did not survive correction for multiple comparisons.

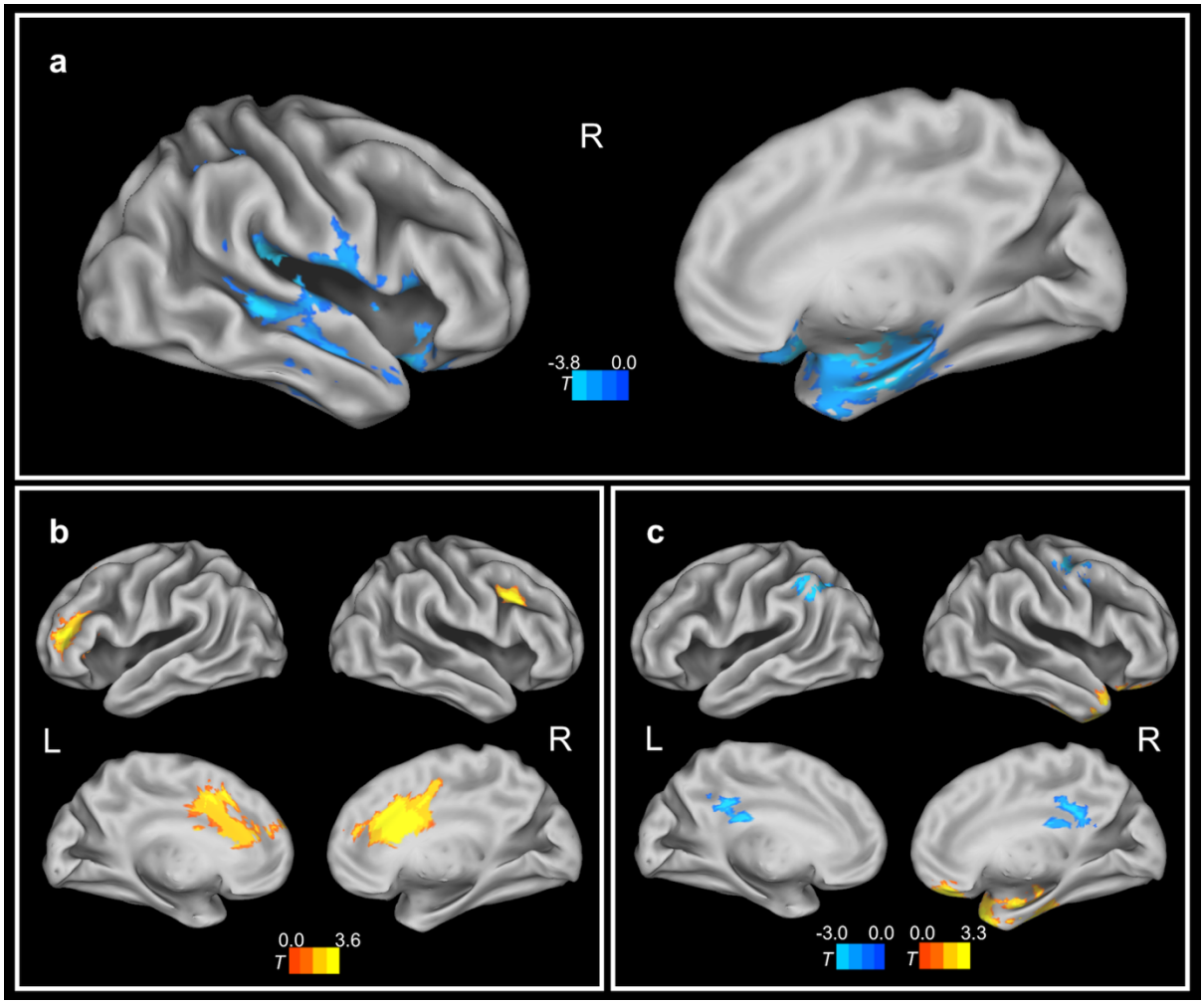


Figure 11. Cortical regions showing effects of condition and group during the Recent Probes task in the theta (5 Hz) frequency band. Panel ***a*** shows the main effect of age group (blue colours show where old adults showed greater theta power compared to young adults), panel ***b*** shows the simple effect of condition within old adults (yellow colours show where non-RN trials produced greater theta power compared to RN trials) and panel ***c*** shows the simple effects of condition within young adults (blue colours show where RN produced greater theta power than non-RN trials and yellow colours show where non-RN trials produced greater theta power than RN trials). The values presented in this figure are *t* values. Panels ***a*** and ***b*** were corrected for multiple comparisons, while panel ***c*** shows uncorrected effects. L = left hemisphere, R = right hemisphere.

Contrast	*k*	$p_{cluster}$	Brain Region	BA	Coordinates X	Y	Z	*t*
Old adults > young adults	528	0.049*	Right trans. temporal gyrus	41	40	-33	13	-3.99
			Right postcentral gyrus	3	59	-11	20	-2.88
			Right insula	13	45	-43	18	-2.70
			Right precuneus	7	21	-50	39	-2.54
			Right anterior cingulate	25	4	1	-2	-2.30
			Right precentral gyrus	6	59	-13	38	-2.28
			Right middle temporal gyrus	21	55	-23	-3	-2.26
RN > non-RN in young adults	52	< .001	Left inferior parietal lobule	40	-48	-60	41	-2.72
	35	< .001	Right precentral gyrus	4	35	-14	51	-3.04
			Right postcentral gyrus	3	40	-24	55	-2.46
	28	< .001	Left cingulate gyrus	31	-2	45	30	-2.46
Non-RN > RN in young adults	207	< .001	Right superior temporal gyrus	38	32	12	-27	3.66
			Right anterior cingulate	32	9	35	-12	3.18
			Right inferior frontal gyrus	47	32	17	-22	3.15
			Right parahippocampal gyrus	-	32	-12	-21	2.91
			Right medial frontal gyrus	25	13	21	-18	2.65
Non-RN > RN in old adults	491	0.049*	Right cingulate gyrus	24	17	-3	38	4.42
			Left cingulate gyrus	24	-11	1	47	4.18
			Left middle frontal gyrus	46	-38	32	18	4.13
			Left medial frontal gyrus	6	-15	5	48	3.94

Table 4. Cortical regions showing main effects of group and simple effects of condition within age groups during the proactive interference task in the theta (5.5 Hz) frequency band. BA = Brodmann Area. *k* =

cluster size in voxels. Coordinates are in Talairach space. *t* = *t*-statistic at source level. * = *family-wise error rate corrected.*

4. Discussion

The present study aimed to characterise PI effects in time-frequency domain EEG data and how these effects change in healthy aging.

PI effects were found in the behavioural performance of all participants, which was observed in both RTs and response accuracy. Contrary to what was hypothesised, we found young adults to show larger PI costs in RT compared to old adults. Previous research has generally found greater behavioural PI effects in old adults compared to young adults (Jonides et al., 2000; Loosli, Rahm, Unterrainer, Weiller, & Kaller, 2014; Loosli et al., 2016; Oberauer, 2001; Yi & Friedman, 2014), demonstrating a reduced ability to inhibit the disruptive effects of irrelevant information in WM in healthy aging. However, we argue that our findings do not contradict this account. In the present study, old adults were generally slower than young adults in both conditions of high and low-PI, and were equally slow in both conditions, whereas young adults were generally faster than old adults but relatively slower on high-PI trials compared to low-PI trials, therefore showing greater differences in RT between PI conditions. We argue that these effects were observed because old adults generally found the task more difficult than young adults did and were therefore operating close to full cognitive capacity even in the low-PI condition.

We found one latent variable in the time-frequency EEG data that showed PI effects to interact with age at frontal, central, parietal and occipital sites of the scalp. Young adults showed greater theta power at these sites between 400 and 900 ms in RN compared to non-RN trials, supporting our hypothesis that conditions of high-PI are related to greater theta activity compared to conditions of low-PI. No such modulation of theta activity was found in old adults at the electrode level. Interestingly, however, old adults showed greater theta power compared to young adults at the electrode level in both conditions of low and high-PI.

Unexpectedly, old adults produced greater theta power than young adults in both RN and non-RN trials. These age differences in theta activity at the electrode level were distributed across the scalp and were therefore not limited to frontal midline electrodes. This is not in line with previous research that has found decreased theta power - predominantly at frontal midline electrodes - in old adults compared to young adults in a Sternberg item recognition WM task (Cummins & Finnigan, 2007), during the retention period of a delayed match to sample WM task (Kardos, Tóth, Boha, File, & Molnár, 2014) and in a visuospatial STM task (Rondina, Olsen, Li, Meltzer, & Ryan, 2019). Furthermore, although old adults produced greater theta power than young adults in both PI conditions, old adults failed to show differences in theta power between PI conditions. A similar pattern of effects has previously been found

in a study by Gazzaley and colleagues (2008); who found that during the encoding phase of a WM task presenting either relevant or irrelevant stimuli, old adults produced greater frontal midline theta power compared to young adults when faced with both relevant and irrelevant stimuli. Furthermore, while young adults showed greater theta power for irrelevant stimuli compared to relevant stimuli, old adults showed no such modulation of theta activity. Gazzaley and colleagues observed these effects during the encoding phase of a WM task rather than the retrieval phase, suggesting that any similarities between their results and ours would be due to the effects of age on inhibiting the disruptive effects of irrelevant information rather than on memory processes such as encoding or retrieval. Furthermore, Gazzaley and colleagues interpreted this greater recruitment of frontal midline theta in old adults as compensation for the general greater difficulty they had in the task compared to young adults. We argue that a similar interpretation is applicable to the findings of the present study.

The aforementioned pattern of between group differences is in line with theories of cognitive aging, such as the Scaffolding Theory of Cognitive Aging (STAC; Park & Reuter-Lorenz, 2009), which posits that old adults recruit neural resources to a greater extent than young adults in order to compensate for reduced efficiency of brain areas. It may be the case that increased recruitment of theta power at the electrode level in old adults reflects an attempt to compensate for the reduced specificity old adults showed between non-RN and RN trials. In other words, old adults showed reduced efficiency of the neural structures supporting cognitive control, leading them to over-recruit theta power to compensate for this deficit even in relatively low cognitive demand conditions. However, it must be noted that this activity likely represents *attempted* compensatory activity, as old adults were generally slower in all conditions of the cognitive task compared to young adults (Cabeza et al., 2018). Nonetheless, this is evidence to suggest that the neural mechanisms underlying cognitive control of WM contents are less efficient in healthy aging.

At the source level, old adults produced theta power across frontal and temporal brain regions in the right hemisphere to a greater extent than young adults across all PI conditions. We argue that this is further evidence of attempted compensatory neural activity in old adults. This pattern of activity has been previously observed in a study by Callaghan, Holland and Kessler (2018), who had young and older adults complete a switching task with conditions of low and high cost. These authors found old adults to produce greater theta activity in frontal and temporal brain areas compared to young adults in all conditions of their attention switching task, suggestive of over-recruitment of neural resources to overcome a general difficulty in the cognitive task. Therefore, it may be the case that the greater

recruitment of theta power in frontal and temporal areas in old adults in the present study also reflects attempted compensatory neural activity for the general difficulty they found in the task compared to young adults. This is also in line with predictions made by the STAC theory of cognitive aging.

Although old adults failed to show modulation of theta activity across PI conditions at the electrode level, they did show such modulation at the source level, although in the opposite direction to that which we hypothesised. Specifically, old adults were found to produce greater theta power in non-RN trials compared to RN trials in bilateral frontal brain areas and did not show any effects in the opposite direction in any brain region. The aforementioned study by Callaghan and colleagues (2018) also found old adults to produce greater theta power at the source level in conditions of low attention switching costs compared to conditions of high switching costs, although this only occurred in occipital regions and was only found in the young-old adult group (40-49 years) and not in the oldest age group (60+ years). It may be the case that the observed pattern of results in old adults at the source level in the present study is further evidence of unsuccessful compensatory recruitment of theta activity in frontal regions. Old adults may have already been operating at close to full cognitive capacity on non-RNs and therefore over-recruited theta power in these frontal regions to compensate for this difficulty, and that this compensatory activity was ineffective in conditions of greater cognitive load in RN trials.

In line with our hypotheses, young adults produced greater theta power at frontal electrodes for RN trials compared to non-RN trials. This difference occurred between 400 and 900 ms post probe stimulus presentation. This supports previous research that has found conditions that require greater cognitive control to produce enhanced synchronisation in the theta frequency band at frontal midline electrodes (e.g. Griesmayr et al., 2010; Nigbur et al., 2011). Furthermore, we argue that this is evidence that an inhibitory mechanism is implemented to overcome PI in WM. PI has been suggested to be the result of a conflict between competing response biases caused by the high familiarity of RN probes and the recollection of contextual information (Oberauer, 2005). Although we do not provide direct evidence of how this conflict is overcome, the finding that conditions of high-PI produce enhanced theta power at frontal electrodes supports the claim that the resistance to PI involves inhibitory control, whether it be the inhibition of familiarity or of irrelevant representations in WM.

However, previous research has generally found enhanced theta power with increasing cognitive control demands at frontal midline sensors (Cavanagh & Frank, 2014), whereas the present study found these effects to manifest themselves differently in terms of its scalp distribution. The present study supports previous research on the role of frontal midline theta in inhibitory control as increases in

theta power were found at frontal midline sensors, but this was also the case at parietal and occipital sensors. Interestingly, in addition to PI effects at the electrode level, young adults were also found to produce theta power to a greater extent in RN trials compared to non-RN trials in clusters in parietal areas of the left hemisphere and posterior frontal areas of the right hemisphere. This is in line with the aforementioned study by Callaghan and colleagues (2018) that found evidence of increased theta power in parietal regions in young adults in conditions of high attention switching costs. Further, this supports the idea that theta power in this region is associated with executive control.

Contrary to our hypotheses, young adults also showed differences in theta power at the source level in the opposite direction. Young adults were found to produce theta power to a greater extent in non-RN trials compared to RN trials in right medial temporal brain areas extending from the anterior frontal cortex to parahippocampal areas. The medial temporal lobe has been suggested to be involved in recognition and familiarity-based processing in long-term memory, and that this involvement is supported by oscillatory activity in the theta band (Ketz, Jensen, & O'Reilly, 2015). Additionally, a study by Luckhoo and colleagues (2012) found theta power produced during a 2-back WM task to be localised to the hippocampus, although this theta power was found during the whole trial epoch, making it difficult to discern during which part of WM processing this hippocampal theta activity was prominent. In sum, it may be the case that the greater theta power seen in young adults in the right medial temporal regions in non-RN trials compared to RN trials reflects uninterrupted memory retrieval processes, and that these processes in right medial temporal regions are somehow disrupted under conditions of high-PI.

In conclusion, at the behavioural level, young adults were found to show greater PI effects compared to old adults, although this was likely due to the general difficulty that old adults had in the task, which subsequently masked PI effects in the old age group. Analysis at the electrode level found old adults to produce greater theta power compared to young adults in both conditions of high and low-PI, suggesting attempted compensatory recruitment of theta activity for the general greater difficulty old adults had in the task compared to young adults. Old adults were also unable to modulate theta activity between PI conditions, suggesting reduced efficiency of the neural structures supporting cognitive control. At the source level, old adults produced widespread theta power across frontal and temporal brain regions to a greater extent than young adults across all PI conditions, suggesting the recruitment of additional brain areas to attempt to compensate for the difficulty they had in the task. Young adults showed greater theta power at the electrode level in RN trials compared to non-RNs trials as well as at the source level in parietal and posterior frontal brain regions, indicative of the potential role of inhibitory

control in PI resolution. However, both groups showed instances of greater theta power in non-RN trials compared to RN trials at the source level that must be explored more comprehensively with further research.

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Chapter V

Neural Correlates of Proactive Interference in Healthy Aging and their Relationship with Working Memory

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Abstract

The present study aimed to understand how proactive interference (PI) effects change in healthy aging and how these changes are influenced by working memory (WM) ability. Seventeen young (20-35 years) and fifteen old (55-76 years) healthy adults completed a Recent Probes task while fMRI data was recorded. PI reaction time (RT) costs were greater in young than old adults. Also, regardless of age, participants with greater WM ability showed greater PI costs in RT. A network of frontal and parietal brain regions were sensitive to PI, all of which showed greater activation in conditions of high-PI compared to low-PI. We found age differences in PI effects in the left precentral gyrus and supplementary motor area that may indicate age differences in biasing response selection and error monitoring when overcoming PI, and these effects were not due to WM ability. Furthermore, age differences in visual brain areas may indicate that, depending on WM ability, aging affects the retrieval of visual information in the face of PI.

1. Introduction

Cognitive theories of aging posit that as we get older our ability to resist interference from irrelevant information causes a decline in cognitive functions, such as Working Memory (WM; Hasher and Zacks, 1988), which is the ability to maintain and manipulate a few items in memory over a short period of time (Baddeley, 2010).

One extensively studied interference effect in WM is proactive interference (PI), which is the disruptive effect of no longer relevant information on current processing (Jonides & Nee, 2006). According to dual process accounts of memory recognition (Yonelinas, 2002), item specific PI in WM is caused by a conflict between item familiarity and context recollection (Oberauer, 2005). For instance, in the Recent Probes task, participants encode a small group of items and maintain them in memory over a brief period of time. They are then presented with a probe stimulus and must decide whether it matches one of the encoded items or not. The probe stimuli that create the most PI do not match any encoded items in the current trial but do match an item encoded in the previous trial. According to dual process theories high-interference probes cause PI due to a conflict between the stimulus' high familiarity and the recollection of the context in which it was encoded (Jonides & Nee, 2006).

PI effects in the Recent Probes task are generally observed as longer reaction times (RT) on high-PI compared to low-PI trials (D'Esposito, Postle, Jonides, & Smith, 1999), with studies also reporting PI effects in both RTs and response accuracy (e.g., Nee et al., 2007). Neuroimaging studies have observed PI effects as the difference in brain activity between conditions of high- and low-PI. fMRI studies using the Recent Probes task have consistently observed the left inferior frontal gyrus (IFG) and left ventrolateral prefrontal cortex (VLPFC) (e.g., Badre & Wagner, 2005; Nee et al., 2007) to show greater activation for high-PI trials compared to low-PI trials. It has been suggested that the left IFG aids the resolution of PI by selecting among competing responses (Jonides & Nee, 2006). However, Nee and co-workers (2007) found the left IFG to distinguish between recent and non-recent positive trials in this paradigm, neither of which involve conflict among competing responses. These authors therefore argue that the left IFG supports the selection of contextual features during memory retrieval. Other studies have also reported sensitivity to PI effects in other frontal and parietal regions such as the right frontopolar cortex, right VLPFC (Badre & Wagner, 2005), right middle frontal gyrus (MFG), right anterior intraparietal sulcus, right precuneus (Mecklinger, Weber, Gunter, & Engle, 2003), insula, left frontal superior medial gyrus (SMG) and left pre-supplementary motor area (pre-SMA; Loosli et al., 2016).

There is evidence that PI effects are altered in healthy aging. For instance, Jonides and colleagues (1998; 2000) found greater PI effects in response accuracy and RT in old than young adults in a Recent Probes task. Loosli and colleagues (2014; 2016) only found greater PI effects in old adults' accuracy compared to young adults in Recent Probes task, while Yi and Friedman (2014) found greater PI effects only in RT in old and not young adults in a directed forgetting task. Age differences in PI effects have also been found in neuroimaging studies. Previous work has found PI effects in the left IFG in old adults, although to a lesser extent than in young adults (Jonides et al., 2000; Loosli et al., 2016). Loosli and colleagues (2016) found evidence of decreased PI effects in healthy aging in other brain areas, with old adults showing smaller differences between high- and low-PI conditions in the right IFG, left insula, and left frontal SMG when compared to young adults. No other studies have found age differences in PI effects in these brain areas. Additionally, Loosli and co-workers (2016) pair-wise matched young and old adults according to WM ability. These authors found that when young and old adults were matched on WM ability, the latter still showed greater PI effects than young adults at the behavioural level, but reduced PI effects at the neural level.

However, the Recent Probes task employed in Loosli and colleagues' (2016) study may have created high item non-specific PI throughout the task due to the relatively small pool of stimuli used. Therefore, as participants were matched based on their performance in low-PI trials, it may be the case that they were matched based on WM ability as well as the ability to overcome item non-specific PI. The present study aimed to build on Loosli and colleagues' findings to understand how PI effects change in healthy aging and how these changes are influenced by WM ability. To that end, a larger pool of stimuli was used to create an exaggerated manipulation of item-specific PI while minimising item non-specific PI. Additionally, by disentangling WM ability from PI effects, we aimed to differentiate regions sensitive to age-related changes in PI effects from regions sensitive to age-related changes in WM ability. Based on previous evidence we expect old adults to show greater PI effects than young adults at the behavioural level as well as reduced PI effects in brain activity in frontal brain areas (bilateral IFG, left frontal SMG) and the left insula.

2. Methods

2. 1. Participants

Sample size was determined by an *a priori* power analysis calculated using G*Power 3.1 (Faul et al., 2007). Using a medium-to-large effect size of $\eta p^2 = 0.10$ (from Loosli et al., 2016), alpha = 0.05, and 4 measurements for a repeated measures ANOVA with between and within subject interaction effects, power analysis yielded a total sample of 36 subjects for 80% statistical power. Consequently 42 participants were invited to take part into the study via a course credit exchange system for participation in studies at University of Minho or via invitation. Before completing the study, participants were screened for exclusion criteria: a) history of or current psychiatric disorder, and b) major medical or neurological disorder. Further, they completed the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) to screen general cognitive functioning. Three participants were excluded as their MoCa score exceeded 2 standard deviations of the normative score for their age and education level. Similarly, to measure depressive symptoms, the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) was used for young adults, and the Geriatric Depression Scale (GDS; Yesavage et al., 1982) for old adults. One participant was excluded given his depression score exceeded respective cut-off scores for moderate depression. Additionally, the Edinburgh Handedness Inventory (EDI; Oldfield, 1971) assessed participants' handedness.

The selected 38 participants completed the entire study, which protocols were in accordance with the principles stated in the Declaration of Helsinki concerning experimentation on humans. Further, these protocols were approved by the local Ethics Committee for Life and Health Science (Ref. SECVS 108/2016). During behavioural and fMRI data processing, one participant was excluded due to excessive head movements and five participants were excluded due to outlying behavioural data (z-score greater than 3 or lower than -3 on at least one variable); and, therefore, a total of 32 right-handed healthy adults were included in the statistical analysis which maintain enough power to detect medium to large effects. These participants were divided into a group of 17 young (20-35 years, 10 females; see Table 5. for sample characteristics) and 15 old adults (55-76 years, 9 females).

	Young Adults	Old Adults
Age	27.3 (± 4.3)	66.1 (± 5.7)
Years of education	16.4 (± 2.9)	12.3 (± 6.1)
MoCA	28.1 (± 1.3)	25.7 (± 3.3)
Handedness	78.0 (± 22.2)	85.5 (± 20.1)

Table 5. Characteristics of participants included in the sample according to age group. Mean values are presented with standard deviations (within brackets). MoCA = Montreal Cognitive Assessment. Handedness was measured by the Edinburgh Handedness Inventory.

2. 2. Experimental Procedure

The Recent Probes task was created using PsychoPy (Peirce, 2007). Images of both faces and scenes were used to ensure any effects were not specific to the type of visual stimuli. Face stimuli were 48 images (24 female faces) of forward-facing emotionally neutral faces from the Karolinska Directed Emotional Faces (KDEF; Lundqvist, Flykt, & Öhman, 1998). Scene stimuli were 48 emotionally neutral images of scenes from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005).

Participants completed the task in an MRI scanner. Stimuli were presented on a screen in colour on a black background, which participants viewed via a mirror mounted onto the head coil. Each trial began with the presentation of an array of six images (target set) around a white fixation cross for 2000 ms (see Figure 12). The target set comprised three images of faces and three images of scenes; two faces and one scene above the fixation cross and two scenes and one face below, or vice versa. After a short delay period of 3000 ms, a probe stimulus was presented in the centre of the screen for 2000 ms, which was an image of either a single face or a single scene. Afterwards a white fixation cross was presented in the centre of the screen for a duration jittered between 2000 and 14000 ms, until the beginning of the following trial. The randomised order of jittered fixation periods throughout the task was optimised using Optseq2 in order to control for the overlap in hemodynamic response function estimates between trials.

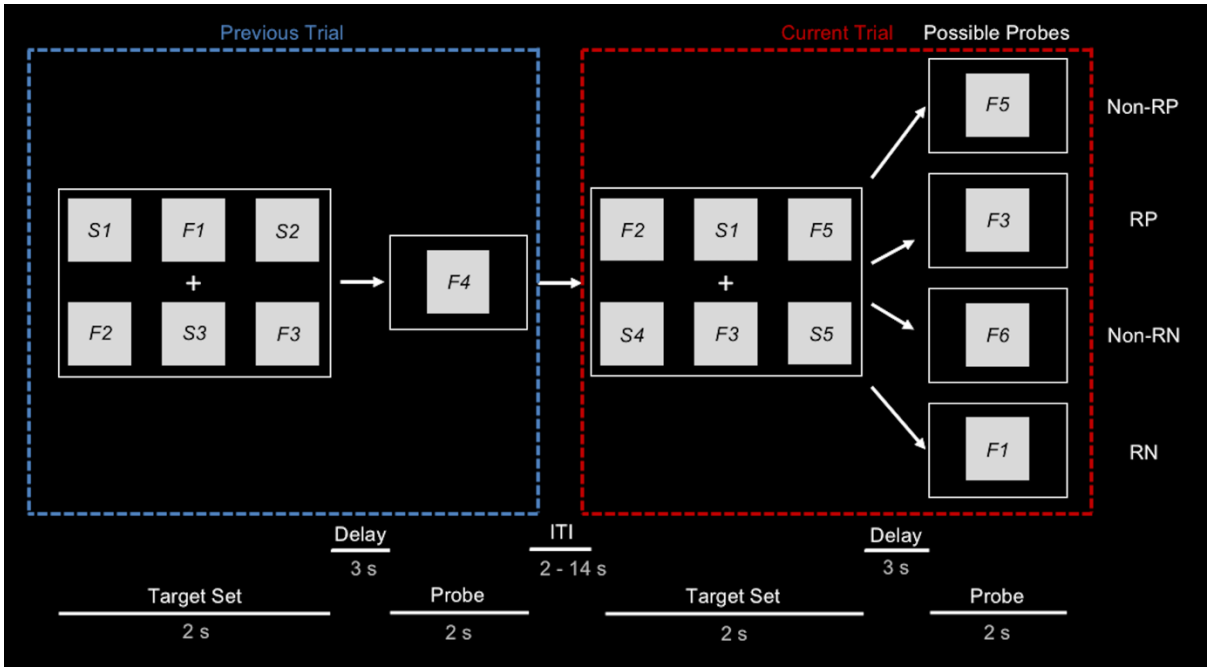


Figure 12. Recent Probes task. This scheme depicts two trials from the face-relevant block. S = scene stimulus, F = face stimulus. ITI = inter-trial interval. Non-RP = Non-Recent Positive, RP = Recent Positive, Non-RN = Non-Recent Negative, RN = Recent Negative.

The task had two blocks of 80 trials, each with a duration of approximately 16 minutes. In one of the blocks the probe was always a face, and participants were instructed to memorise only the face stimuli in the target set. In the other block, the probe stimulus was always a scene, and participants were told to memorise only the scenes in the target set. Face and scene stimuli were presented together in the target set to increase the ecological validity of the task. The order of completion of the blocks was randomly counterbalanced across participants.

Participants had to decide whether the probe stimulus matched any stimulus present in the target set of the current trial or not by pressing a button for 'yes' or 'no' on a Cedrus Lumina response pad (Cedrus®, model LP-3B). Participants responded with their right hand. The buttons corresponding to 'yes' and 'no' were counter-balanced across participants. Participants were encouraged to respond as quickly and as accurately as possible. Fifty percent of trials had a probe matching a stimulus in the target set of the current trial (positive probes), and 50% of trials did not (negative probes). Fifty percent of positive probes also matched a stimulus in the target set of the previous trial (recent positive [RP] probes), while the other 50% of positive probes did not match a stimulus in the target sets of the previous 6 trials (non-recent positive [Non-RP] probes). Conversely, 50% of negative probes matched a stimulus in the

target set of the previous trial (recent negative [RN] probes), and 50% of negative probes did not match a stimulus in the target set of the previous 6 trials (non-recent negative [Non-RN] probes). PI was measured as the difference between RN and Non-RN trials. The presentation of target set and probe stimuli was pseudo-random. In all trials the target set had three stimuli (two faces and one scene, or, vice versa) that were also presented in the target set of the previous trial, and three items that were not presented in the previous six trials, to avoid confounding familiarity with PI.

2. 3. Behavioural Data Analysis

Participants' accuracy (percentage of correctly responded trials) and reaction time (RT; the time between probe stimulus presentation and response) were measured for correct Non-RN and RN trials. Repeated measures (RM) ANOVAs – within subjects factors Block Type (face-relevant vs. scene-relevant) and PI Condition (Non-RN vs. RN), between subjects factor Age Group (young vs. old) – were carried out on accuracy and RT. Greenhouse-Geisser corrections were applied when appropriate. We also analysed correlations between WM ability (the average accuracy in non-recent trials across both blocks) and PI costs (i.e. (RN – Non-RN)/Non-RN) in RT and accuracy. PI costs in RT and accuracy were calculated as proportional differences in order to take into account between-group differences in baseline (low interference) trials.

2. 4. fMRI Data Acquisition

Structural and functional images were acquired using a Siemens Magnetron TrioTrim 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. The following parameters were used in the magnetized prepared rapid acquisition gradient echo (MPRAGE) sequence to acquire high-resolution 3D T1*weighted structural images: Repetition time (TR) = 2700 ms, echo time (TE) = 2.33 ms, flip angle = 7°, slice thickness = 0.8 mm, in-plane resolution = 0.8 x 0.8 mm, field of view (FoV) = 256 mm. 240 slices were acquired in the structural volume. The T2*weighted echo-planar imaging sequence for functional images had the following parameters: slice thickness = 3 mm, gap between slices = 0.75 mm, acquisition matrix = 74 x 74, in-plane resolution = 3 x 3 mm, FoV = 222 mm, TR = 2000 ms, TE = 29 ms, echo spacing = 0.6 ms, flip angle 90°. There were 39 interleaved transversal slices per volume, and 515 volumes per block of trials.

2. 5. fMRI Data Analysis

2. 5. 1. Processing of the fMRI Data

fMRI pre-processing was performed using SPM12. fMRI volumes were realigned using a rigid body transformation with 6 parameters: x, y and z rotations and x, y and z translations. Participants' structural images was nonlinearly transformed into Montreal Neurological Institute (MNI) space. Images were smoothed with a Gaussian kernel with a Full Width at Half Maximum of 8 x 8 x 8 mm. Volumes with head movements greater than 1.5 mm along x, y or z axis were interpolated.

2. 5. 2. GLM Analysis

A general linear model (GLM) was applied to the fMRI time series. The following events of interest were entered into the first-level model as regressors: onset of the target set, delay period, probe stimulus onset of correct trials (4 conditions), probe stimulus onset of incorrect/missed trials and null trials. This resulted in one estimate for each of the 7 regressors, which along with 6 motion parameters that were entered as nuisance regressors resulted in the first-level model. Trials from each Block Type were treated as separate sessions. The estimate of the BOLD signal was carried out on the first-level model, resulting in a beta value image per regressor. Beta value contrast images were created by contrasting each PI condition regressor estimate against the null trials regressor estimate. Contrast images for correct Non-RN and RN trials were submitted to second-level analysis.

Second-level analysis was done using a flexible-factorial model using GLM FLEX (http://mrtools.mgh.harvard.edu). This model accounted for variance due to subjects, PI Condition, Block Type and Age Group, as well as their interactions. First, we carried out a whole brain analysis to identify brain regions sensitive to PI Condition. Seven clusters were sensitive to PI Condition when applying a voxel-wise false discovery rate (vFDR) correction of alpha = 0.05 and an extent threshold of 50 voxels. We then created regions of interest (ROI) for each cluster of voxels sensitive to PI Condition. ROIs were created using MarsBar (Brett et al., 2002) as spheres of 6 mm radius centred on the peak *t* value in each cluster of voxels sensitive to PI. As the largest cluster spanned a considerable number of voxels, two ROIs were created, each centred on one of the top two largest peak *t*values. This resulted in a total of 8 ROIs. We then looked for main effects of Age Group, and interactions between Age Group, PI Condition and Block Type within each ROI, carrying out a small volume correction (SVC) for each analysis. The SVC was done using vFDR of alpha = 0.05 and extent threshold of 5 voxels. In the case of significant interaction effects for any given ROI, we subsequently carried out post-hoc simple contrasts within the voxels that showed significant interaction effects within that ROI. SVC was carried out for post-hoc contrasts using vFDR of alpha = 0.05 and extent threshold of 5 voxels. Main effects or interactions with Block Type are reported in the Supplementary Material.

2. 5. 3. Brain-Behaviour Correlation Analysis

In order to understand how neural activity in the ROIs related to participants' performance in the task, Pearson correlations were carried out between PI RT costs and fMRI data PI effects, and between WM ability scores and fMRI data PI effects. The latter were not analysed in the pairwise-matched sample. fMRI data PI effects were calculated as the subtracted difference between the mean adjusted beta values on RN trials and Non-RN trials collapsed across blocks. These mean adjusted beta values were calculated from all voxels in a given ROI. In the case of significant correlations, correlations were also carried out separately on each age group, and the resultant coefficients compared between groups using Fisher Z transformations.

2. 5. 4. Analysis of Multivariate-Matched Subsample

To analyse the contribution of WM to age-related differences in PI effects at the behavioural and neural level, we pairwise matched participants' WM ability (average accuracy in non-recent trials), on which we repeated the behavioural and fMRI analyses. fMRI analyses on the matched sample were carried out in the PI-sensitive ROIs identified in the whole sample. Participants were matched on gender, within-group age variance (in the form of z-scores) and WM ability. The matching procedure was based on their estimated propensity scores, which were estimated using a logistic regression model, with gender, within-group age variance and WM ability as covariates. The logit of the propensity scores were submitted to 1:1 multivariate matching without replacement using the Matching package (Sekhon, 2011) in R (R Core Team, 2017). Balance was tested using the bootstrapped Kolmogorov-Smirnov test with 1000 bootstrap samples (see Table 6). The matched sample consisted of 8 young (*M* age = 27.38, *SD* age = 4.66) and 8 old adults (*M* age = 66.25, *SD* = 5.34). As an additional analysis, we ran the same analysis on behavioural and fMRI data comparing the old adults that were matched with young adults (*N* = 8) against the remaining unmatched old adults (*N* = 7). Results of these analyses are presented in the Supplementary Material.

		Before Matching	After Matching
Gender	Old adults *N* females	9	5
	Young adults *N* females	10	5
Age	Old adults *M*	< .01	0.03
	Young adults *M*	< .01	0.02
	SMD	< .01	1.43
	K-S *p*-value	0.45	0.92
WM	Old adults *M*	74.5	78.13
	Young adults *M*	86.44	77.66
	SMD	-146.44	6.91
	K-S *p*-value	0.01	0.89

Table 6. Balance testing of participants scores on variables before and after the matching procedure. *SMD* = standard mean difference. K-S = Kolmogorov-Smirnov test. WM = Working Memory ability scores.

3. Results

3. 1. Behavioural Results

Accuracy and RT results are shown in Figure 13. A RM ANOVA on accuracy showed a main effect of PI Condition, $F(1,30) = 53.93$, $p < .001$, $\eta_p^2 = .64$: Non-RN trials ($M = 92.12$, $SD = 1.48$) were answered more accurately than RN trials ($M = 81.02$, $SD = 2.42$). There was a main effect of Age Group, $F(1,30) = 16.61$, $p < .001$, $\eta_p^2 = .15$: young adults ($M = 90.81$, $SD = 2.55$) had greater accuracy than old adults ($M = 82.33$, $SD = 2.71$). There was also a main effect of Block Type, $F(1,30) = 15.67$, $p < .001$, $\eta_p^2 = .34$: scene-relevant trials ($M = 90.32$, $SD = 1.55$) had greater accuracy than face-relevant trials ($M = 82.82$, $SD = 2.51$). We found no significant interaction effects on accuracy.

A RM-ANOVA on participants' RT showed a main effect of PI Condition, $F(1,30) = 16.61$, $p < .001$, $\eta_p^2 = .36$, which showed Non-RN trials ($M = 1167.50$, $SD = 42.32$) to have shorter RTs than RN trials ($M = 1248.33$, $SD = 35.28$). We also observed a main effect of Age Group, $F(1,30) = 20.23$, $p < .001$, $\eta_p^2 = .40$: old adults ($M = 1377.36$, $SD = 54.92$) generally had longer RTs than young adults ($M = 1038.47$, $SD = 51.59$). Furthermore, PI Condition significantly interacted with Age Group, $F(1,30) = 4.55$, $p = .04$, $\eta_p^2 = .13$: old adults (Non-RN: $M = 1358.09$, $SD = 57.95$; RN: $M = 1396.62$, $SD = 51.42$) had longer RTs than young adults (Non-RN: $M = 976.09$, $SD = 57.95$; RN: $M = 1100.03$, $SD = 48.30$) on both Non-RNs and RNs. Additionally, young adults had shorter RTs on Non-RNs ($M = 976.09$, $SD = 57.95$) than RNs ($M = 1100.03$, $SD = 48.30$), meaning that PI effects were only observed in young adults. We also observed a significant interaction between Block Type and PI Condition, $F(1,30) = 5.95$, $p = .02$, $\eta_p^2 = .17$: Non-RNs (face-relevant $M = 1194.10$, $SD = 51.85$; scene-relevant $M = 1140.90$, $SD = 39.24$) had shorter RTs than RNs (face-relevant $M = 1242.39$, $SD = 38.14$; Scene-relevant: $M = 1254.27$, $SD = 37.80$) in the scene-relevant block. WM ability scores were positively correlated with PI RT costs across participants, $r = .47$, $p = .007$. This correlation was not significant when calculated separately for each age group. PI RT costs did not significantly correlate with PI accuracy costs.

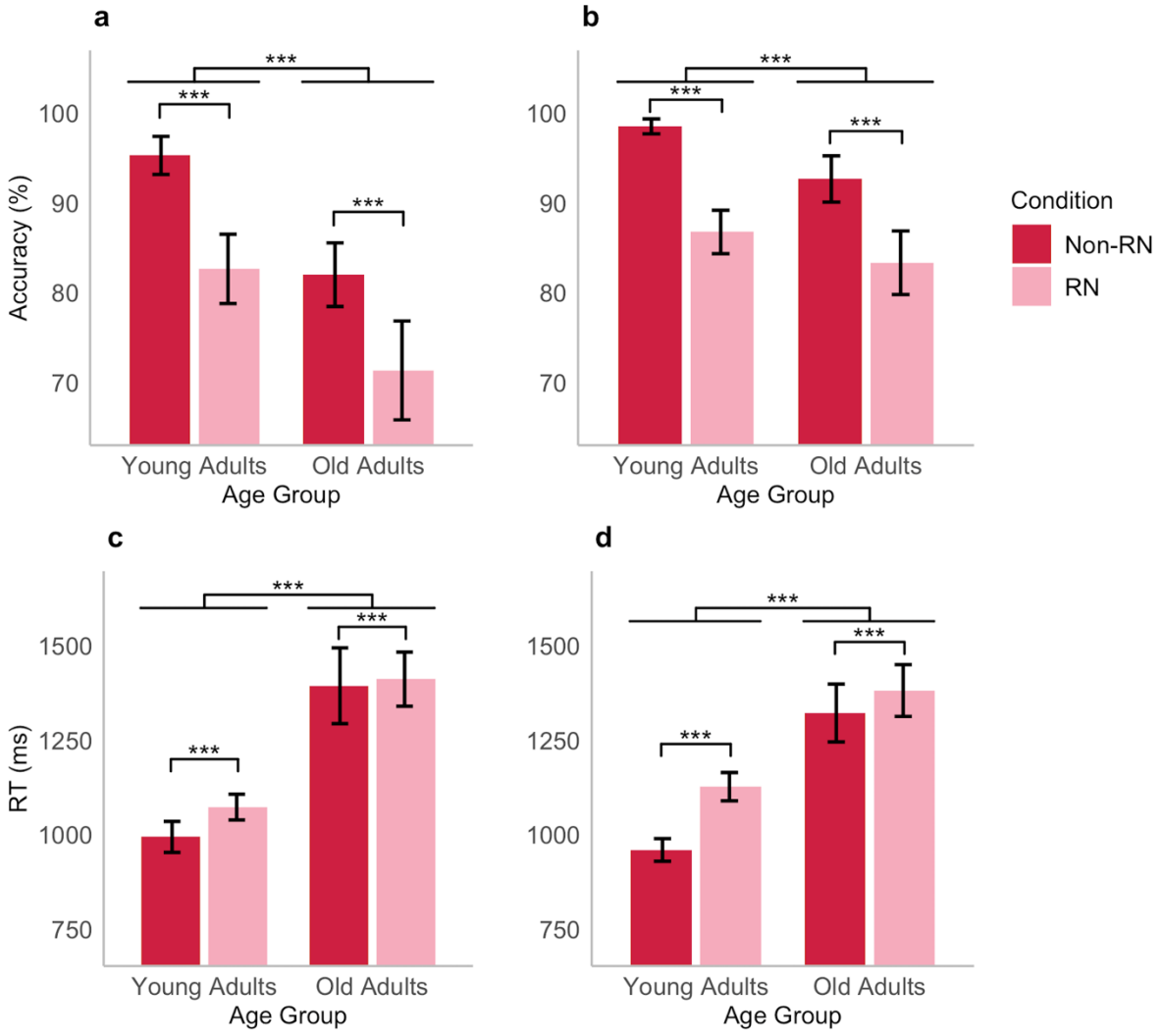


Figure 13. Accuracy and RT for young and old adults in each PI Condition (non-RN and RN) separated by Block Type. Panel *a* is accuracy in the face-relevant block, panel *b* is accuracy in the scene-relevant block, panel *c* is RT in the face-relevant block and panel *d* is RT in the scene-relevant block. *** = $p <$ .001

3. 2. fMRI Results

A RM-ANOVA conducted on the whole brain using a vFDR of 0.05 and extent threshold of 50 voxels revealed a significant main effect of PI condition in 7 clusters (see Figure 14), which showed peak intensities in the left precentral gyrus, left SMA, left calcarine sulcus, left inferior parietal lobule (IPL), right angular gyrus, right lingual gyrus and right MFG (see Table 7). RN trials had greater activity than Non-RN trials in all of these clusters. Significant interaction effects between Age Group and PI Condition were found in 3 ROIs centred on the peak intensities of these clusters: left precentral Gyrus, left SMA

and left calcarine sulcus (see Table 8). Post-hoc contrasts (see Supplementary Table 1) revealed that in left precentral gyrus, young adults showed greater activation than old adults in both PI conditions, as well as greater activation in RN compared to Non-RN trials. Additionally, young adults showed greater activation than old adults for RN trials in left SMA, as well as greater activation in RN trials compared to Non-RN trials. Old adults showed greater activation than young adults in both Non-RN and RN trials in the left calcarine sulcus, although young adults showed greater activation on RN trials than on Non-RN trials. No main effects of Age Group were found in any ROI.

Significant interaction effects between Age Group, PI Condition and Block Type were found in the ROI centred on left IPL. Details are presented in Supplementary Material (Supplementary Tables 2 and 3).

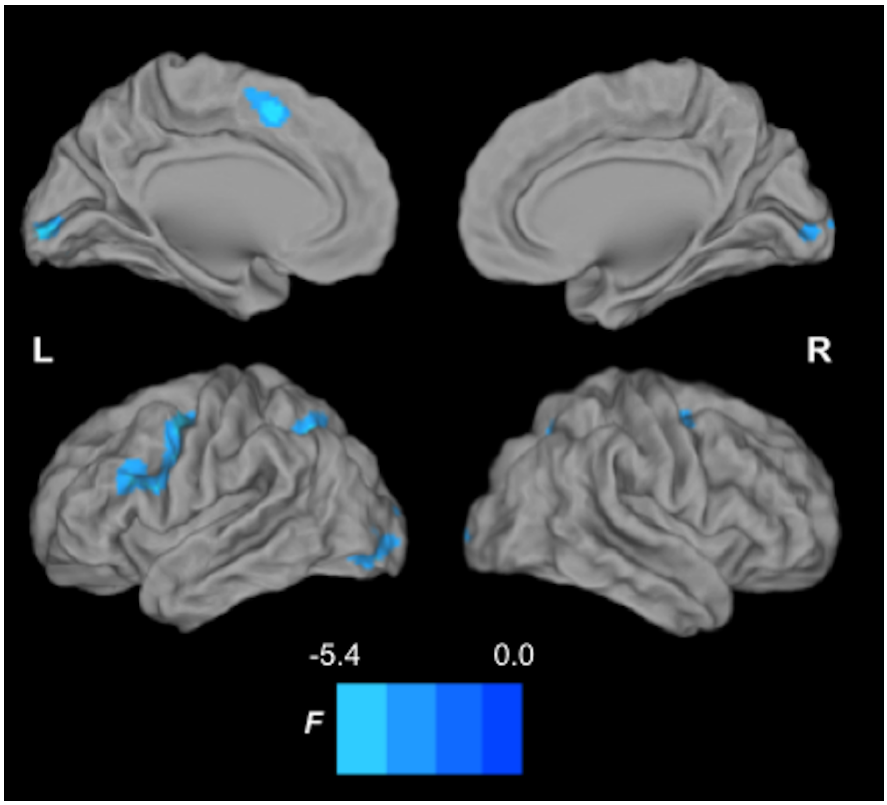


Figure 14. Voxels that showed significant main effects of PI condition across the whole brain. Voxel-wise false discovery rate was maintained at 0.05, with an extent threshold of 50 voxels. L = left hemisphere, R = right hemisphere.

			MNI Coordinates			
Region	**k**	***t***	**X**	**Y**	**Z**	***p***
Left Precentral Gyrus	1510	-5.43	-40	0	54	0.025
Left Middle Frontal Gyrus	1510	-4.87	-52	14	36	0.025
Left Supplementary Motor Area	271	-5.01	-6	14	52	0.025
Left Calcarine Sulcus	841	-4.83	-8	-94	-4	0.025
Left Inferior Parietal Lobule	721	-4.50	30	-58	48	0.025
Right Angular Gyrus	142	-4.17	28	-58	44	0.025
Right Lingual Gyrus	299	-3.97	24	-82	-8	0.026
Right Middle Frontal Gyrus	78	-3.94	30	0	54	0.026

Table 7. Brain regions that showed main effects of PI condition. Peak intensities for each region. k = cluster size. *t*-values are peak intensities. *P*-values are adjusted by voxel-wise false discovery rate correction. Note that the first two regions are part of the same cluster.

			MNI Coordinates			
ROI	**k**	***F***	**X**	**Y**	**Z**	***p***
Left Precentral Gyrus	71	16.61	-38	4	52	0.003
Left Supplementary Motor Area	123	16.46	-4	18	56	0.01
Left Calcarine Sulcus	89	16.93	-4	-94	-4	0.007

Table 8. Brain regions within regions of interest (ROI) that showed interaction effects between Age Group and PI Condition. k = cluster size. *F* = peak *F* value. *p*-values are adjusted by voxel-wise false discovery rate correction.

3. 3. Brain-Behaviour Relationship in Whole Sample

Significant positive correlations between fMRI data PI effects and PI RT costs (see Figure 15) were observed across all participants in the left MFG ($r = .35$, $p = .047$), left SMA ($r = 0.51$, $p = .003$), left calcarine sulcus ($r = .46$, $p = .008$), left IPL ($r = .43$, $p = .014$) and right MFG ($r = .39$, $p = .026$). A significant positive correlation was also found in the left precentral gyrus across all participants, $r = .63$, $p < .001$, although when calculated separately for each age group this correlation was only significant in young adults ($r = .61$, $p = .009$). There were, however, no differences between age groups' correlation coefficients. No significant correlations were found in the other ROIs.

Significant positive correlations were found between fMRI data PI effects and WM ability scores (see Figure 16) in the left precentral gyrus ($r = .48$, $p = .006$), left calcarine sulcus ($r = .57$, $p = .001$) and right MFG ($r = .35$, $p = .049$). There were no differences between age groups' correlation coefficients.

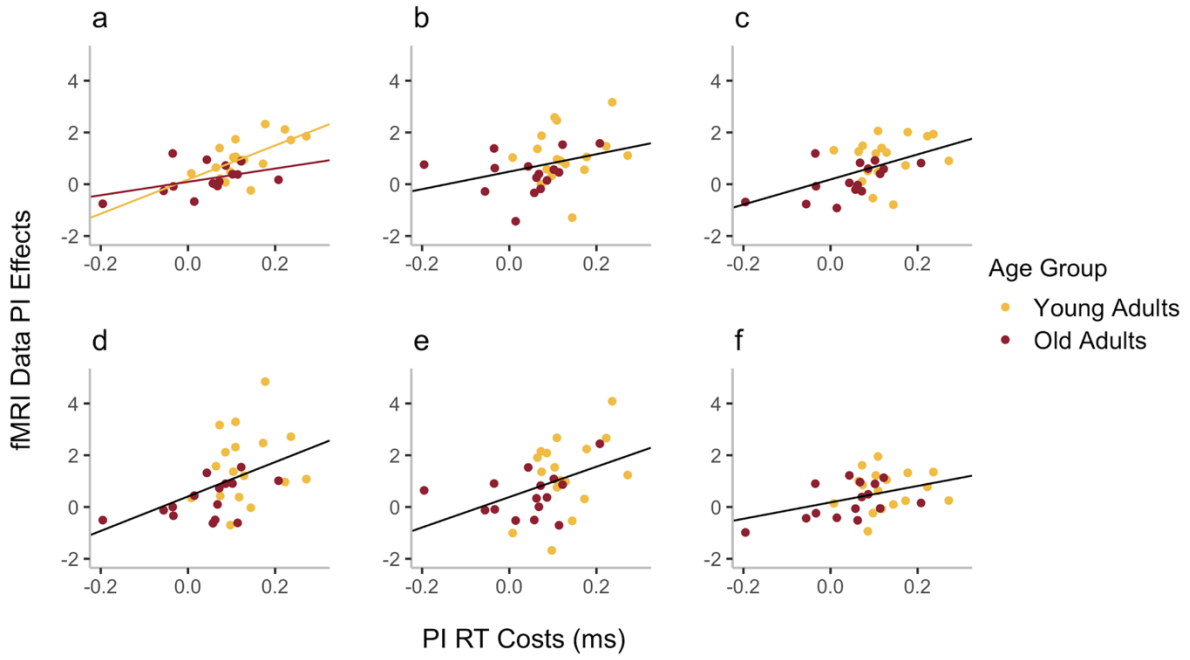


Figure 15. Significant correlations between fMRI data PI effects and PI RT costs. In the case of significant correlations only in one age group, regression lines are drawn per group. Letters correspond with ROIs: a = left Precentral Gyrus, b = left MFG, c = left SMA, d = left Calcarine Sulcus, e = left IPL, f = right MFG.

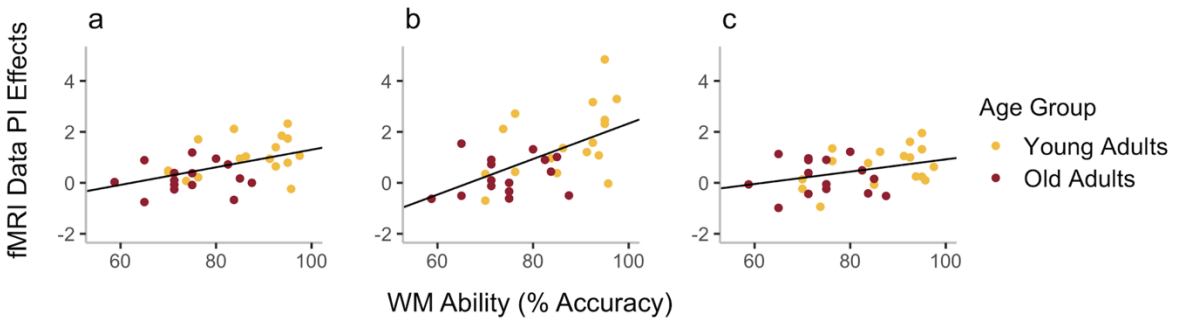


Figure 16. Significant correlations between fMRI data PI effects and WM ability scores. Letters correspond with ROIs: a = left Precentral Gyrus, b = left Calcarine Sulcus, c = right MFG.

3. 4. Results in Pairwise-Matched Subsample

A RM ANOVA on RTs showed a main effect of PI Condition $F(1,14) = 16.74$, $p = .001$, $\eta_p^2 = .55$: Non-RN trials ($M = 1096.39$; $SD = 34.94$) had shorter RTs compared to RNs ($M = 1178.42$; $SD = 34.45$). There was also a main effect of Age Group, $F(1,14) = 13.49$, $p = .003$, $\eta_p^2 = .49$: young adults had shorter RTs ($M = 1015.43$; $SD = 46.98$) than old adults ($M = 1259.38$; $SD = 46.98$). There were no main effects of Block Type or interactions between PI Condition, Age Group and Block Type.

A RM-ANOVA showed a significant interaction between Age Group and PI Condition in left precentral gyrus, left MFG and left SMA (see Supplementary Table 4). Post-hoc contrasts (see Supplementary Table 5) showed that in both left precentral gyrus and left SMA young adults had greater activation than old adults on RN trials, and young adults showed greater activation on RN than on Non-RN trials. In left MFG, young adults showed greater activation than old adults in both Non-RN and RN trials. Further, in left MFG young adults showed greater activation on RN compared to Non-RN trials. No main effects of Age Group were found for any ROI.

Significant positive correlations between fMRI data PI effects and PI RT costs (see Figure 17) were found in the left calcarine sulcus ($r = .56$, $p = .023$), left IPL ($r = .74$, $p = .001$), right lingual gyrus ($r = .58$, $p = .019$) and left MFG ($r = .65$, $p = .006$). Significant positive correlations were also found across all matched participants in the left SMA ($r = .67$, $p = .005$), right angular gyrus ($r = .66$, $p = .005$) and in left precentral gyrus ($r = .71$, $p = .002$). However, when calculated separately for each age group only old adults showed significant positive correlations in the left SMA ($r = .74$, $p = .037$) and right angular gyrus ($r = .83$, $p = .010$), while only young adults showed a significant positive correlation in left precentral gyrus ($r = .86$, $p = .006$). None of these correlation coefficients significantly differed between age groups.

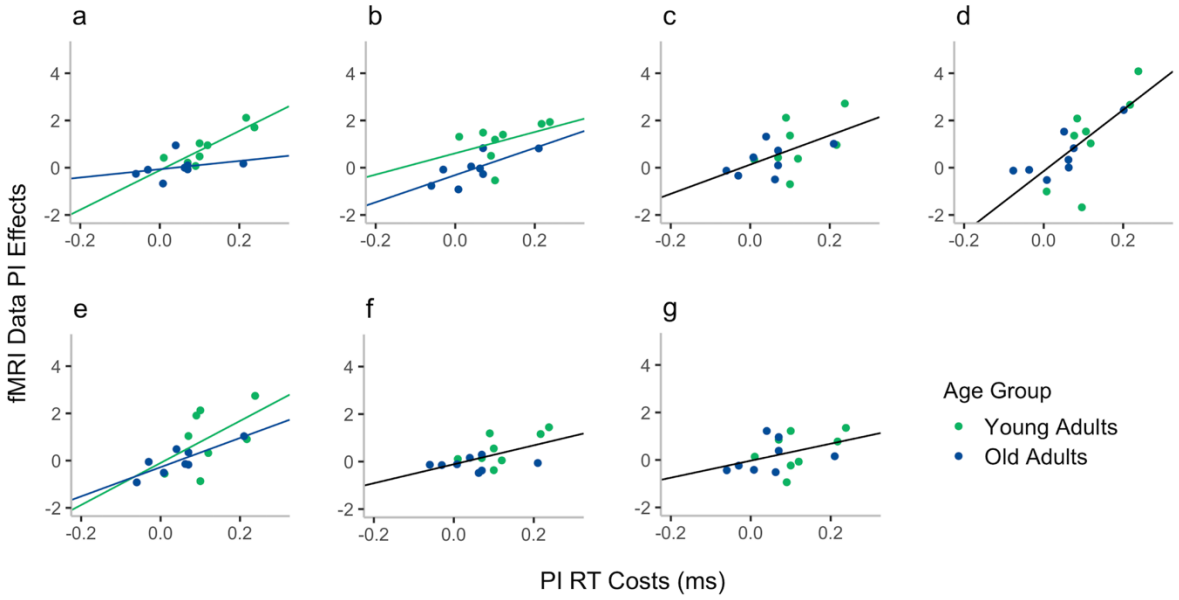


Figure 17. Significant correlations between fMRI data PI effects and PI RT costs in the pairwise matched sample. In the case of significant correlations only in one age group, regression lines are drawn per age group. Letters correspond with ROIs: a = left Precentral Gyrus, b = left SMA, c = left Calcarine Sulcus, d = left IPL, e = right Angular Gyrus, f = right Lingual Gyrus, g = right MFG.

4. Discussion

In this study we assessed the behavioural and neural correlates of overcoming PI and how they change in healthy aging. PI accuracy effects were found across participants, such that Non-RN trials were responded to with greater accuracy than RN trials, although old adults were generally less accurate than young adults. In contrast, PI effects were found in the RTs in young adults alone, who had shorter RTs on Non-RNs compared to RNs. Old adults showed no PI RT costs and were generally slower than young adults. This is not consistent with previous research that has found greater PI effects in old compared to young adults (Jonides et al., 2000; Yi and Friedman, 2014). However, the larger PI effects in young adults in the present study are likely due to a general difficulty that old adults had performing the task, which meant their RTs on RN and Non-RN trials were both relatively long.

Furthermore, analysis of fMRI data at the whole-brain level showed a network of frontal, parietal and occipital brain regions to be sensitive to PI (left precentral gyrus, left and right MFG, left SMA, left calcarine sulcus, left IPL, right angular gyrus and right lingual gyrus), all of which showed greater activation in RN trials compared to Non-RN trials. PI condition was found to interact with age group in the left precentral gyrus, left SMA and left calcarine sulcus.

In the left precentral gyrus, young adults had greater activation than old adults, and only young adults showed PI effects: RN trials had greater activation than Non-RN trials. This effect may reflect lateralised motor-related brain activity elicited during decision making when overcoming PI. Similar activity has been previously found to be involved in the selection of competing motor responses in a sensorimotor task. Iacoboni, Woods and Mazziotta (1996) presented participants with visual stimuli on either the left or right side of a screen and participants had to press a button on the same (compatible) or opposite (incompatible) side that the stimulus was presented. Incompatible responses showed greater activity in the left precentral gyrus compared to compatible responses. Consistent with this, the left premotor cortex was found to be sensitive to PI in a directed forgetting task (Nee et al., 2007), suggesting that this brain region was recruited in order to bias responses to overcome PI. Furthermore, Burgess and colleagues (2011) found the left precentral gyrus to be activated during lure trials in an n-back task. This is consistent with the current results as RNs had greater activation in the left precentral gyrus than Non-RNs, although this was only the case in young adults, suggesting that old adults did not recruit this brain area to bias responses when overcoming PI.

The same effects as in the left precentral gyrus were also observed in the left SMA. Loosli and colleagues (2016) found PI effects in the pre-SMA, although these PI effects did not interact with age.

Veltman, Rombouts and Dolan (2003) found the SMA to be related to increasing load in *n*-back and Sternberg tasks, and others have suggested the SMA to be associated with error monitoring and cognitive control in WM (Braver & Barch, 2006). Bonini and colleagues (2014) used intracerebral EEG recordings to provide strong evidence that the SMA is involved in correcting covert errors in a Simon task and is therefore involved in action monitoring and error correction in executive functioning. Therefore, it may be the case that in the present study the recruitment of both the SMA and left precentral gyrus may guide response selection in order to avoid making errors in conditions of high-PI. Young adults displayed greater activation than old adults in the left SMA but only on RN trials, suggesting that young adults may have been more able to monitor and correct covert errors in conditions of high-PI compared to old adults.

An interaction between PI and age group was also found in the left calcarine sulcus, a region known to be involved in producing and evaluating mental images (Klein et al., 2000) and in visual processing of familiar faces (Joassin et al., 2011). Schedlbauer and colleagues (2014) found the bilateral calcarine sulcus to be part of a network of brain areas involved in the retrieval of episodic temporal and spatial contextual information, in particular the retrieval of visual details. In the present study, PI effects were found in the left calcarine sulcus only in young adults, with RN trials having greater activation than Non-RN trials, which is also in line with previous results of a study using the directed forgetting paradigm to manipulate PI (Nee et al., 2007). This may suggest that the retrieval of visual information is more taxing under conditions of high-PI compared to low-PI, and this effect may have been masked in old adults as they found both PI conditions equally difficult. Nevertheless, old adults showed greater activation than young adults across conditions in the left calcarine sulcus, suggesting an increased effort in old adults to retrieve visual details related to probe stimuli in all conditions of the task. These results are not in line with previous research that shows young and old adults to activate the left calcarine gyrus to the same extent in an episodic memory task using faces as stimuli (Oedekoven, Jansen, Kircher, & Leube, 2013). This finding is also contrary to theories of cognitive aging that suggest that in healthy aging there is compensation for decreased functionality in visual regions via recruitment of frontal regions (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). This finding is, however, in line with reports of reduced differentiation of neural activity in cognitive aging. Reduced neural differentiation (or dedifferentiation) is a decrease in the selectivity of a neural response to different stimuli and has been found to occur in healthy aging in regions such as the visual cortex (Park et al., 2002). Although reduced differentiation in healthy aging has been found to be inconsistent in some stimulus modalities, it seems to be a robust effect when using face and scene stimuli (see Koen & Rugg, 2019).

There were other areas sensitive to PI on the whole brain level, which did not show interactions with age. The left IPL has been found to be sensitive to lure-related activity in an *n*-back task by Burgess and colleagues (2011). Burgess and colleagues also found the right MFG to be sensitive to lures, as did Jacobs and D'Esposito (2011). Further, Mecklinger and co-workers (2003) found the right MFG to show PI effects in a Recent Probes task, a result consistent with those of the present study. This was also the case in a study by Bunge and colleagues (2001) that manipulated WM load in a Recent Probes task and found increased activation in the right MFG on high-interference trials compared to low-interference trials. We also found the right angular gyrus to be sensitive to PI effects. This region has been found to deactivate during verbal WM retrieval (Jonides et al., 1998), and to be involved in inhibition processes in a go/no-go task (Nee, Wagner & Jonides, 2007).

4. 1. Matched Subsamples

When young and old adults were matched on WM ability, old adults were still found to be generally slower than young adults, although both age groups showed PI effects to same extent in their RTs. This suggests that the absence of PI effects in RT originally observed in the old age group in the whole sample was due to general poor WM performance in the cognitive task. Similarly, in the left precentral gyrus young adults still had greater activation than old adults, although only on RN trials, suggesting that age group differences in conditions of low-PI were due to age group differences in WM ability. Furthermore, it suggests that in conditions of high-PI, young adults recruit areas that may aid biasing responses in the face of PI more successfully than old adults, and that this effect is not due to age differences in WM ability. Also, young adults still showed PI effects in this region, with RN trials having greater activation than Non-RN trials.

In the left SMA young adults still showed greater activation than old adults on RN trials. Further, young adults still showed PI effects in this area, with RN trials having greater activation than Non-RN trials. This suggests that the observed effects are unaffected by group differences in WM ability, and that age-related changes in error monitoring when resisting PI do not necessarily depend on age-related changes in WM ability. In contrast, for the matched subgroups, we failed to observe an interaction between PI and age in the left calcarine sulcus, suggesting that the effect observed in this region in the whole sample was mainly driven by group differences in WM ability. This suggests that the retrieval of visual details in order to overcome PI may at least partly be supported by WM ability.

Conversely, for these matched subgroups, an interaction between PI and age group emerged in the left MFG: greater activity on RN trials compared to Non-RN trials was found in young adults, whereas

no such differences were found in old adults. Previous research has considered activity in the left IFG and left VLPFC to be a neural index of PI resolution (e,g., Badre & Wagner, 2005; D'Esposito et al., 1999; Nee et al., 2007). The left IFG is a neighbouring frontal region slightly more inferior to the left MFG, which lies in the dorsolateral prefrontal cortex (DLPFC). Nee and colleagues (2007) found the left DLPFC to distinguish conditions of high- and low-PI in both Recent Probes and directed forgetting paradigms, with high-PI trials having greater activation than low-PI trials (Nee et al., 2007). Furthermore, the left DLPFC has been found to be sensitive to lures in an *n*-back task and to be related to WM span and fluid intelligence (Burgess et al., 2011). Burgess and colleagues suggested that the left DLPFC plays a similar role to the left IFG in overcoming PI, in that it resolves conflict between competing response biases. In our study, the left MFG was found to be sensitive to PI although only in young adults. This effect was only present when young and old age groups were matched in WM ability, which suggests the dedifferentiated activity between conditions of high- and low-PI in old adults occurred independently of age differences in WM ability.

4. 2. Brain-Behaviour Relationship

WM ability was positively correlated with PI costs in RTs across all participants. This means that participants with greater general WM ability in the task showed greater PI costs in RT. Similar patterns of results have been reported in other studies of PI, such as that of Burgess and colleagues (2011) who found WM span to be positively correlated with RT on both lure and non-lure trials in an *n*-back task. Loosli and colleagues (2014) also found a composite score of PI costs in accuracy and RT to be correlated with WM ability in young adults in a Recent Probes task. This suggests that participants who show smaller PI costs have lower WM capacity. As participants with low WM capacity had similarly long RTs in Non-RN trials and RN trials, it may be the case that in conditions of low-PI these participants were already operating close to their full capability, leaving little extra resources to deal with the extra demands required to successfully respond to high-PI trials.

It has been argued that when responding to high-PI trials a conflict is created between the familiarity of the stimulus and the retrieval of its contextual information (Oberauer, 2005). According to theories on memory recognition, responding based on an item's familiarity is a relatively fast process compared to the slow process of recollecting a stimulus' contextual information (Yonelinas, 2002). Therefore, it may be the case that larger PI costs in RT on high-PI trials are indicative of the extra time needed to retrieve contextual information in order to successfully overcome PI. This is supported by the fact that we did not find PI costs in RT to be associated with PI costs in accuracy i.e., participants who

were slowed in conditions of high-PI were not necessarily less accurate on these same trials. Alternatively, it may be the case that participants who have low-PI RT costs rely on retrieving contextual information in conditions of low-PI, causing a relatively long RT in this condition. This would suggest that participants with higher WM capacity do not rely so much on the retrieval of contextual information in Non-RN trials and do so to a greater extent in RN trials, causing the disproportionately long RTs in RN trials compared to Non-RN trials.

We also found PI effects in brain activity in the left precentral gyrus, left calcarine sulcus and right MFG to be correlated with WM ability in all participants, indicating that greater PI-related activity in these regions is associated with greater WM ability. A similar pattern of results has been reported in previous research by Burgess and colleagues (2011), who found activity in ten brain regions (including bilateral MFG and left precentral gyrus) that showed lure-related activity in an *n*-back task to positively correlate with WM span. Neural PI effects in these three areas were also positively correlated with PI effects in RT. This suggests that participants with higher WM ability are also more capable of modulating brain activity in PI sensitive regions than those with lower WM ability.

Furthermore, we found PI effects in RT to be correlated with PI effects at the neural level in the left MFG, left SMA, and left IPL, although in these regions there was no correlation between brain activity and WM ability. This suggests that the left MFG, left SMA and left IPL may be implicated in maintaining high levels of performance when facing higher levels of PI. A similar pattern of results has been previously reported in other studies, such as Badre and Wager (2005) who found a positive correlation between PI neural effects in the left VLPFC and PI RT costs. This finding was replicated by Nee and colleagues (2007) who also found PI effects in the left VLPFC to positively correlate with PI RT costs. Nee and colleagues suggest that this association between brain activity and behaviour is the result of increased selection demands due to increased conflict. In other words, in more demanding situations we recruit these brain areas to a greater extent to meet the increase in demand. Badre and Wagner (2005) similarly interpret their finding as increased recruitment of the left VLPFC to deal with greater PI. Therefore, it may be the case that we recruit PI-related regions to a greater extent in order to successfully overcome PI and thereby successfully operate WM.

When age groups were matched on WM ability the pattern of brain-behaviour correlations differed slightly but generally followed a similar pattern, suggesting that the association between PI-related brain activity and PI behavioural costs are independent of age differences in WM ability. However, in the matched sample positive correlations emerged in the right angular and lingual gyri.

In conclusion, we found a network of frontal and parietal brain regions to be sensitive to PI, all of which showed greater activation in conditions of high-PI compared to low-PI. When considering the whole sample, we found age differences in PI effects in the left precentral gyrus and SMA that may indicate age differences in biasing response selection and error monitoring when overcoming PI. These effects were found to be independent from age differences in WM ability. Furthermore, age differences in visual brain areas may indicate that aging affects the retrieval of visual information in the face of PI, although this effect was related to WM ability.

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6. Supplementary Results

6. 1. fMRI Results

Significant interaction effects between Age Group, PI Condition and Block Type:

Significant interaction effects between Group, PI Condition and Block Type were found in the Left Inferior Parietal Lobule (IPL) ROI (Supplementary Table 2). Post-hoc contrasts (Supplementary Table 3) revealed that young adults had greater activation in Non-RN trials in the face-relevant block compared to the scene-relevant block. Old adults showed PI effects although only in the face-relevant block, with RN trials having greater activation than Non-RN trials. Young adults showed greater activation than old adults on RN trials in both the face-relevant and scene-relevant blocks.

6. 2. fMRI Results in Pairwise-Matched Subsample

Significant interaction effects between Age Group, PI Condition and Block Type:

In the pairwise-matched sample a significant interaction between Group, PI condition and Block Type was found in the Right Lingual Gyrus (Supplementary Table 6). Post-hoc contrasts (Supplementary Table 7) showed that on Non-RN trials, young adults showed greater activation in the face-relevant block compared to the scene-relevant block, whereas old adults showed greater activation in the scene-relevant block compared to the face-relevant block. Young adults showed PI effects in the scene block, with higher brain activation being observed in RN trials comparing to Non-RN trials. In the face-relevant block, old adults had greater activation on Non-RN trials compared to young adults, whereas in the scene-relevant block, young adults had greater activation compared to old adults. The reverse was true for RN trials: in the face-relevant block young adults had greater activation than old adults, whereas in the scene-relevant block old adults showed greater activation than young adults.

6. 3. fMRI Results for Matched and Unmatched Old Adult Subsamples

When comparing the matched old adults against the rest of the old adults who were not in the matched subsample, a RM-ANOVA showed a significant interaction between Group and PI condition in the Right Lingual Gyrus (see Supplementary Table 8). Post-hoc contrasts (see Supplementary Table 9) showed that in this area the matched old adults showed greater activation in both Non-RN and RN trials compared to the unmatched old adults, whereas the unmatched old adults showed greater activation in RN trials compared to Non-RN trials. No main effects of Age Group were found in any ROI.

7. Supplementary Tables

ROI	Contrast	k	*t*	MNI Coordinates X	Y	Z	*p*
Left Precentral Gyrus	Young Non-RN *vs.* Old Non-RN	62	6.57	-38	-2	56	< .001
	Young RN *vs.* Old RN	71	10.17	-38	0	56	< .001
	Young Non-RN *vs.* Young RN	71	-6.69	-40	0	54	< .001
Left Supplementary Motor Area	Young RN *vs.* Old RN	123	4.34	-1	16	53	0.003
	Young Non-RN *vs.* Young RN	123	-5.98	-6	16	52	< .001
Left Calcarine Sulcus	Young Non-RN *vs.* Old Non-RN	89	-11.88	-4	-92	-6	< .001
	Young RN *vs.* Old RN	89	-7.50	-5	-91	-5	< .001
	Young Non-RN *vs.* Young RN	89	-6.22	-6	-94	-4	< .001

Supplementary Table 1. Significant post hoc contrasts within regions of interest (ROI) that showed significant interaction effects between Group and PI Condition. k = cluster size. *t* = peak *t* value. *p* values are adjusted by voxel-wise false discovery rate correction.

ROI	k	*F*	MNI Coordinates X	Y	Z	*p*
Left Inferior Parietal Lobule	123	10.43	-34	-58	44	0.038

Supplementary Table 2. Interaction between Group, PI condition and Block Type in whole sample. k = cluster size. *F* = peak *F* value. *p* values are adjusted by voxel-wise false discovery rate correction.

ROI	Contrast	k	*t*	MNI Coordinates X	Y	Z	*p*
Left Inferior Parietal Lobule	Young adults Faces non-RN *vs.* Young adults Scenes non-RN	123	5.28	-30	-56	44	< .001
	Old adults Faces non-RN *vs.* Old adults Faces RN	123	-3.52	-30	-58	42	0.019
	Young adults Faces RN *vs.* Old adults Faces RN	123	5.98	-30	-56	44	< .001
	Young adults Scenes RN *vs.* Old adults Scenes RN	123	6.65	-34	-56	44	< .001

Supplementary Table 3. Post-hocs of interaction between Group, PI condition and Block Type in whole sample. k = cluster size. *t* = peak *t* value. *p* values are adjusted by voxel-wise false discovery rate correction.

ROI	k	*F*	MNI Coordinates X	Y	Z	*p*
Left Precentral Gyrus	71	15.54	-40	4	54	0.024
Left Middle Frontal Gyrus	62	13.50	-48	16	36	0.029
Left Supplementary Motor Area	123	15.73	-4	16	56	0.018

Supplementary Table 4. Brain regions within regions of interest (ROI) that showed interaction effects between Group and PI Condition in the pairwise matched sample. k = cluster size. *F* = peak *F*-value. *p*-values are adjusted by voxel-wise false discovery rate.

ROI	Contrast	k	*t*	MNI Coordinates X	Y	Z	*p*
Left Precentral Gyrus	Young RN *vs.* Old RN	71	5.67	-36	4	54	0.002
	Young Non-RN *vs.* Young RN	71	-4.92	-40	4	54	0.001
Left Middle Frontal Gyrus	Young non-RN *vs.* Old non-RN	39	4.00	-50	10	40	0.022
	Young RN *vs.* Old RN	62	-7.12	-50	10	40	< .001
	Young non-RN vs. young RN	62	-5.41	-48	16	36	< .001
Left Supplementary Motor Area	Young RN *vs.* Old RN	123	5.13	-8	16	56	0.002
	Young Non-RN *vs.* Young RN	123	-5.23	-6	14	52	0.001

Supplementary Table 5. Significant post hoc contrasts within regions of interest (ROI) that showed significant interaction effects between Group and PI Condition in the pairwise matched sample. k = cluster size. *t* = peak *t*-value. *p*-values are adjusted by voxel-wise false discovery rate.

ROI	k	*F*	MNI Coordinates X	Y	Z	*p*
Right Lingual Gyrus	123	25.53	22	-84	-4	.01

Supplementary Table 6. Interaction between Group, PI condition and Block Type in pairwise matched sample. k = cluster size. *F* = peak *F*-value. *p*-values are adjusted by voxel-wise false discovery rate.

ROI	Contrast	k	*t*	MNI Coordinates X	Y	Z	*p*
	Young adults Faces non-RN *vs.* Young adults Scenes non-RN	109	7.81	20	-84	-6	<.001
	Old adults Faces non-RN *vs.* Old adults Scenes non-RN	113	-7.65	22	-84	-4	<.001
	Young adults Scenes non-RN *vs.* Young adults Scenes RN	123	-4.92	22	-84	-6	0.002
Right Lingual Gyrus	Young adults Faces non-RN *vs.* Old adults Faces non-RN	123	-7.58	28	-80	-4	<.001
	Young adults Scenes non-RN *vs.* Old adults Scenes non-RN	123	17.02	25	-82	-4	<.001
	Young adults Faces RN *vs.* Old adults Faces RN	123	6.74	26	-82	-7	<.001
	Young adults Scenes RN *vs.* Old adults Scenes RN	123	-9.01	25	-80	-7	<.001

Supplementary Table 7. Post-hocs of interaction between Group, PI condition and Block Type in pairwise matched sample. k = cluster size. *t* = peak *t*-value. *p*-values are adjusted by voxel-wise false discovery rate.

ROI	k	*F*	MNI Coordinates X	Y	Z	*p*
Right Lingual Gyrus	123	18.91	26	-80	-12	0.025

Supplementary Table 8. Brain regions within regions of interest (ROI) that showed greatest interaction effects between Group and PI Condition in the pairwise matched old adults and the unmatched old adults. k = cluster size. *F* = peak *F*-value. *p*-values are adjusted by voxel-wise false discovery rate.

ROI	Contrast	k	*t*	MNI Coordinates			*p*
				X	Y	Z	
Right Lingual Gyrus	matched Non-RN *vs.* unmatched Non-RN	123	15.67	28	-82	-10	< .001
	Matched RN *vs.* unmatched RN	122	10.24	22	-82	-11	< .001
	Unmatched Non-RN *vs.* unmatched RN	123	-4.63	26	-80	-10	0.006

Supplementary Table 9. Significant post hoc contrasts within regions of interest (ROI) that showed significant interaction effects between Group and PI Condition in the pairwise matched old adults and the unmatched old adults. k = cluster size. *t* = peak *t*-value. *p*-values are adjusted by voxel-wise false discovery rate.

Chapter VI

General Discussion

The studies presented in this thesis aimed to further understanding of how PI effects change in healthy aging at the behavioural, electrophysiological and neural level in order to contribute to theories of cognitive aging. In order to do so we studied PI effects in both EEG and fMRI data in young and old adults during a Recent Probes task, which was carried out in three parallel experimental studies presented in chapters III, IV and V.

As expected, all three studies found both young and old adults to show PI effects in their behavioural performance on the Recent Probes task. However, in all three studies young adults showed greater PI effects in RT compared to old adults, which was not in line with our hypotheses.

The study presented in Chapter III aimed to advance knowledge on the age-related changes in PI effects in EEG time domain data, using a factor analytic technique (tsPCA) that allows the extraction of time courses and spatial distributions of components of covariance in electrophysiological activity. This study found PI effects on a temporo-spatial component in the EEG data at ~670 ms, although contrary to our hypothesis, these effects were not modulated by age. However, we did find PI effects on a component at ~260 ms at central electrodes to be modulated by age, with both age groups showing differences in amplitude of this component between PI conditions, although in opposite directions. Finally, age differences were also observed in a late temporo-spatial component at ~1300 ms, although only in conditions of low-PI.

As we aimed to observe the oscillatory neural activity associated with PI resolution, which is unobservable when analysing time-domain EEG data, the study presented in Chapter IV aimed to understand how the effects of healthy aging on resistance to PI are manifested in EEG time-frequency data. The advantages of analysing time-frequency EEG data are that the oscillatory activity detected at the scalp is a directed reflection of the oscillations occurring at the neural level, and that variance in EEG data time-locked to an event can be observed in both phase-locked and non-phase-locked activity, something which is not possible in time domain EEG data (Cohen, 2014). At the electrode level, this study found young adults to show greater theta power in conditions of high- PI compared to low-PI, which is in line with our hypotheses. Old adults, however, did not show theta power modulation according to conditions of high- and low-PI, which is also in line with our predictions. Furthermore, old adults were found to show greater theta power compared to young adults at the electrode level in both conditions of high- and low-PI. Analysis at the cortical level showed old adults to produce greater theta power in right frontal and temporal regions compared to young adults, and to show greater theta power on non-RN trials in bilateral frontal regions than on RN trials. Young adults showed greater theta power in parietal

and posterior frontal brain areas on RN trials compared to non-RN trials, although they also showed greater theta power in right medial temporal regions on non-RN trials compared to RN trials.

In order to understand the functional brain organisation underlying PI effects, we carried out the study presented in Chapter V with fMRI. In this study, we found PI effects in haemodynamic activity in a network of frontal, parietal and posterior brain regions, and as expected to a certain degree, these effects were differentially modulated by age. Furthermore, we found evidence to suggest that changes in functional activity in frontal and parietal areas due to aging were not driven by age group differences in WM ability. However, we did find that age differences in activity in visual brain areas were attributable to group differences in WM ability.

1. The Present Findings in Relation to Previous Research

The results from the present thesis both confirm and diverge from the current literature on PI in healthy aging. In the Recent Probes task, greater PI effects in RT were found in young adults compared to old adults. This is not in line with our original hypotheses nor with studies that have found greater PI effects in old adults compared to young adults (Jonides et al., 2000; Loosli, Rahm, Unterrainer, Weiller, & Kaller, 2014; Loosli et al., 2016; Oberauer, 2001; Yi & Friedman, 2014); results which support the account of cognitive aging that posits that healthy aging is characterised by a reduced ability to inhibit the disruptive effect of irrelevant information (Hasher & Zacks, 1988). However, we argue that our results are also consistent with this account of cognitive aging. Specifically, although greater PI effects were found in young adults compared to old adults, old adults were generally slower in both conditions of high- and low-PI compared to young adults. Furthermore, as old adults were equally slow in both non-RN and RN trials, they showed a relatively small difference in RT between PI conditions, thereby masking potential PI effects. This general slowing in old adults appears to support the processing speed theory of cognitive aging, but we argue that this pattern of results is likely due a general difficulty that old adults had in the task caused by the presence of distracting information during the encoding phase, perhaps due to worse WM ability than young adults. If the general difficulty old adults showed was due to age-related slowing of processing speed rather than WM ability, we would expect old adults to be equally slow on both non-RN and RN trials and therefore showed smaller PI effects than young adults even when they were matched with young adults on WM ability. In contrast to this, we found that when a subsample of young and old adults was matched on WM ability, old adults were still found to be generally slower than young adults, although both age groups showed PI effects to same extent in their RTs. This means that when age groups did not differ in WM ability, old adults were still slower than young adults on non-RN and RN

trials, but they showed a difference between the PI conditions to the same extent as young adults. Therefore, when old adults have worse WM ability than young adults, they find non-RN and RN trials similarly difficult, whereas when they are matched to the WM ability of young adults, they find RN trials more difficult than non-RN trials.

We argue that old adults (in the context of the whole sample) had a general difficulty in the task caused by distracting information during the encoding phase of the cognitive task, which was likely due to reduced WM ability in old age. This subsequently was reflected in the generally longer RT they showed across all conditions of the task. We found evidence in EEG data to support this claim. The EEG data recorded during the encoding phase showed age groups to differ on two EEG temporo-spatial factors (TSFs), with young adults showing greater factor scores for both factors. Furthermore, the factor scores of both of these TSFs were negatively correlated with RT in RN as well as non-RN trials, suggesting that participants who showed greater factor scores on these TSFs generally had shorter RT in the cognitive task. This relationship between TSFs and behaviour during the encoding phase, and the reduced activity found in old adults, may indicate that a decreased ability to recruit neural resources in order to suppress distraction from irrelevant stimuli hindered performance on the task in old adults. Similar results have been previously found in a study by Gazzaley and colleagues (2005), who found old adults to be less able to suppress brain activity associated with encoding irrelevant stimuli in a WM task, and the ability to suppress this activity was correlated with performance on the task. Therefore, it may be the case that in the present study the irrelevant stimuli in the encoding phase disproportionately disrupted old adults to the extent that low-interference trials were nearly as difficult as high-interference trials or at least difficult enough to mask a larger effect of PI in old adults.

The study presented in Chapter III found evidence of PI effects at the electrophysiological level that share temporal and spatial similarities with those found in previous studies. PI condition was found to modulate a temporo-spatial factor in the EEG data at around 670 ms after the presentation of the probe stimulus that was prominent at central electrodes, with low-PI trials showing greater amplitude compared to high-PI trials. In a previous study using the Recent Probes task, PI effects were found on a LPC that peaked between 400-600 ms at central and centro-parietal sensors, with low-PI trials showing greater amplitude than high-PI trials (Zhang, Wu, Kong, Weng, & Du, 2010). Yi and Friedman (2014) also found a late positive ERP at fronto-central electrodes to have greater amplitude on low-PI trials compared to high-PI trials in a modified Sternberg paradigm, and these effects on amplitude also did not differ between young and old adults. As previous research has found the LPC to be implicated in

recollection of contextual information in short-term memory (Danker et al., 2008), it may be the case that this result shows the intact efficiency of the neural mechanism that supports the recollection of contextual information in healthy aging.

The study presented in Chapter IV found results in EEG time-frequency data that are in line with previous research that has found frontal midline theta power to be a neural correlate of inhibitory control (see Cavanagh & Frank, 2014, for a review). Young adults were found to recruit greater theta power in high-PI trials compared to low-PI trials, which suggests that inhibitory control may play a role in overcoming PI in WM. Furthermore, analysis of oscillatory activity at the cortical level showed young adults to have greater theta power in parietal and posterior frontal brain regions in conditions of high-PI compared to low-PI, suggesting that these brain areas generate oscillatory activity that is recruited to inhibit PI in WM.

The study presented in Chapter V found conditions of high-PI to produce greater haemodynamic activity than conditions of low-PI in a network of frontal, parietal and occipital brain regions (left precentral gyrus, left and right middle frontal gyrus (MFG), left supplementary motor area (SMA), left calcarine sulcus, left inferior parietal lobule (IPL), right angular gyrus and right lingual gyrus). Furthermore, we found that PI effects in the fMRI data differed between age groups in the left precentral gyrus, left SMA and left calcarine sulcus. Previous research has also found increases in brain activity in cortical areas in conditions of high-PI compared to low-PI (e.g., Loosli et al., 2016), although the functional organisation of the effects observed in the present study diverge from that found in previous research. Neuroimaging studies on PI have generally found the neural index of PI resolution to be the left IFG and the left VLPFC (Badre & Wagner, 2005; D'Esposito, Postle, Jonides, & Smith, 1999; D'Esposito et al., 1999; Jonides et al., 2000; Loosli et al., 2016; Mecklinger, Weber, Gunter, & Engle, 2003; Nee, Jonides, & Berman, 2007). Although PI effects were also found in frontal brain areas, the present study found no modulation between conditions of high- and low-PI in the left IFG and the left VLPFC in the whole-brain analysis. Furthermore, previous studies have found age differences in PI effects in the left IFG (Jonides et al., 2000; Loosli et al., 2016), which was not the case in the present thesis.

The study presented in Chapter V used a Recent Probes task with a relatively large stimulus pool in order to create an exaggerated manipulation of item-specific PI while minimising item-nonspecific PI. It can be argued that previous studies of PI have used a small pool of stimuli that inadvertently created a build-up of item non-specific PI across all trials due to the repetition of stimuli across trials. Therefore, it may be the case that the functional organisation of PI effects and their modulation by age group in the

present study depart from those found in previous research due to differences between studies in the build-up of item non-specific PI. Additionally, Loosli and colleagues (2016) found age differences in PI effects in a network of bilateral frontal brain regions to not be driven by age differences in WM ability, which was also found in the present study, albeit in different frontal and parietal brain areas to those found by Loosli and colleagues. However, we did find age differences in PI effects in visual brain regions to be driven by age differences in WM ability, which may suggest that age differences in the retrieval of visual information when resolving PI may at least partly be supported by WM ability.

2. Compensation Effects in Healthy Aging

The present thesis presents evidence of how the neural activity associated with cognitive control is altered in healthy aging. Evidence in both EEG and fMRI data was found to point to reduced neural efficiency of brain regions that support cognitive control in healthy aging. Finding evidence of such effects in both electrophysiological and neuroimaging data offers insight into the temporal and spatial characteristics of these patterns of reduced neural efficiency.

We found evidence of reduced neural efficiency in healthy aging in time-frequency EEG data. At the electrode level we found young adults to recruit greater theta power in conditions of high-PI compared to low-PI, whereas no such modulation of theta power was found in old adults, who recruited theta power to the same extent in both PI conditions. Given the putative role of frontal midline theta oscillatory activity in inhibitory control, this finding supports cognitive theories of aging that posit that healthy aging is characterised by reduced inhibitory control of irrelevant information (Hasher & Zacks, 1988). As old adults were unable to modulate theta power between PI conditions this finding suggests that the neural mechanism supporting inhibitory control is less efficient in healthy aging.

Further evidence of reduced efficiency of brain areas in healthy aging was found in fMRI data in the present thesis. Young adults showed greater haemodynamic activity in high-PI trials compared to low-PI trials in the left precentral gyrus, whereas old adults did not show such modulation. BOLD activity in the left precentral gyrus has been previously found to be sensitive to motor selection in a Simon task (Iacoboni, Woods, & Mazziotta, 1996), suggesting that this lateralised motor-related brain activity observed in the present study was recruited during decision making when overcoming PI. Additionally, these age-group differences persisted in the data even when age groups were matched on WM capacity, suggesting that these effects were not driven by age differences in WM ability. Further, given that old adults activated the left precentral gyrus to the same extent in both non-RN and RN trials, it may be the case that old adults recruited this region to a relatively greater extent in non-RN trials in order to

compensate for the general difficulty they had in the task. This is consistent with the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008), which predicts that old adults recruit neural resources to a greater extent than young adults in conditions of low cognitive load to compensate for declines in efficiency of neural processing. In conditions of high cognitive load this increase in the use of neural resources does not help old adults perform better, which may be the reason why old adults showed the same level of activity in the left precentral gyrus in non-RN and RN trials.

We also found evidence of reduced neural efficiency of brain areas that support general WM processing, as indicated by main effects of age group on the amplitude of temporo-spatial factors in time-domain EEG data. The retrieval phase of the Recent Probes task was found to produce a component in EEG data around 260 ms after the presentation of the probe stimulus at fronto-central electrode sites, whose amplitude was smaller (i.e. less negative) for old adults compared to young adults. The differences between age groups on this temporo-spatial factor were localised to the right medial frontal gyrus, which is a brain area previously found to differentiate young and old adults on an item-recognition WM task, in which old adults performed slower and less accurately than young adults (Rypma, Prabhakaran, Desmond, & Gabrieli, 2001). In addition to the fact that old participants were generally slower than young adults in the Recent Probes task, this temporo-spatial factor may reflect the general difficulty that old adults experienced in the task and therefore demonstrate a reduced capacity to recruit neural resources that support WM.

Aside from evidence of reduced neural efficiency in healthy aging, the present studies also found evidence of compensatory recruitment of brain resources to overcome declines in neural efficiency in healthy aging. Compensatory activity in old age has been suggested to occur in various forms and must fulfil certain criteria to be classed as compensatory (Cabeza et al., 2018). For a neural response to be considered compensatory, it is assumed that the neural response of old adults is ameliorating some deficit that would otherwise not occur if they were younger. Examples of scenarios that must be compensated for in healthy aging are neural inefficiency or task difficulty. Additionally, the compensatory neural activity is assumed to benefit old adults in some way, often seen as a positive correlation between the compensatory activity and gains in performance in a cognitive task. However, Zarahn and colleagues (2007) argue that this is not necessary for a neural response to be deemed compensatory in nature, as it may be the case that old adults would perform *even worse* than observed if it were not for this compensatory neural activity. Compensatory neural activity in healthy aging has been suggested to occur

in various forms (Cabeza et al., 2018). Some of which are relevant to the present discussion, namely when old adults engage the same or similar neural response to young adults but to a greater extent (upregulation), and when old adults recruit additional or different brain areas compared to young adults (selection). The present studies found evidence of both upregulatory and selective compensatory neural activity in healthy aging.

The presentation of the probe stimulus in the Recent Probes task was found to produce a late temporo-spatial component at around 1300 ms after the presentation of the probe stimulus, which shares similarities with a Slow Positive ERP component previously associated with error monitoring and conflict adaption (Larson, Kaufman & Perlstein, 2009). Old adults showed greater amplitude on this component, although only in conditions of low-PI. As old adults were generally slower in all trials compared to young adults, it may be that this activity reflects increased recruitment of neural resources that support performance monitoring in order to compensate for the general difficulty they found in the cognitive task. This is also in line with the aforementioned CRUNCH model of cognitive aging (Reuter-Lorenz & Cappell, 2008).

Evidence of compensatory recruitment of neural activity in old adults was also found in EEG time-frequency data. As already mentioned, at the electrode level old adults failed to modulate theta power between non-RN and RN trials, although they also showed greater theta power than young adults across both conditions of PI. As enhanced frontal midline theta power has been previously associated with increased cognitive demand (Onton, Delorme, & Makeig, 2005), it may be that this pattern of results in old adults demonstrates compensation for the general difficulty they found in the task by means of upregulating the recruitment of theta power. A similar pattern of results was found by Gazzaley and colleagues (2008), who found old adults to produce greater frontal midline theta power compared to young adults in conditions that both did and did not require the inhibition of irrelevant stimuli, whereas young adults were able to modulate theta activity according to the relevance of the stimuli. Likewise, in the present thesis, results at the cortical level followed such a pattern, although old adults also showed compensatory recruitment of additional brain regions compared to young adults. Old adults showed greater theta power than young adults in a cluster in the right hemisphere that spanned frontal and temporal areas, which may have been recruited in an attempt to compensate for the general difficulty they had in the cognitive task.

Further evidence of compensation of reduced neural efficiency in healthy aging was found in fMRI data. PI effects were found in the left calcarine sulcus only in young adults, with RN trials having

greater activation than Non-RN trials. However, old adults showed no such modulation of haemodynamic activity in the left calcarine sulcus according to PI condition. Additionally, old adults showed greater activity in the left calcarine sulcus area compared to young adults in both conditions of low- and high-PI, indicative of dedifferentiation and therefore reduced neural efficiency of this brain region. Dedifferentiation of neural responses has previously been described as a functional "challenge" in healthy aging and is characterised by reduced specificity of neural responses to different situations that require varying levels of cognitive effort or control (Reuter-Lorenz & Park, 2014). Furthermore, neural dedifferentiation has been found to occur in healthy aging in regions such as the visual cortex (Park et al., 2002). Although reduced differentiation in healthy aging has been found to be inconsistent in some stimulus modalities, it seems to be a robust effect when using face and scene stimuli (see Koen & Rugg, 2019). Therefore, it may be the case that old adults in general recruited greater activity in the left calcarine sulcus to compensate for the reduce specificity of activity in this area between conditions of high- and low-PI.

3. Neural Mechanisms Underlying Proactive Interference Resolution

The present thesis put forward findings which shed light on the neural mechanisms supporting specific processes that aid the resolution of PI, and how these mechanisms are altered in healthy aging. We found evidence to suggest that familiarity-based processing when resolving PI can be observed with EEG data, namely in a temporo-spatial component occurring around 260 ms after probe stimulus onset that had differential amplitude depending on PI condition. However, this sensitivity to PI was found to be different in young and old adults, such that young adults showed greater negativity in conditions of low-PI compared to high-PI, whereas old adults showed effects in the opposite direction. Given that previous research has found a similar negative ERP component to be sensitive to familiarity in episodic memory retrieval (Curran, 2000), we argue that the PI effects found on this temporo-spatial component reflect the processing of familiarity in PI. There is evidence to suggest that PI is the result of a conflict between item familiarity and context recollection (Oberauer, 2005), and therefore resistance to PI may involve resolving this conflict by inhibiting the high familiarity of the stimulus producing PI or by retrieving the context in which it was seen or heard. If the temporo-spatial component observed at 260 ms does indeed represent familiarity processing, the different sensitivity in young and old adults suggests that the neural mechanism supporting the inhibition of familiarity processing may be altered in healthy aging.

We also found evidence of the potential role of the recollection of contextual information in PI resolution, and that this process is unaltered in healthy aging. We found a temporo-spatial component in

the EEG data around 630 ms after the presentation of the probe stimulus at central electrodes to be modulated by PI condition, such that low-PI trials elicited greater amplitude of this component compared to high-PI trials. This temporo-spatial component has similar characteristics to an ERP component that has previously been associated with the retrieval of contextual information in short-term memory (Danker et al., 2008). As both young and old adults were found to modulate the amplitude of this temporo-spatial component according to PI condition, it may be the case that the retrieval of contextual information in order to resolve PI is preserved in healthy aging.

We also found evidence to suggest that PI resolution involves a degree of inhibitory control. As already mentioned, there is evidence to suggest that PI is not only overcome by the inhibition of no longer relevant representations in WM, but rather by also recollecting contextual information in order to overcome the unreliable familiarity of a stimulus (Oberauer, 2005). In the present thesis, high-PI trials were found to evoke greater theta power compared to low-PI trials in young adults at the electrode level. This finding suggests that PI resolution involves some degree of inhibition, although the exact nature of this inhibitory control is unclear. We additionally found evidence to suggest that clusters of brain regions in parietal and posterior frontal areas are neural generators responsible for increased theta power in conditions of high-PI in order to exert inhibitory control to correctly resolve PI. Furthermore, as old adults did not show evidence of greater recruitment of theta activity in RN trials compared to non-RN trials it may be the case that inhibitory control in PI resolution is somewhat disrupted in healthy aging.

The present thesis also observed evidence of the possible involvement of error monitoring in PI resolution. Young adults were found to show greater haemodynamic activity in the left SMA in conditions of high-PI compared to low-PI. The SMA has been previously suggested to be associated with error monitoring and cognitive control in WM (Braver & Barch, 2006). Furthermore, previous research using intracerebral EEG recordings provides strong evidence that the SMA is involved in correcting covert errors in a Simon task and is therefore involved in action monitoring and error correction in executive functioning (Bonini et al., 2014). Therefore, it may be the case that young adults recruited activity in the left SMA in order to monitor performance during conditions of high-PI. Furthermore, as old adults failed to show such sensitivity, it may be the case that this neural mechanism is disrupted in healthy aging. Additionally, age-differences in brain activity in the left SMA were still observed after age groups were matched on WM ability, suggesting that disruption of this neural mechanism is not driven by age-related declines in WM capacity.

The present thesis also presents results that suggest that the retrieval of visual information in WM is more taxing in conditions of high-PI compared to low-PI. PI effects in fMRI data were found in the left calcarine sulcus in young adults, with RN trials showing greater activation than non-RN trials. Previous research has found the bilateral calcarine sulcus to be part of a network of brain areas involved in the retrieval of episodic temporal and spatial contextual information, in particular the retrieval of visual details (Schedlbauer, Copara, Watrous, & Ekstrom, 2014). As greater BOLD effects were found in conditions of high-PI compared to low-PI, it may be the case that the retrieval of visual information is more taxing under conditions of high-PI compared to low-PI, and that young adults recruited activity in this brain area to deal with the greater demands on visual processing or the retrieval of contextual information. Furthermore, the positive correlation between brain activity in the left calcarine sulcus and WM ability suggests that sensitivity to PI in this brain region aided general performance in the cognitive task. These effects were not found in the old age group, suggesting that old adults may have been less able to respond to increases in demand in the retrieval of visual details in order to overcome PI. However, these age differences disappeared when age groups were matched on WM ability, suggesting that age differences in the retrieval of visual information when resolving PI may partly be supported by WM ability.

Additionally, the present thesis found further evidence of the role of WM ability in the ability to resist PI and how it is altered in healthy aging. Participants' WM ability was found to be positively correlated with PI effects in RT, suggesting that higher WM ability is related with larger PI effects. Although this was not in line with our original hypotheses, previous research has found WM capacity to positively correlate with RT on lure trials that create PI in an *n*-back task (Burgess, Gray, Conway, & Braver, 2011). This relationship suggests that participants with low WM ability had similarly long RT in conditions of both high- and low-PI, which may signify that they were performing close to the limit of their cognitive capacity in conditions of low-PI, which left them with little resources to deal with the increased cognitive demands required in conditions of high-PI. It may also be the case that the larger PI costs found in participants with higher WM ability are indicative of the extra time needed in high-PI trials to retrieve contextual information. This view is supported by the fact that PI effects in RT did not correlate with PI costs in accuracy. In other words, the extra time taken on high-PI trials did not necessarily mean that participants would be less accurate on these same trials, leaving open the suggestion that PI costs in RT are an adaptive response to PI in WM.

Additionally, we found evidence of reduced sensitivity of neural regions that support PI resolution when age groups were matched on WM ability. Young adults were found to have greater haemodynamic

activity in the left MFG in conditions of high-PI compared to low-PI, whereas old adults showed no such sensitivity to the PI manipulation. The left MFG lies in the dorsolateral prefrontal cortex (DLPFC), which has previously been found to be sensitive to PI in a directed-forgetting paradigm (Nee et al., 2007). This pattern of results suggests that even when age groups were matched on WM ability, young adults showed sensitivity in their recruitment of the left MFG in that they recruited brain activity to a greater extent in conditions of high PI. As old adults showed no such selectivity in recruitment of this activity, it may be the case that they were already operating close to full cognitive capacity in conditions of low-PI and were unable to recruit activity in the left MFG to meet the even greater demands of high-PI trials.

4. Limitations and Future Research

The present thesis is not without limitations. The studies presented in this thesis showed results of within-subject and between-subject effects in relatively small sample sizes. Small sample sizes in experimental psychology increases the impact of both within- and between-subject variance on noise in results that are achieved by analysing group- and condition-averages. Small samples lead to studies having relatively low power, which increases the likelihood of encountering Type I errors in the results. Furthermore, the use of small samples makes it less likely that a statistical analysis will detect small effect sizes while increasing the likelihood that the sizes of the detected effects are inflated (Cremers, Wager, & Yarkoni, 2017). Due to the increased inter-subject variability that is symptomatic of small samples, it can be argued that underpowered studies in experimental psychology may lead to low replicability of results (Turner, Paul, Miller, & Barbey, 2018), such that consensus between scientific studies is harder to achieve. Therefore, it may be the case that the small sample sizes included in the presented studies were the underlying factor behind the reported discrepancies between the present results and those in the literature. In conclusion, we argue that further research is needed to confirm our results using larger sample sizes.

Another limitation of the present thesis is the age range of the old adult samples included in the studies. It has been previously suggested that adults are considered to be old at 65 or more years (Grady, 2012). However, other studies reviewed in the present thesis have studied and found age differences in cognitive functioning between young adults and old adults of 60 (Yi & Friedman, 2014) and 61 (Jonides et al., 2000) years or more. Furthermore, the current thesis included participants as young as 53 years old in the old adult sample. Despite this disagreement in age range, Park and colleagues (2002) administered various cognitive tasks to groups of participants from each decade of life from 20 to 90 years of age and found measures of STM and WM to linearly decline with increasing age. Therefore, we

might expect old adults at 53 years to follow the same linear decline in cognitive functioning as old adults at 65 years, although perhaps to a lesser extent. Therefore, future research should replicate the presented results using an old age group with a sufficient number of old adults that would permit dividing old adults into young-old and old-old age groups in order to see whether changes in cognitive functioning between younger old adults and older old adults are linear in nature.

As already discussed, it can be argued that the Recent Probes task employed in the present study may have caused distractor interference during the encoding phase of the task. This may be the case given that it has previously been argued that in the absence of interference, it is unlikely that old adults show deficits in WM ability compared to young adults on a simple maintenance task such as the Recent Probes task (Reuter-Lorenz & Sylvester, 2005). Furthermore, previous research has found old adults to be more susceptible to distracting information during WM encoding, and that this is directly related with behaviour (Gazzaley et al., 2005). However, the extent to which old adults' general difficulty in the task was due to an increased susceptibility to distracting stimuli during the encoding phase of the Recent Probes task compared to young adults must be confirmed by further research.

Future research is also needed to investigate the extent to which old adults were affected by WM load in the Recent Probes task. In the present thesis old adults were found to have a general difficulty when completing the cognitive task, as shown by reduced accuracy and longer RT in all experimental conditions compared to young adults. We found evidence to suggest that this difficulty was partly due to age differences in the encoding phase of the task, which may have been caused by the presence of distracting information. Another possibility is that the number of items that participants had to encode had a detrimental impact on old adults' performance. Old adults have been previously found to be more affected by the number of items to be encoded compared to young adults. In a study by Pinal and colleagues (2015), young and old adults had to memorise a stimulus with either 2, 3 (low WM load condition), 4 or 5 dots (high WM load condition) and then decide whether the encoded stimulus matched one of three probe stimuli. Young adults were unaffected by WM load, whereas old adults were less accurate in the high WM load condition compared to the low WM load condition. Furthermore, this effect was accompanied by age differences in amplitude and latencies of N2 and P2 ERP components, and N2 latency was correlated with old adults' accuracy, suggesting a link between brain activity and behaviour. Therefore, we argue that modulating the WM load of the Recent Probes task in future research would provide further evidence on whether the general difficulty experienced by old adults was only due to the presence of distracting information during encoding or due to WM load.

It can also be argued that further research is needed on the nature of the recruitment of brain activity during PI resolution and how it is affected by aging. The present study found localised activity in specific brain regions to differ between PI conditions and that some of these patterns of isolated activation differed between age groups. However, it has been argued that brain regions are unlikely to act in isolation during cognitive processing (Mesulam, 1990). This shift in the way we think about cognition has led fields of the cognitive neurosciences to think of the active brain as a network of functionally connected areas rather than isolated nodes of localised activation (Soares et al., 2016). Functional connectivity measures the temporal correlation between separate nodes of brain activity (Friston et al., 1993), thereby allowing the observation of how localised brain activations correlate and interact with each other. Functional connectivity is an ideal way to understand how different brain regions interact with each other in time given fMRI's capacity to accurately estimate the BOLD effect with high spatial precision throughout the whole brain. This technique has been adapted to analyse task-related fMRI data, allowing the observation of functional connectivity between brain regions during specific parts of trials in cognitive tasks (Rissman, Gazzaley, & D'Esposito, 2004). Nee and colleagues (2007) applied a functional connectivity analysis technique developed by Rissman, Gazzaley and D'Esposito (2004) to fMRI data recorded during the retrieval phase of RN trials in the Recent Probes task combined with the retrieval phase of lure trials in a modified Sternberg task. Although two regions found to be sensitive to PI (left VLPFC and anterior PFC) were not correlated with each other, they found these regions to each correlate with activation in distinct networks of brain regions. This suggests that these regions are not operating as solitary units during PI resolution but that they may function as part of a wider network of connected regions whose activity goes undetected when contrasting activity in a brain region (or the whole brain) between experimental conditions. Therefore, we argue that future research should apply functional connectivity analysis to the Recent Probes task in a group of young and old adults in order to understand how networks of functionally connected brain regions are altered in healthy aging during PI resolution.

5. Conclusion

The current thesis presents evidence of cognitive aging at the behavioural, electrophysiological and functional level. Reduced ability in healthy aging to control the contents of WM and avoid the disruptive effect of no longer relevant information provides evidence that supports accounts of cognitive aging that suggest declines in WM are due to a decreased ability to inhibit the deleterious effect of irrelevant stimuli. We also found evidence in electrophysiological and neuroimaging data of reduced efficiency in healthy aging of the neural structures that underlie cognitive control, as demonstrated by

less selective recruitment of neural resources in conditions of high and low cognitive demand in old adults. Furthermore, the present thesis provides evidence supporting theories of cognitive aging that posit that decreased neural efficiency in healthy aging is combatted by the compensatory over-recruitment of brain activity, which was observed in both EEG and fMRI data. Finally, the time course and functional organisation of the neural mechanisms that support the resolution of interference caused by no longer relevant information in WM was indexed in the present study, offering greater perspective on the roles of different brain areas and cognitive mechanisms employed in situations that require high cognitive control.

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Universidade do Minho

SECVS

Subcomissão de Ética para as Ciências da Vida e da Saúde

Identificação do documento: SECVS 108/2016

Título do projeto: *Os correlatos comportamentais e neuronais da memória operacional ao longo da vida* ("Electrophysiological correlates of proactive interference and attentional control over working memory in healthy aging")

Investigador(a) responsável: Doutora Adriana Sampaio, Escola de Psicologia, Centro de Investigação em Psicologia, Universidade do Minho; Doutor Diego Pinal Fernández, Escola de Psicologia, Centro de Investigação em Psicologia, Universidade do Minho; e Harry Moore, aluno de doutoramento na Escola de Psicologia, Centro de Investigação em Psicologia, Universidade do Minho

Subunidade orgânica: Escola de Psicologia, Universidade do Minho

PARECER

A Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS) analisou o processo relativo ao projeto intitulado *"Os correlatos comportamentais e neuronais da memória operacional ao longo da vida".*

Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na experimentação com humanos, em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde.

Face ao exposto, a SECVS nada tem a opor à realização do projeto.

Braga, 20 de fevereiro de 2017.

A Presidente

MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO

Assinado de forma digital por MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
DN: c=PT, o=Cartão de Cidadão, ou=Cidadão Português, ou=Autenticação do Cidadão, sn=DE LEMOS PINTO ESTRELA LEÃO, givenName=MARIA CECÍLIA, serialNumber=BI014512203, cn=MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
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