

THE BEHAVIORAL AND NEURAL CORRELATES OF COGNITIVE CONTROL ACROSS THE LIFESPAN

by

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ABSTRACT

This dissertation investigates which brain mechanisms are involved in proactive and reactive cognitive control across the lifespan, how the function of those brain mechanisms is affected by age, and how those functional changes translate to differences in behavior. Chapter 1 provides a comprehensive literature review covering proactive and reactive control in an ageing context, the contributions of the left IPS and left TPJ to suppression of salient distractors, and how these two topics may be interrelated. Chapter 2 examines the neural correlates of proactive inhibition in a young and aging cohort, with focus on the contribution of left IPS and/or left TPJ. It was found that while young participants only engaged proactive mechanisms (Left IPS) to engage the task, old participants engaged both proactive (Left IPS) and reactive (Left TPJ) mechanisms simultaneously. Further, age-related reductions in resting state functional connectivity suggested that both proactive and reactive inhibition mechanisms were impaired in aging populations. Chapter 3 assesses if there are detectable behavioral deficits during a reactive inhibition task in old age. Elderly participants showed an impaired ability to reactively use a salient distractor as an anti-cue. Chapter 4 uses TMS to explicitly test the role of the left TPJ during reactive control. It was found that applying TMS to the left TPJ impaired participants' ability to reactively engage a salient distractor as an anti-cue and, surprisingly, that applying TMS to the left IPS enhanced this ability. Chapter 5 tests if the allocation of attention to a distractor prior to inhibition is impaired in aging participants. The result revealed no age-related impairment to attentional control prior to inhibition. Chapter 6 summarizes the findings, discusses their broader implications, and proposes avenues for future research.

*To my partner,
Jeanette Rose Moreland,*

and

*To my parents,
Leslie Ann Ashinoff and Emanuel Martin Kay.*

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TABLE OF CONTENTS

CHAPTER 1: THE BEHAVIORAL AND NEURAL CORRELATES OF PROACTIVE AND REACTIVE INHIBITION ACROSS THE LIFESPAN.....	1
INTRODUCTION	2
THE DUAL MECHANISMS OF COGNITIVE CONTROL FRAMEWORK	2
<i>Ageing and the DMC Framework</i>	4
SALIENCE SUPPRESSION IN THE LEFT PPC	9
<i>What is Salience?</i>	10
<i>The Left IPS and the Suppression of Salience</i>	11
Historical Context.....	11
Current State of the Literature	14
The Suppression of Physical Salience	14
The Suppression of Internally Generated Salience	16
<i>The Left TPJ and the Suppression of Salience</i>	18
Historical Context.....	18
Current State of the Literature	20
SALIENCE SUPPRESSION AND THE DMC FRAMEWORK.....	22
<i>Proactive Control and the Left IPS</i>	23
<i>Reactive Control and the Left TPJ</i>	26
CONCLUSION	29
CHAPTER 2: THE NEURAL CORRELATES OF AGE-RELATED DIFFERENCES IN NON-SPATIAL SALIENCE SUPPRESSION	30
INTRODUCTION	31
METHODS.....	36
<i>Participants</i>	36
<i>Stimuli</i>	37
<i>Procedure</i>	38
<i>fMRI Data Acquisition</i>	40
<i>fMRI Data Analysis</i>	40
<i>ROI Definitions</i>	43
<i>Resting State Functional Connectivity Analysis</i>	45
RESULTS	49
<i>Behavioral Analysis</i>	49
<i>fMRI Analysis</i>	52
GLM Contrasts	52
Regions of Interest.....	58
Brain Activity and Behavior.....	61
<i>Resting State Functional Connectivity</i>	64
Within Network Connectivity.....	64
Between Network Connectivity	65
Connectivity with the left IFG	66
General Summary of RSFC Results.....	66
<i>Analyzing the Link between RSFC, BOLD Activity, and Behavior</i>	67
DISCUSSION.....	69
<i>Conclusion</i>	77

CHAPTER 3: IS REACTIVE INHIBITION IMPAIRED IN AGING POPULATIONS?	79
INTRODUCTION	80
METHODS.....	85
<i>Participants</i>	85
<i>Stimuli and Procedure</i>	86
RESULTS	89
DISCUSSION.....	93
<i>Conclusion</i>	98
CHAPTER 4: THE ROLE OF THE LEFT IPS AND LEFT TPJ DURING REACTIVE SALIENCE SUPPRESSION	99
INTRODUCTION	100
METHODS.....	103
<i>Participants</i>	104
<i>TMS</i>	104
<i>Stimuli and Procedure</i>	105
RESULTS	108
<i>Response Time Analysis</i>	108
<i>Accuracy Analysis</i>	112
<i>Speed/Accuracy Trade-off Analysis</i>	115
DISCUSSION.....	118
<i>Stimulating the left TPJ</i>	118
<i>Stimulating the left IPS</i>	121
<i>Conclusion</i>	122
CHAPTER 5: THE ALLOCATION OF ATTENTION PRIOR TO SUPPRESSION ACROSS THE LIFESPAN	123
INTRODUCTION	124
METHODS.....	130
<i>Participants</i>	130
<i>Stimuli and Procedure</i>	131
RESULTS	134
<i>Flanker Task Performance</i>	134
<i>Temporal Order Judgment Task</i>	137
DISCUSSION.....	145
CHAPTER 6: SUMMARY AND FUTURE DIRECTIONS	150
INTRODUCTION	151
PROACTIVE AND REACTIVE COGNITIVE CONTROL IN AGING	156
<i>A New Paradigm?</i>	159
THE DMC FRAMEWORK AND INDIVIDUAL DIFFERENCES.....	163
PRACTICAL APPLICATIONS	166
CONCLUSION	167
REFERENCES	168

LIST OF FIGURES

Chapter 2

FIGURE 1. EXAMPLE OF STIMULI IN THE GLOBAL/LOCAL TASK.....	38
FIGURE 2. FIND LAB ROI'S FOR THE VISUOSPATIAL NETWORK (GREEN), EXECUTIVE CONTROL NETWORK (BLUE), AND THE SALIENCE NETWORK (YELLOW).....	48
FIGURE 3. ADJUSTED RESPONSE TIME AS A FUNCTION OF THE SALIENCE AND RESPONSE CONDITIONS.	52
FIGURE 4. SIGNIFICANT GROUP-LEVEL BOLD RESPONSES FOUND IN THE DISTRACTOR SALIENT > TARGET SALIENT CONTRAST. YELLOW/RED REFLECTS ACTIVITY FOR ELDERLY PARTICIPANTS AND BLUE/LIGHT BLUE REFLECTS ACTIVITY FOR YOUNG PARTICIPANTS.	55
FIGURE 5. SIGNIFICANT GROUP-LEVEL BOLD RESPONSES FOUND IN THE ELDERLY > YOUNG CONTRAST OF DISTRACTOR SALIENT > TARGET SALIENT.	56
FIGURE 6. SIGNIFICANT GROUP-LEVEL BOLD RESPONSES FOUND FOR THE ELDERLY > YOUNG CONTRAST OF LOCAL SALIENT > GLOBAL SALIENT (GREEN CLUSTERS).....	57
FIGURE 7. MEAN BOLD SIGNAL CHANGE WITHIN THE LEFT IPS (A), LEFT TPJ (B), AND LEFT IFG (C) NODE AS A FUNCTION OF RELATIVE SALIENCE AND AGE GROUP.....	60
FIGURE 8. SIGNIFICANT GROUP-LEVEL BOLD RESPONSES FOUND IN THE DISTRACTOR SALIENT > TARGET SALIENT CONTRAST THAT CORRELATE POSITIVELY (A & B) AND NEGATIVELY (C) WITH THE ADJRT CONGRUENCY EFFECT DURING DISTRACTOR SALIENT TRIALS.....	63

Chapter 3

FIGURE 1. DIAGRAM OF THE REACTIVE CONTROL T-TASK.....	88
FIGURE 2. GRAPH REFLECTING MEAN PROPORTION OF CORRECT RESPONSES FOR SALIENT AND SIMILAR CONDITIONS ACROSS AGE GROUPS.....	90
FIGURE 3. GRAPH REFLECTING RESPONSE TIME DATA (MSEC) FOR SALIENT AND SIMILAR CONDITIONS ACROSS AGE GROUPS.	91
FIGURE 4. SCATTERPLOT COMPARING AGE AND RT BENEFIT SCORE FOR THE ELDERLY PARTICIPANTS	93

Chapter 4

FIGURE 1. THE RESPONSE TIME BENEFIT AS A FUNCTION OF TMS AND BLOCK.	109
FIGURE 2. RESPONSE TIME DURING BLOCK 1 AS A FUNCTION OF TMS AND SALIENCE.....	111
FIGURE 3. RESPONSE TIME BASED PERFORMANCE BENEFIT (SIMILAR RT – SALIENT RT) DURING BLOCK 1 AS A FUNCTION OF TMS CONDITION. IT SHOULD BE NOTED THAT THIS IS THE SAME DATA FROM FIGURE 1, JUST SIMPLIFIED FOR EXPLANATORY PURPOSES.....	111
FIGURE 4. THE ACCURACY BENEFIT AS A FUNCTION OF TMS AND BLOCK	112
FIGURE 5. PROPORTION OF CORRECT RESPONSES DURING BLOCK 1 AS A FUNCTION OF TMS AND SALIENCE	114
FIGURE 6. ACCURACY BASED PERFORMANCE BENEFIT (SALIENT PERFORMANCE CORRECT – SIMILAR PERFORMANCE CORRECT) DURING BLOCK 1 AS A FUNCTION OF TMS CONDITION. IT SHOULD BE NOTED THAT THIS IS THE SAME DATA FROM FIGURE 2, JUST SIMPLIFIED FOR EXPLANATORY PURPOSES.	114
Figure 7. Raw response time data as a function of TMS, Salience and Block.....	116
Figure 8. Raw accuracy data as a function of TMS, Salience, and Block.....	117

Chapter 5

FIGURE 1A. ILLUSTRATES THE LOW CONTRAST DISPLAY WITH DISTRACTORS IN THE UPPER RIGHT/LOWER LEFT FLANKER CONFIGURATION. 1B ILLUSTRATES THE EQUAL CONTRAST DISPLAY WITH DISTRACTORS IN THE UPPER LEFT/LOWER RIGHT FLANKER CONFIGURATION. 1C ILLUSTRATES THE DOT DISPLAY.....	132
FIGURE 2. FLANKER TASK RESPONSE TIME DATA AS A FUNCTION OF CONGRUENCY, DISTRACTOR LOCATION, DISTRACTOR CONTRAST, AND AGE GROUP. ERROR BARS REFLECT STANDARD ERROR OF THE MEAN.	135
FIGURE 3. FLANKER TASK ACCURACY DATA AS A FUNCTION OF CONGRUENCY, DISTRACTOR LOCATION, DISTRACTOR CONTRAST, AND AGE GROUP. ERROR BARS REFLECT STANDARD ERROR OF THE MEAN.	136

Chapter 5 (continued)

FIGURE 4. PROPORTION OF “LEFT” RESPONSES ON DOT TASK AS A FUNCTION OF DISTRACTOR LOCATION, DISTRACTOR CONTRAST, AND AGE GROUP. UL/LR REFERS TO UPPER LEFT/LOWER RIGHT AND UR/LL REFERS TO UPPER RIGHT/LOWER LEFT. ERROR BARS REFLECT STANDARD ERROR OF THE MEAN..... 139

FIGURE 5. PROPORTION OF “LEFT” RESPONSES ON DOT TASK WHEN THE DISTRACTORS WERE IN THE UPPER LEFT/LOWER RIGHT LOCATIONS AS A FUNCTION OF DISTRACTOR CONTRAST AND AGE GROUP. ERROR BARS REFLECT STANDARD ERROR OF THE MEAN. THE INTERACTION WAS MARGINALLY NOT SIGNIFICANT ($p = .059$). 141

FIGURE 6. SCATTERPLOT REFLECTING THE DATA FOR YOUNG AND ELDERLY PARTICIPANTS DURING LOW CONTRAST TRIALS AS A FUNCTION OF THE WHITE BEAR STATISTIC AND THE RESPONSE TIME CONGRUENCY RATIO..... 143

Chapter 6

FIGURE 1. EXAMPLE OF NON-SPATIAL TASK. IF THE SUBJECT WERE BEING ASKED TO RESPOND TO THE LOCAL LETTER, THEY WOULD RESPOND THAT THE TARGET WAS NOT PRESENT. IF THEY WERE BEING ASKED TO RESPOND TO THE GLOBAL LETTER, THEN THEY WOULD RESPOND THAT THE TARGET IS PRESENT. 162

FIGURE 2. EXAMPLE OF A SPATIAL TASK. IN THIS EXAMPLE, THE SUBJECT WOULD RESPOND THAT THE TARGET IS PRESENT. 162

LIST OF TABLES

Chapter 2

TABLE 1. MNI COORDINATES OF LOCAL MAXIMA AND ACTIVATED BRAIN REGIONS FOR SIGNIFICANT CLUSTERS OBTAINED FROM THE 3 RD LEVEL BETWEEN GROUP GLM ANALYSIS.	54
TABLE 2. MNI COORDINATES OF LOCAL MAXIMA AND ACTIVATED BRAIN REGIONS FOR SIGNIFICANT CLUSTERS OBTAINED FROM THE 3 RD LEVEL WITHIN GROUP ANALYSES INCLUDING THE ADJRT CONGRUENCY EFFECT AS A COVARIATE	62
TABLE 3. AGE DIFFERENCES IN WITHIN- AND BETWEEN- NETWORK RESTING STATE FUNCTIONAL CONNECTIVITY.....	67

Chapter 1:
The Behavioral and Neural Correlates of
Proactive and Reactive Inhibition across
the Lifespan

Introduction

As we age, our cognitive abilities often deteriorate. However, contrary to how it may feel, not everything may be impaired as it appears. According to the inhibition deficit theory of cognitive ageing (Lustig et al, 2007), many of the apparent cognitive deficits in old age can in fact be attributed to an underlying deficit in distractor inhibition. Ostensibly, the impact of impaired distractor inhibition cascades throughout the information processing stream and makes it appear as if other cognitive abilities are impaired. Recent research has highlighted the role of proactive and reactive inhibition mechanisms in distractor suppression, particularly in the context of aging. Current evidence suggests that proactive inhibition mechanisms are impaired in aging populations, whereas reactive inhibition mechanisms are intact, though the research is by no means conclusive. The purpose of this dissertation is to investigate the neural and behavioral correlates of proactive and reactive inhibition across the life span. However, in order to properly discuss these issues some relevant background is necessary. This chapter will review the literature on proactive and reactive control in aging populations, the current state of research on suppression mechanisms in healthy young populations (with a focus on the left posterior parietal cortex), and the possible relationship between the two literatures.

The Dual Mechanisms of Cognitive Control Framework

Cognitive control is a term that is not always used consistently within the literature. Most often it is referred to it as a function that falls under the heading of executive functions (Niendam et al, 2012; Garavan et al, 2002), but some refer to cognitive control and executive functions as independent processes (Davidson et al, 2006). In either case, it typically refers to the ability to flexibly shift between thoughts and actions (which is also

sometimes referred to as mental or cognitive flexibility; Diamond, 2013). For the purposes of this review, we will consider cognitive control to be a distinct, albeit complex, function and we will adopt the definition of cognitive control proposed by Braver (2012). Braver (2012) describes cognitive control as “the ability to regulate, coordinate, and sequence thoughts and actions in accordance with internally maintained behavioral goals.” Crucially, we refer to cognitive control as a single overall function, where the mechanisms that subserve this function are numerous and complex. For example, as this dissertation will highlight, attentional mechanisms like salience suppression often subserve cognitive control functions. Braver (2012) proposed that there are two distinct brain networks – the proactive and reactive networks – that work in conjunction with each other in order to subserve the overall function of cognitive control, hence he named this hypothesis the dual mechanisms model of cognitive control (DMC).

According to Braver (2012), proactive control is an “early selection” mechanism that actively updates and maintains task goals and uses that information to apply top-down biases to attentional control in preparation for an expected event. Proactive control has been associated with sustained and anticipatory activation in the lateral prefrontal cortex, initiated and maintained by a phasic dopamine-mediated gating signal. Conversely, reactive control is a “late correction” mechanism that typically responds in a bottom-up fashion after an unexpected event by reactivating and updating task goals. Reactive control has been associated with transient activation of the lateral prefrontal cortex and an extended network of many other brain regions (including the anterior cingulate cortex, in the context of error detection). Critically, reactive control does not require a phasic DA-mediated gating signal for initiation. Essentially, while proactive control works through a relatively slow process to prevent interference from occurring in the first place, reactive control has to

relatively quickly identify the presence of interference and then resolve it. The engagement of these control modes is typically measured using the 'AxCPT' paradigm, which will be described in detail in the next section.

Ageing and the DMC Framework

There is clear evidence that cognitive functions typically deteriorate with age (Hoogendam et al, 2014; Pettigrew and Martin, 2014; Unverzagt et al, 2001; WPIPA/WHO and Levy, 1994; See chapter 3, pages 96-96 for age-related effects of attentional orienting). Hoogendam et al (2014) found that healthy aging was associated with declines in general cognition, including fine motor skills, processing speed, and visuospatial abilities. In particular, inhibition deficits have been identified as being particularly prominent in healthy aging populations (Bloemendaal et al, 2016; Vadaga et al, 2015; Sebastian et al, 2013; Anguera and Gazzaley, 2012; Lustig et al, 2007; Kramer et al, 1994; Hasher and Zacks, 1988). The inhibition deficit theory of cognitive ageing (Lustig et al, 2007; Hasher and Zacks, 1988) argues that inhibition deficits are a core deficit as we age and that errors or low-quality information due to inhibition deficits cascade through the information processing stream and give the impression that other cognitive functions are also impaired. Consistent with this, Darowski et al (2008) has argued that distractor inhibition is fundamental in facilitating cognitive control. Moreover, this theory argues that different inhibition mechanisms can be independently impaired. For example, Vadaga et al (2015) tested for age-related inhibition deficits in three distinct inhibitory functions: "(a) controlling access to attention's focus, (b) deleting irrelevant information from attention and working memory, and (c) suppressing or restraining strong but inappropriate responses" (referred to as access, deletion, and restraint, respectively; Lustig, 2007). They found that the presence and magnitude of a

deficit depended on which inhibitory function was being tested; restraint was impaired more than deletion, and access was not impaired at all. As another example, Anguera and Gazzaley (2012) assessed motor inhibition and sensory filtering in a stop-signal task in an aging population. They found that these inhibitory modalities were independently impaired as a function of aging. Other studies have also shown age-related inhibition deficits whose presence or magnitude varied as a function of the type of inhibition being tested (Kramer et al, 1994; Hasher and Zacks, 1988; Sebastian et al, 2013; Bloemendaal et al, 2016). It should be noted that

The DMC framework provides a potential explanation for why some inhibition mechanisms become impaired in aging populations and others do not. Specifically, there is evidence that proactive inhibition mechanisms become impaired over time and that people switch to the predominant use of reactive inhibition mechanisms. Braver et al (2005) had subjects engage in an 'AxCPT' task. They were presented with temporally separated cue-probe letter pairs and had to respond when the letter X appeared, but only if it was preceded by the letter A ('Ax' trials). Braver et al (2005) argued that subjects who naturally engaged proactive control would start responding when presented with the cue (the first letter) and those who naturally engaged reactive control would start responding when presented with the probe (second letter). Based on this, it was predicted that subjects engaging proactive control mechanisms should make fewer errors during the trials where there was a non-A letter followed by the letter X ('Bx' trials), compared to trials where the letter A appeared but was followed by a non-X letter ('Ay' trials). Because "proactive" participants would pre-emptively begin responding when presented with an "A," they would be more likely to accidentally respond before realizing the probe was not an "X," producing more errors on "Ay" trials. When they are presented with a non-A letter first, they would

start inhibiting the probe regardless of its identity and are more likely to not respond, reducing errors on “Bx” trials. In contrast “reactive” would only trigger decision processes following the probe letter and therefore would accidentally respond when an “X” was a probe because they weren’t focusing on the first letter, increasing errors on “Bx” trials. Similarly, as long as the second letter is not an “X,” they would be unlikely to respond, reducing errors on “Ay” trials. The usefulness of this paradigm in the ageing context is apparent as in Braver et al (2005), young subjects showed a proactive pattern of results and the older subjects showed a reactive pattern of results.

Brain imaging studies using this paradigm have also supported the notion of increased reactive processing in old age. Paxton et al (2008; study 1) replicated the results from Braver et al (2005; study 1) in a scanner and showed decreased delay-related activity in the dorsolateral PFC, suggesting a possible impairment to proactive control mechanisms. In study 2, despite finding no behavioral evidence of a maintenance deficit for elderly subjects (“Ay” vs “Bx” performance), they did find significant differences in brain activity. They found decreased cue-related activity in elderly subjects relative to young subjects which was interpreted as being consistent with the decreased use of proactive control. Additionally, they found increased probe related activity in elderly subjects that was most prominent on ‘Bx’ trials. Even though there were no behavioral differences, the elderly subjects were showing a unique temporal processing signature which was in accord with increased reliance on reactive control.

However, the ‘AxCPT’ paradigm is not without its limitations. First, it is unclear if differences in performances in aging reflect a shift towards reactive control due to impairments in proactive control, or if the shift towards reactive control is simply due to a shift in strategy. A shift towards reactive control could be considered due only to

impairments in proactive control if there was no apparent strategic benefit to making the switch. It should be noted that this interpretation does not assume that proactive control could not be used at all if it were impaired. Proactive control can still be used even when impaired (Braver et al, 2009), but in its impaired state may be less effective than using reactive control. In the standard AxCPT (Braver et al, 2005; Paxton et al, 2008; Braver et al, 2009; Carter et al, 1998) task there is a performance trade-off between 'Ay' and 'Bx' trials when switching between proactive and reactive strategies, so there is always some 'benefit' to switching. Braver et al (2009) has shown that young and elderly subjects can be incentivised to perform an AxCPT task more reactively and proactively, respectively. This supports the notion that the results of the AxCPT may be due to changes in strategy.

A second problem is that the argument that 'proactive' subjects will respond based on the identity of the cue and that 'reactive' subjects will respond based on the identity of the probe assumes that proactive and reactive control are independent and that people can only engage either one or the other. It also ignores the possibility that proactive control in particular could act upon the probe as well as the cue. With this in mind, another way to distinguish between mechanisms is to consider that if someone engages only proactive mechanisms to complete the task, one might expect impaired performance on both "Ay" and "Bx" trials, as proactive control could prime subjects in advance to make a response to an "A" or "X". On the other hand, if someone engages proactive and reactive mechanisms to complete the task, one would expect improved performance on "Ay" and "Bx" trials, because subjects would be able to inhibit the primed response to the "A" or "X." Critically, these two perspectives on how to distinguish between proactive and reactive control are not mutually exclusive. It may be possible to see overall differences in "Ay" and "Bx" performance between groups while also observing an age group by trial type interaction.

Braver et al (2005) divided their age groups into a young (18-24 yrs), young-old (66-75), and an old-old group (76-92). Comparing the young and the young-old group, they reported that the young-old group made fewer errors on “Ay” trials than young subjects in general, but had equivalent performance on “Bx” trials. Unfortunately, they did not compare the young and the old-old groups, but they did show that the old-old group made fewer errors than the young-old group on “Ay” trials in the long delay condition.

While much of the evidence for a shift to reactive control in ageing comes from studies using the ‘AxCPT’ paradigm, other studies have also come to similar conclusions. For example, Jimura and Braver (2010) found, in a task switching paradigm, that elderly subjects showed reduced sustained activation in general and increase in transient activation during switch trials in the anterior prefrontal cortex. They also found that younger subjects demonstrated cue-related activity in the posterior parietal cortex on all trials, whereas older subjects showed that activity only on switch trials. These findings are consistent with the idea that older subjects switch to the use of reactive control mechanisms because proactive mechanisms are impaired. Although it should be noted that there are no studies that explicitly test if reactive control is impaired; it is simply assumed that reactive control is intact because older participants use it more often. Chapter 3 will explicitly test this assumption.

Similarly, although it is clear there is a shift in the relative use of proactive and reactive control, the explicit evidence that proactive inhibition mechanisms are impaired is also surprisingly limited. Most of the studies which have identified impairments involved tasks that could have been completed with either proactive or reactive mechanisms, thus allowing for the possibility that there is simply a shift in strategy over the lifespan. As mentioned, in the AxCPT task, there was a performance trade-off between ‘Ay’ and ‘Bx’

trials when switching between proactive and reactive strategies. In one notable study, Tsvetanov et al., (2013) showed a specific age-related proactive inhibition deficit in the non-spatial inhibition of salient distractors. Subjects were presented with a compound letter task designed so that either the global or local form could be more salient. Despite knowing in advance, with 100% validity, which element of the display was the target and which was the distractor, the elderly subjects were significantly more susceptible to salient distractors than younger subjects. Furthermore, Mevorach et al (2008a) has shown that the ability to ignore salient distractors in this paradigm relies on a preparatory (proactive) process mediated by the left intraparietal sulcus (left IPS). And crucially, there is no apparent trade-off or benefit for engaging reactive control mechanisms in this task. Therefore, these results can be taken as evidence that proactive inhibition is specifically impaired in ageing populations. Chapter 2 will further investigate the notion that proactive control is impaired in aging populations by observing participants in an fMRI scanner while they engage in the paradigm from Tsvetanov et al. (2013).

Brain regions in the left posterior parietal cortex have been shown to be implicated in the suppression of salient distractors, a process that appears to be impaired in proactive control and intact in reactive control. The second part of this chapter will review the role of the left posterior parietal cortex in salience suppression. This will provide background that is necessary to assess if there is a relationship between these brain regions and proactive and reactive control.

Salience Suppression in the Left PPC

The left posterior parietal cortex has been implicated in the suppression of salience in numerous contexts, such as in global/local tasks (Mevorach et al, 2008b, 2010b; 2016;

Tsvetanov et al, 2013), self-reported cognitive failure questionnaires (Kanai et al, 2011), contextual cueing tasks (Geng and DiQuattro, 2010; DiQuattro and Geng, 2011; Geng and Mangun, 2008; Geng and Vossel, 2013), and motor planning tasks (Chapman et al, 2011). In addition, this region has been implicated in the suppression of social salience as well, such as in self-association tasks (Sui et al, 2013a; 2013b) and perspective taking tasks. Finally, there is some evidence that the left PPC is involved in the suppression of alternative functional uses for a given brain region (Hubbard et al, 2004) and the suppression (and/or coordination) of processing of alternative sensory modalities (Foxe and Snyder, 2011; Calvert, 2001). Of course, the left PPC is a large brain region consisting of numerous functionally distinct sub-regions which also perform functions unrelated to salience suppression (Anderson, 2007a; 2007b; 2007c; 2010). This review will focus on two sub-regions in particular and their role in salience suppression: the left intraparietal sulcus (left IPS) and the left temporoparietal junction (left TPJ)

What is Salience?

Salience refers to the extent a stimulus stands out relative to all other currently perceived stimuli. A stimulus that is highly salient in one context may be of low salience in different context. Stimuli can stand out on the basis of both internally (i.e. behavioral goals) and externally (i.e. color, shape, brightness, etc.) generated features. Many influential models of selective attention are based on the idea that the brain generates saliency maps, which represent the relative saliency of all perceived stimuli. In these models, attention is directed toward the stimuli that is represented by the highest saliency values (Treisman and Gelade, 1980; Wolfe et al, 1989; Wolfe, 2001; Humphreys, 2016). Critically, these models often implicate multiple specialised saliency maps that must interact with each other to

determine overall the relative saliency of incoming sensory information (Treue, 2003; Fecteau and Munoz, 2006; Itti and Koch, 2000). For example, there is evidence that there are multiple different saliency maps for physical stimuli. Some studies suggest saliency maps exist at the level of sensory map (vision, audition, etc), whereas others suggest that there are distinct saliency maps at the level of simple features (contrast, orientation, color, etc). There is also evidence for saliency maps based on behavioral goals (Assad, 2003) and, arguably, for social salience (Sui et al, 2015).

These concepts are important to this chapter as the mechanisms that facilitate the suppression of salience may do so through the creation and updating of saliency maps (Falkner et al, 2010; Shipp, 2004). At first glance, the need for multiple specialized saliency maps seems to imply the existence of multiple distinct suppression mechanisms. However, this is not necessarily the case. It is possible for different types of salience to be processed by similar brain regions and through similar cognitive processes. Indeed, the left intraparietal sulcus (Molenberghs et al, 2007; Vandenberghe et al, 2009) has been implicated in both the generation and maintenance of saliency maps (REFS), and in the suppression of both physical (Mevorach et al, 2008b; 2010c) and social salience (Sui et al 2015).

The Left IPS and the Suppression of Salience

Historical Context

Research showing the relationship between the left IPS and the suppression of salience came about as a result of research into the processing of hierarchical images. The classic theory of lateralization in the parietal cortex states that the left posterior parietal cortex is involved in the processing of local features in a display, whereas the right posterior

parietal cortex is involved in the processing of global features of a display (Fink, 1996; Christie et al, 2012). This left hemisphere-local/right hemisphere-global dichotomy is supported by both neuroimaging and neuropsychological evidence. For example, patients with lesions in the left PPC exhibit impairments in making judgements about and processing local items and patients with right PPC lesions are impaired with respect to global items (Robertson and Ivry, 2000; Delis et al, 1986). In another study, Chechlacz et al (2015) conducted a topological and hodological fMRI analysis of sub-acute stroke patients (n = 248; Mean age = 72.02) in conjunction with a complex figure-copying task. According to their results, the processing of local features was mediated by a left lateralized neural network (including the parietal, occipital, and insular lobes, but with an emphasis on the posterior parietal cortex), whereas the processing of global features was mediated by a right lateralized neural network.

However, other studies appeared to contradict this theory. Lux et al. (2004; Sasaki et al, 2001) found that there was no difference in hemispheric activation when subjects were attending to different levels of an hierarchical stimulus. And Martinez et al (1997) had subjects perform a global/local discrimination task and found that there was greater activation in the right occipital-temporal region when processing global forms compared to local forms, but no differences in the activation of the left occipital-temporal region. Furthermore, based on the classic global/local theory, processing global forms in the left visual field – right hemisphere – should improve performance and there should be a similar effect for local forms and the right visual field. Yet, these hierarchical image hemifield advantages do not present in every study (Blanca Mena, 1992; VanKleeck, 1989). In fact, Fink et al (1997a) found a reversal of the typical global-right/local-left relationship. Then, evidence began to emerge that the classical global/local lateralized effects were due more

to attentional constraints, rather than the processing of hierarchical levels. Switching between hierarchical levels is an attentionally demanding task. Kimchi and Merhav (1991) showed that typical global/local hemispheric differences presented when the task required focused attention, but when the task involved distributed attention the differences were not present. These results can be interpreted as evidence that global/local hemispheric effects are not driven by processing of hierarchical levels but by the availability of attentional resources, which in turn can directly influence the relative saliency of the elements of the display (Carrasco et al, 2004; 2006; Yeshurun and Carrasco, 1998; 1999).

Another issue with the classic global/local theory is its apparent elegance. There are two hemispheres in the brain and research into global/local processing usually only refers to two hierarchical levels. This gives the appearance of a seemingly parsimonious relationship such that each hemisphere deals with a different type of information, yet it ignores a critical element of visual perception namely that there are often more than two hierarchical levels in real world stimuli. Of course, this also assumes that real world objects can be described in terms of discrete hierarchical levels (Krakowski et al, 2015; Rijpkema et al, 2007), even though a continuous hierarchical gradient is also a possibility (Yeari and Goldsmith, 2011; Eriksen and James, 1986; Klein and McCormick, 1989; McCormick and Klein, 1990; Anderson and Kramer, 1991). Three level (or more) hierarchical stimuli, for example, presented a clear problem for the global/local theory: Would the intermediate form be processed in the left or right hemisphere? And would any benefit be conferred upon the processing of the intermediate form based on the hemifield location? Unfortunately, there have been no studies investigating this issue, but it still casts doubt on the validity of the classic global local theory.

Current State of the Literature

The Suppression of Physical Salience

In order to resolve these contradictory results, Mevorach et al (2006a; 2006b) argued that the left hemisphere-local/right hemisphere-global dichotomy was co-varying with other lateralized factors, namely attentional control (also see Fink et al, 1997b; Fink et al, 1998). In particular, they argued that the left posterior parietal cortex was involved in the biasing of attention away from salience and that the right posterior parietal cortex was involved in the biasing of attention towards salience. In Mevorach et al (2006a), subjects were presented with compound letters designed so the local letters were more salient than the global letter (evidenced by a local precedence effect in control subjects). Patients with left parietal lesions (n = 5; Mean age = 59.8) showed significant local interference when attempting to identify the global letter, but only if the local level was more salient. Similarly, they showed increased global interference when they had to identify the local letters, but only if the global level was more salient.

In a complementary paper, using repetitive transcranial magnetic stimulation (rTMS), Mevorach et al (2006b) provided causal evidence that the left posterior parietal cortex (left PPC) was involved in the suppression of salient distractors. Prior to the task rTMS was applied to the left or right PPC (P3 and P4, respectively on the 10-20 EEG coordinate system; the subject engaged in one experimental session for each TMS condition). Healthy, typically developing, adult subjects (n = 9; Mean age = 31.4) were presented with a more refined version of the compound letter task previously described in the previous paper. Essentially, it was further developed such that either the global or local form could be the more salient feature. The results showed a double dissociation in terms of the effect of rTMS on the left and right PPC. rTMS to the right PPC increased the interference from low salience

distractors, when the target was high salience; however, there was no effect of rTMS for trials with a high salience distractor and a low salience target. Conversely, rTMS to the left PPC resulted in increased interference for trials with high salience distractors and low salience targets; and there was no effect of rTMS for trials with a low salience distractor and high salience target. Mevorach et al (2006b) concluded that this was evidence that the right PPC was critical for biasing selection toward salient stimuli, whereas the left PPC was involved in biasing selection away from salient stimuli.

Mevorach et al (2008) further showed that it is specifically the left intraparietal sulcus (Left IPS) that is the subregion of the left PPC that is responsible for the suppression of highly salient distractors. The intraparietal sulcus is a bilateral region that bisects the post-central sulcus and extends posteriorly until it intersects with the trans-occipital sulcus. Using the global/local task with an orthogonal salience manipulation, they found significant activation in the left IPS when subjects were presented with trials where the target was the feature with lower salience and the distractor was the feature with high salience. Next, Mevorach et al (2010) showed that the left IPS inhibited salience by applying a top-down inhibition signal directly to the visual cortex. In experiment 1, subjects were exposed to 20 minutes of 1hz rTMS over the left or right intraparietal sulcus, placed into an fMRI scanner, and then presented with the global/local task with an orthogonal salience manipulation. They found that on trials with salient distractors and no TMS, there was increased activity in the left IPS and decreased activity in the occipital cluster. However, when TMS was applied over the left IPS there was greater activity in the occipital cluster compared to the no TMS condition. This suggested that the left IPS was actively suppressing the occipital cluster when salient distractors were present. When TMS was applied to the left IPS, this process was interrupted and resulted in increased activation in the occipital cluster. To confirm that

the left IPS/occipital cluster circuit was indeed the mechanism being used to suppress salient distractors, in experiment 2, TMS was directly applied to the left occipital pole prior to engaging in the task. The logic was that if activity in the left IPS inhibits activity in the occipital cluster, then disrupting activity in the left occipital pole with TMS pulses should have the same suppressive effect. Essentially, they argued that applying TMS to the left occipital pole should improve performance on trials with salient distractors. Indeed, this is the result that was found. It was concluded that the left IPS suppressed activity in the visual cortex in the presence of salient distractors, which prevents attentional capture of the distractor (Mevorach et al, 2010).

The Suppression of Internally Generated Saliency

One of the major questions about left IPS mediated saliency suppression is whether it can deal with saliency generated through many different means or through a limited subset of means. The previous section demonstrated its role in suppressing externally generated saliency (i.e. distractors salient based on a distinct color, brightness, size, etc.), however there is also evidence that it is involved in the suppression of internally generated saliency (i.e. behaviorally relevant distractors). Chapman et al (2011) found activity in the left IPS and in the early visual cortex while subjects had to reach for and grab an object while avoiding obstacles. A cue was presented to participants, prior to a 'go' signal, indicating which way to grab the object: with the thumb on the front of the object or on the side. They made three discoveries relevant to this chapter. First, they found that left IPS activity was modulated based on the degree of obstacle interference (no obstacle, obstacle behind the target object, or obstacle next to the target object). Second, a left posterior IPS area (Talairach coordinates: -21,-85, 25) showed sustained higher activity throughout the

entire planning phase (after the grasping cue, but before the 'go' signal) in conditions with obstacle interference relative to no interference. And third, a left anterior IPS area (Talairach coordinates: -46,-42, 56) showed activity started at a higher level and peaked higher in conditions with obstacle interference relative to those without interference. In this study, the salience of the distractor (the obstacle object) was primarily generated through its behavioral relevance (how likely it was to interfere with the grasping motion) and the left IPS still appeared to be critical during suppression. This suggests that left IPS mediated salience suppression is not specific to externally generated salience.

One concern about the previous study is that the behavioral measure was testing motor control, rather than attention per se. Therefore, it's possible that the left IPS was involved in the suppression of movement, rather than the suppression of attention. However, other studies have also implicated left IPS in the suppression of internally generated salience. In a now seminal paper, Tajfel et al (1971; Diehl, 1990) showed that subjects would display different behaviors towards others whom they believed were part of a different 'group' than themselves, even when group membership was determined on the basis of an arbitrary criteria. Recent evidence suggests that the effect of these social influences can be seen even at the level of basic perception. Sui et al (2012a; 2012b) showed that when subjects were asked to associate simple shapes, such as a circle, with themselves and different shapes with other people, subjects were faster in a subsequent task to respond to the shape they associated with themselves. This suggests that subjects were able to guide perception on the basis of internally generated social salience toward the self-associated shape in the same way they can use physical salience to guide perception to the red shape (or the big shape, or the circle, and so on).

Sui et al (2013) then investigated the neural correlates of suppressing stimuli that is salient on the basis of social associations. In the first phase of this study, subjects had to associate different shapes with themselves, their best friend, and a stranger. In the second phase, subjects were presented with hierarchical images constructed out of the shapes from the first phase of the study. For example, they might be presented with a square constructed out of circles. On some blocks the subject would be required to identify the global shape (the square in the previous example) and in other they would have to identify the local shape (the circles in the previous example). Due to the associations from the first phase of the study, on some blocks the subject would have to identify the shape associated with a stranger while ignoring the shape associated with themselves. Since the self-associated shape was considered to be more salient than the other person-associated shape (Sui et al, 2012), on these trials subjects would be suppressing a salient distractor and selecting a non-salient target on the basis of internally generated social salience. Significant activation in the left IPS (using the same ROI from Mevorach et al, 2009) was found in the conditions where the salient self-associated shape was a distractor, suggesting that the suppression of internally generated social salience (and by extension, possibly all forms of internally generated salience) arises through the use of the same parieto-occipital circuit identified by Mevorach et al (2010).

The Left TPJ and the Suppression of Salience

Historical Context

The temporo-parietal junction (TPJ) is a bilateral region located posterior to the sylvan juncture and anterior to the occipital lobe. It is comprised of the border regions between the temporal lobe and the parietal lobe, including the inferior parietal lobe and the

posterior portion of the superior temporal lobe. In the broadest sense, the TPJ appears to be involved in bottom-up attentional capture (Behrmann et al, 2014; Cabeza et al, 2008) through the biasing of attention in response to relevant, but unexpected stimulus events (Vandenberghe et al, 2009; DiQuattro and Geng, 2011). Corbetta and Shulman (2002; Chang et al., 2013; Astafiev et al, 2006; Corbetta et al, 2000) implicated a right lateralized ventral network (comprised of the right TPJ and the right inferior frontal cortex) that inhibits a top-down dorsal network (comprised of the bilateral IPS and bilateral superior frontal cortex) and reorients attention towards unexpected, but relevant stimuli. They described the function of the ventral network as an attentional “circuit breaker.” There has also been some evidence suggesting that the right TPJ is involved in the reorienting of attention towards internally generated stimuli, such as switching between internal representations of one’s self and of others (Sowden and Catmur, 2013).

Neuropsychological studies also highlighted the right hemisphere as more critical than the left in spatial attention. Spatial neglect is an attentional disorder (Corbetta and Shulman, 2011) in which, due to damage to the inferior parietal cortex, patients are unable to orient towards and attend to the neglected side of space. Typically, it is expressed as “right neglect” (damage to the right inferior parietal cortex and neglect to the left side of space) and while “left neglect” does occur, it is much less severe (Stone et al, 1983). The most notable explanation for this functional asymmetry was that damage to the ventral regions of the right hemisphere impairs communication between the ventral and dorsal networks, resulting in neglect (Corbetta and Shulman, 2011; but also see Mesulam, 1981; Kinsbourne, 1987). Thus, it was argued that the right inferior parietal cortex plays a significantly more important role in attentional orienting and processing compared to the left inferior parietal cortex (Hodsoll et al, 2009; Corbetta et al, 2000; Coull et al, 1998).

However, Geng and Vossel (2013) identified two major problems with a solely right lateralized network. First, if the function of the ventral network is to interfere with the function of the dorsal network, then the ventral system has to activate in response to stimuli before the dorsal network has time to orient or bias attention. However, electrophysiological and TMS evidence largely suggests that the dorsal network is activated first. In particular, the frontal eye fields (FEF) tend to activate before the TPJ (O'Shea et al., 2004; Neggers et al., 2007; Bardi et al., 2012; Meister et al., 2006). And second, they argued that the emphasis on the right hemisphere was simply unwarranted considering growing evidence that the left parietal cortex, and the left TPJ in particular, may in fact play a significant role in attentional control (Wilson et al, 2005; Coull et al, 2000; Cabeza et al, 2008). In fact, one particularly notable study argued that previous fMRI studies of spatial attention may have been unintentionally missing evidence of left TPJ involvement because of how the data was being analysed (Macaluso and Doricchi, 2013; Doricchi et al, 2010). They found that just the left TPJ responds to validly cued targets, whereas the left and right TPJ respond to invalidly cued targets. However, many fMRI studies on spatial attention generate activation maps by comparing performance during validly cued and invalidly cued trials directly, rather than comparing them to a neutral cue condition. The result is that activation in the left TPJ is effectively subtracted out of the final activation maps, masking the fact that it may be playing a significant role in spatial attention.

Current State of the Literature

In light of these problems, Geng and Vossel (2013) proposed the contextual updating hypothesis which essentially argues that the left TPJ does not control bottom-up attentional reorienting, like the right TPJ, but rather evaluates and integrates bottom-up and top-down

information and then directs attention. DiQuattro and Geng (2011) had subjects perform a visual search task for a low contrast target in the presence of either a high or low contrast non-target, each of which would appear in one of two pre-defined locations (i.e. the t-task from chapter 4). Despite being task irrelevant, the non-target was contextually relevant as the presence of a high contrast non-target informed the subject that the target was in the other location. At the group level, the left TPJ and left inferior frontal gyrus (IFG) were significantly more active when there was a high salience non-target compared to a low salience non-target, although this was mostly due to deactivation of these regions when there was a low-salience non-target (compared to baseline). In addition, dynamic causal modelling revealed a network in which TPJ projects to IFG, which then projects to the frontal eye fields (FEF). They concluded that the left TPJ is sensitive to non-spatial features with contextual relevance that, in conjunction with the IFG, integrates that contextual knowledge with incoming sensory information in order to generate an attentional control signal. Moreover, they argued that the TPJ and IFG were effectively generating a “reactive” control signal that allowed subjects to use the contextually relevant distractor to their advantage.

Converging evidence for this proposed role of the left TPJ/IFG network was provided by Kucyi et al (2011), who assessed the resting state functional connectivity of the left and right TPJ with the whole brain, but particularly a salience/ventral attention network (defined as an ICA component that included the anterior insula, mid-cingulate cortex, and dorsolateral prefrontal cortex at a threshold of $z > 4.6$). They found that right TPJ was more strongly connected to the salience/ventral network than the left TPJ, but the left TPJ was more strongly connected to executive control regions (such as the dorsomedial prefrontal cortex, supplementary eye fields, and the dorsolateral prefrontal cortex cerebellar regions).

They argued that this was evidence that the right TPJ is involved in salience detection, whereas the left TPJ is involved in integrating sensory and contextual information and the facilitation of attentional control.

Based on these studies, the right TPJ appears to direct attention towards salience, but the left TPJ is necessary to assess if the salience is contextually relevant and to reorient attention away from salience if it's task irrelevant (in conjunction with the left IFG and left FEF). The terminology can be a bit confusing because it's a point of semantics if something is relevant or irrelevant. For example, in the case of DiQuattro and Geng (2010), the salience of the distractor indicates if the distractor is the target or not and therefore it is informative (and relevant), but also it is a distraction from the task (and therefore irrelevant). For clarity, we make a distinction between contextual relevance, which refers to how informative the salience is, and task relevance, which refers to whether the salience inherently draws attention towards or away from information relevant to the task.

Salience Suppression and the DMC Framework

In the second part of this chapter, two sub-regions in the left PPC were described that are involved in the suppression of salient distractors across different paradigms. The left IPS appears to be involved in the suppression of distractors that are salient on the basis of externally generated physical stimulus properties and internally generated stimulus properties (behavioral relevance and social salience). And the left TPJ appears to be involved in the suppression of distractors that are salient and contextually relevant. The next part of the chapter will evaluate the possible relationship between proactive and reactive inhibition and these two suppression mechanisms. In particular, the intent here is to evaluate evidence that Left IPS and left TPJ mediated salience suppression mechanisms have also

been implicated, though not explicitly, in the proactive and reactive networks, respectively, and that their time courses resemble their presumed control mode. Here, we define proactive control processes as those that occur prior to stimulus presentation and reactive control processes as those that occur after stimulus presentation.

Proactive Control and the Left IPS

Irlbacher et al (2012) argued that proactive control is mediated by a fronto-parietal network that consists of three sequential stages. First, there is activation in the pre-supplementary motor area (to signal the need for increased cognitive control). Second, there is activation in the left dorsolateral prefrontal cortex and the posterior parietal cortex (to generate and activate task goals and representations). And third, there is activation of the left IFG and medial temporal lobe (MTL; to update and maintain goal relevant information). Similar to the second stage of this process, the left intraparietal sulcus has been implicated as part of a fronto-parietal network involved in mediating top-down attention; Corbetta and Shulman, 2002).

In addition to similarities in the localization function, the time course of proactive control also appears to correspond to that of left posterior parietal cortex (PPC) mediated salience suppression. West et al (2012) identified the temporal dynamics of proactive control, particularly those related to error monitoring and conflict processing (both aspects of cognitive control). West et al (2012) had subjects engage in the counting Stroop task (Bush et al, 1998) or a blackjack game (intended to be a more “naturalistic” task) while being monitored for event related brain potentials (ERP’s). They found slow wave activity over the lateral frontal region and concomitant activity over posterior brain regions during the response-to-stimulus interval in the stroop task and following feedback in the blackjack

task. This was interpreted as evidence that proactive cognitive control was mediated by communication between the lateral PFC and structures within the posterior cortex. Furthermore, in the blackjack task, the slow wave activity began at a similar time as a feedback related negativity signal (which reflects the integration of past expectations and present experiences, particularly in terms of salience; Hauser et al, 2014; Talmi et al, 2013; Moser and Simons, 2009) and persisted for 500-2000 ms, suggesting sustained, rather than transient, activity that reflects “the updating of goal representations that support proactive cognitive control” (West et al, 2012; see here for explanation of why this reflects updating rather than maintenance). This means that the activity took place after feedback, but before the presentation of the next stimulus.

A possibly confusing issue is that it is somewhat subjective that we operationalize the brain activity as being prior to stimulus $n+1$, defining it as a proactive process, rather than after stimulus n , and defining it as a reactive process. In fact, both of these interpretations ignore the possibility that the activity might reflect both proactive and reactive processes simultaneously. This is related to the issue discussed earlier regarding the AxCPT task and whether it's appropriate to assume 'proactive' subjects will respond based on the identity of a cue and that 'reactive' subjects will respond based on the identity of a probe. In general, this is a persistent issue in all studies investigating proactive and reactive control, particularly because most paradigms in the literature could arguably be completed with either proactive or reactive control. For this reason, there is currently no satisfying method of generating clear linking hypotheses between behavior and brain activity in this field. At the moment, the best option is to use tasks that heavily favor or reward the engagement of one control mode over the other to increase the likelihood that the behavior or brain activity is indeed associated with the intended control mode.

Taking this into consideration, there is further evidence that Left IPS mediated suppression may be involved in proactive control. Earlier a global/local paradigm with an orthogonal salience manipulation was described as the most convincing evidence that proactive control is impaired in aging populations (Tsvetanov et al, 2013). This paradigm was notable because engaging proactive control is inherently encouraged during this task for strategic reasons. Using this task, Mevorach et al (2008) established unique time courses for the function of the left and right PPC with regard to salience suppression. Keep in mind that the source of left PPC mediated suppression was ultimately localized to the left IPS. Crucially, the identified time course left IPS mediated salience suppression roughly corresponds with the time course of proactive control related activity in the posterior cortex identified by West et al (2012). In experiment 2, rTMS was applied over the left PPC (P3 on the 10-20 EEG coordinate system) between either 150 – 50 ms before stimulus presentation or 50 – 150 ms after stimulus offset (in each condition, 3 TMS pulses were applied with a 50ms delay between each pulse). They only found an effect of rTMS on the left PPC when the distractor was the most salient item in the display and when the rTMS was applied before the stimulus presentation. When rTMS was applied to the left PPC after stimulus presentation, there was no effect on performance. Based on these results, it was concluded that the left PPC (but essentially the left IPS when taken in conjunction with other literature) is involved in the preparatory suppression of high salience distractors (also see Mevorach et al, 2006b).

Taken together, this evidence makes a case for left IPS mediated salience suppression being part of the proactive control network. It is part of a fronto-parietal network that functions within the timescale of proactive control (prior to stimulus

presentation) and it performs a function necessary to proactive control (suppressing salient distractors).

Reactive Control and the Left TPJ

The time course of reactive control and left TPJ mediated salience suppression are also similar, though this relationship is a bit more complex than proactive control and the left IPS. According to Irlbacher et al (2014), reactive control can be parsed into an early and late mechanism and that each mechanism provides a unique method of identifying and resolving conflict. In the context of working memory inhibition, both mechanisms resolve interference that occurs when a familiar stimulus is identified, but must be ignored.

Familiarity-inhibition models favor speed over accuracy and are considered to be a quick and early acting reactive control mechanism, engaging around 300-450 ms after stimulus presentation (Du et al, 2008). In these models, the interference is resolved through the inhibition of the familiar stimulus (Mecklinger et al, 2003). On the other hand, context retrieval models favor accuracy over speed and are considered to be a slower and late acting reactive control mechanism, engaging around 550 ms after stimulus presentation (Zhang et al, 2010). In these models, the interference is resolved by selecting for the relevant target features more strongly (by retrieving the appropriate contextual information; Badre and Wagner, 2005; 2007).

For our purposes, we are interested in the suppression of salient distractors (rather than working memory inhibition) and indeed there is converging evidence for an early and late reactive mechanism in this context as well. Geng and DiQuattro (2010) identified two parallel mechanisms that mediated the use of a salient distractor as an anti-cue: A fast acting inhibitory mechanism when participants' initial saccades went towards the target and

a slower rapid rejection mechanism when their initial saccades went towards the salient distractor. This was the same task used in DiQuattro and Geng (2011), which showed that the left TPJ worked in conjunction with the left IFG and left FEF to bias attention away from the salient distractor. This is consistent with the idea that left TPJ mediated salience suppression is part of the reactive control network.

However, it is less clear if the left TPJ mediates an early form of reactive control like inhibition, a late form of reactive control like rapid rejection, or both. Early and late reactive control appear to act through mostly distinct neural mechanisms. One common factor in both mechanisms of reactive control appears to be activation of the left inferior frontal gyrus between 0-250 ms after stimulus presentation (Irlbacher et al, 2014). Feredoes and Postle (2010) used online rTMS to assess the temporal profile of Left Inferior Frontal Gyrus (LIFG) activation in reactive control. Subjects were presented with a set of 4 stimulus letters simultaneously and, after a delay, presented with a probe letter. They had to indicate if the probe letter matched any of the stimulus letters. Delay time between the target and probe letters was parametrically manipulated (100, 200, 300, 500, 800, or 1200 msec). There were also four probe types. Non-recent match and non-recent non-match, where the probe letter was not present in the target display for at least the previous two trials, and recent match and recent non-match, where the probe letter was present in the target display in the previous two trials. They found that with no rTMS, errors increased for recent non-match trials at lags of 100-200 msec and that error rates did not recover until lags of 500 msec. They argued that this reflected a strong influence of familiarity based information early on, with contextual information influencing processing later on. Critically, early rTMS (3 pulses, 0-250 msec after probe onset) to the LIFG significantly accuracy relative to control stimulation, whereas there was no difference for late rTMS (3 pulses, 500-750 msec after

probe onset). While Feredoes and Postale (2010) argue that this is evidence of LIFG activation in early proactive control, here we argue that, in conjunction with the converging conclusions in Irlbacher et al (2014), this in fact reflects early reactive control since the stimulation was taking place after stimulus and probe presentation. This is another example of how operationalizing brain activity can be difficult in this field. According to Irlbacher et al (2014), LIFG activation is accompanied by activation in the dorsolateral prefrontal cortex and the posterior parietal cortex, and followed by activation in the pre-supplementary motor area. These brain regions have been implicated in various aspects of cognitive control including maintenance of task goals, salience processing, and predictions of expected cognitive demand, respectively.

In late reactive control, there are three stages of processing, rather than two. First, there is activation of the left IFG. Second, there is activation of the anterior ventrolateral prefrontal cortex and the medial temporal lobe, which have been implicated in retrieval of episodic details. And third, there is activation of the left IFG again (for post-retrieval selection), the fronto-polar cortex and anterior cingulate cortex (for evaluation, monitoring, and the biasing of response processes), and the pre-supplementary motor area (to predict cognitive demands; Irlbacher et al, 2014). The brain regions presumably involved in early reactive control appear to match the brain regions identified by DiQuattro and Geng (2011) as involved in reactive inhibition, suggesting the left TPJ/left FEF/left IFG may mediate an early form of reactive control, like inhibition. However, DiQuattro and Geng (2011) also argued, based on a dynamic causal model, that ventral network activity (including the left TPJ) occurs later than dorsal network activity (3 seconds vs. 5 – 6 seconds in their model). From this, they inferred that the ventral network is updating the dorsal network reactively with contextual information to facilitate behavior. While it is difficult to compare timescales

across different studies and mechanisms (working memory inhibition vs attentional control), this is tentative evidence that the left TPJ may mediate a late form of reactive control, like rapid rejection.

Overall, this evidence suggests that left TPJ mediated salience suppression is part of the reactive control network, but it is unclear if it mediates an early or late form of reactive control (or both).

Conclusion

In this chapter, it has been established that proactive and reactive inhibition mechanisms appear to engage distinct neural substrates to mediate top-down attentional control. Converging, though by no means explicit, evidence suggests that proactive inhibition engages the left intraparietal sulcus, part of the dorsal attentional network, whereas reactive control engages the left temporoparietal junction, part of the ventral attentional network. Moreover, proactive and reactive attentional control appears to be influenced by age. However, there are a number of unanswered questions. This dissertation will further investigate which brain mechanisms are involved in proactive and reactive attentional control across the lifespan, how the function of those brain mechanisms is affected by age, and how those functional changes translate to differences in behavior. Chapter 2 will investigate the neural correlates of proactive inhibition in a young and aging cohort, with an emphasis on assessing if the left IPS and/or left TPJ play a significant role in either age group. Chapter 3 will assess if there are detectable behavioral deficits in reactive control in old age. Chapter 4 will use TMS to explicitly test the role of the left TPJ during reactive control. And chapter 5 will test if the allocation of attention to a distractor prior to inhibition is impaired in aging participants.

Chapter 2: The Neural Correlates of Age-Related Differences in Non-Spatial Saliency Suppression

Introduction

As people get older, it becomes more difficult to ignore distractors. According to the inhibition deficit theory of cognitive ageing (Lustig et al, 2007), this is due to changes in the ability to suppress irrelevant distractors. While there is evidence that older participants can compensate for these impairments by generally favoring the use of reactive, over proactive, cognitive control strategies (see Chapter 1; Jimura and Braver, 2010; Paxton et al, 2008; Braver et al, 2005; Grady, 2012), in some tasks the compensatory strategies still produce sub-optimal performance (especially, but not limited to, tasks where reactive control is counterproductive). For example, Tsvetanov et al (2013) found behavioral evidence of an age-related performance deficit in the ability to suppress salient, non-spatial distractors. They had young (N = 25; Mean Age = 24 yrs; Age Range = 19-29 yrs) and elderly (N = 19; Mean Age = 74 yrs; Age Range = 65 – 84 yrs) participants engage in a task with hierarchical stimuli where the conditions were designed such that either the global or local form could be the more salient feature. The global and local form could be either the letter 'H' or 'S.' Additionally, the global and local forms could be the same (congruent) or different (incongruent). On any given trial, participants had to identify either the local or global level of the display. The non-target element acted as a distractor. They found that performance (measured through response times and compatibility effects) during trials with low-salience targets and high-salience distractors was worse for the older participants relative to the young participants, even after accounting for generalized slowing of processing speed over the lifespan.

Mevorach et al (2008a; Mevorach et al, 2010a; 2010b) previously established that the left intraparietal sulcus (Left IPS) mediates the suppression of highly salient distractors. Using a similar global/local task, they showed that the left IPS was significantly active on

trials where the distractor element was more salient than the target element. Additionally, they showed that this activity positively correlated with the magnitude of distractor interference. Furthermore, Mevorach et al (2008b) has shown that the left posterior parietal cortex (eventually localized to the left IPS) acts in a preparatory manner to suppress salient distractors, as performance was only affected by TMS stimulation applied prior to stimulus presentation. In a complementary study, Mevorach et al (2010) showed that increased activity in the left IPS was accompanied by a concomitant decrease in activity in the occipital cluster. However, when TMS was applied over the left IPS the activity in the occipital cluster increased significantly relative to the 'No TMS' condition. It was argued that the left IPS suppressed activity in the occipital cluster in the presence of salient distractors, and that applying TMS to the left IPS interrupted this process, resulting in greater activation in the occipital cluster. Indeed, when TMS was applied directly to the left occipital pole, in order to simulate the effect of the left IPS, performance improved on trials with salient distractors.

Notably, the elderly participants' performance in Tsvetanov et al (2013) is similar to the young participants' performance during the IPS inhibition condition in Mevorach et al (2008; 2010). Based on this similarity, it follows that the impaired salience suppression exhibited in old age may be attributed to irregularities in left IPS function. These irregularities may be due to a specific age-related impairment to Left IPS function (including with respect to its effective connectivity with other regions) or it may be the result of a shift in cognitive strategy that does not rely uniquely on the IPS. In particular, older participants tend to favor reactive, over proactive, strategies. Since the left IPS appears to act in a preparatory manner in these paradigms, it could be thought of as implementing a proactive control signal. On the other hand, reactive salience suppression has been associated with a left ventral network including left TPJ and IFG (DiQuattro and Geng, 2010). This network

may in turn drive dorsal control regions in the FEF and IPS when implementing a reactive control signal. If elderly participants favor reactive control, they may not engage the Left IPS in the same way as young participants to complete the task. Additionally, reactive control is strategically sub-optimal in the global/local task. Therefore, a bias toward reactive control in elderly subjects, rather than dysfunctions in left IPS mechanisms, might lead to the impaired performance reported in Tsvetanov et al (2013). Although it should be noted that, while Left IPS impairments may not be directly responsible for the behavioral impairments, they may be driving the general bias towards reactive control in elderly participants (i.e. given a choice between an impaired and an unimpaired mechanism, participants may simply engage the unimpaired, or less impaired, one). Of course, without more data, this is speculative.

Here, we used fMRI to investigate how healthy aging mediates the role of the left intraparietal sulcus (IPS), the left temporoparietal junction (TPJ), and the left inferior frontal gyrus (IFG) in the suppression of salient distractors. We employed a salience suppression task (a global/local task) that has been shown to be impaired in old age (Tsvetanov et al, 2013) and to be reliant on preparatory involvement of the left IPS in young participants (Mevorach et al, 2008; 2010a; 2010b). Based on the previous literature, we expect one of two outcomes. If the behavioral impairments in Tsvetanov et al (2013) are due to a specific age-related impairment in the Left IPS or its functional connectivity, we would expect to identify similar circuitry involving the left IPS across old and young participants during distractor salient trials but perhaps with different magnitudes. Alternatively, if the behavioral impairments are due to a strategic shift to reactive control (or to a combination of both explanations), we would expect to see additional engagement of a left ventral network (TPJ and IFG) only in the old participants.

While previous literature has identified a role for the engagement of the left IPS, left TPJ, and left IFG during unimpaired salience suppression, another possibility is that the age-related behavioral deficits are being driven by changes in the functional connectivity of these regions, or through an interaction between the engagement of brain structures and their functional connectivity. A number of studies have examined resting state functional connectivity (RSFC) across the lifespan (Goldstone et al, 2016; Tsventanov et al, 2016; Tomasi and Volkow, 2012; Ferreira and Busatto, 2013; Damoiseaux et al, 2008; Onoda et al, 2012; Toussaint et al, 2014; Chen et al, 2016; Salami et al, 2016). Typically, an increase in between network connectivity in aging populations has been reported in the literature (Goldstone et al, 2016; Betzel et al, 2014; Salami et al, 2014; Geerligts et al, 2014). Due to the consistency of these results, some researchers have interpreted this as evidence of dedifferentiation (Geerligts et al, 2014; Andrews-Hanna, et al, 2007; Madden et al, 2010; Grady et al, 2010; Dennis and Cabeza, 2011; Park et al, 2004; Cabeza, 2001), where brain networks become less specialized over time. However, the literature is more inconsistent with regard to within network connectivity. Other than aging differences in the default mode network (where elderly participants typically have reduced within network RSFC), results seem to change depending on the age of the cohort and the specific network being tested. For example, Onoda et al (2012) and Tsventanov et al (2016) found decreased within-network connectivity for elderly participants relative to young participants between regions of a salience network. And Tsventanov et al (2016) also found decreased within network connectivity between regions of the dorsal attention network. On the other hand, Toussaint et al (2014) found that elderly participants had increased within-network connectivity, relative to young participants, in attention-related frontal and parietal networks.

Despite these inconsistencies, Geerlings and Tsvetanov (2016; though see Campbell and Schacter, 2016 for an alternative view) have argued that integration of structural and functional measures of brain activity is essential in the study of aging populations. Tsvetanov et al (2016) showed that both between and within network connectivity could account for a significant portion of variance in a number of cognitive tasks in both young and aging cohorts. Further, they found that “effective connectivity” (connectivity determined by fitting neural and vascular fMRI signals to a spectral dynamic causal model) in general was more important for cognitive function in older participants; connectivity profiles (within a salience network and dorsal attention network, and between a salience network and a default mode network) similar to that of younger participants was associated with higher performance on the cognitive tasks. Therefore, we also assessed how healthy aging mediates the role of between and within functional connectivity of resting state networks that incorporate the left IPS, left TPJ, and left IFG nodes.

In this study, a version of the global/local task developed by Mevorach et al (2008,2010a,2010b; Tsvetanov et al, 2013) was administered to a cohort of young (18-30) and elderly (59-77) participants while fMRI data was recorded. Resting state fluctuation amplitude (RSFA; Kannurpatti et al, 2008) was used to scale brain activation to correct for the neurovascular effects of old age (Kannurpatti et al, 2011; Tsvetanov et al, 2015). We were particularly interested in examining the possible age-related differences in activity in the left IPS and left TPJ. A region of interest (ROI) analysis (extracting mean BOLD signal change within this region) was conducted on a left IPS node (MNI Coordinates: -30,-68, 34) that was previously identified as being involved in the proactive suppression of salient distractors (Mevorach et al, 2008; 2010), and on a TPJ (MNI coordinates: -46, 50, 34) and IFG node (MNI coordinates: -50, 30, 8) that were identified as being involved in reactive

suppression (DiQuattro and Geng, 2011). We are also interested in age-related within and between network resting state functional connectivity differences that may provide context to the ROI analysis described. To assess this, seed-based RSFC analyses were conducted using the left IPS and left TPJ nodes as seeds and their respective large scale networks (executive control, salience, and visuospatial) as targets.

Methods

Participants

15 young participants (Mean Age: 22.67 yrs, SEM of Age: .85, Age Range: 18 - 30; 13 Females) and 15 elderly participants (Mean Age: 66.07 yrs, SEM of Age: 1.26, Age Range: 59-77 yrs; 7 Females) took part in the study. Young participants were recruited from the undergraduate population of the University of Birmingham, UK. They were compensated for their participation with course credits. The elderly participants were recruited from a volunteer pool maintained by the School of Psychology at the University of Birmingham. They were compensated for their time with a single payment of £25. Participants were screened for MRI contraindications and were healthy with no history of head injury, mental health issues or neurological disorders. The old participants were screened for decline in cognitive functions using the Montreal Cognitive Assessment (MoCA). All of the elderly participants scored within the normal range (greater than or equal to 26; Mean Score: 28.2, SEM of Score: .312). The study was approved by the institutional ethics committee at the University of Birmingham and conformed with the Declaration of Helsinki. All participants gave informed consent prior to taking part in the study.

Stimuli

Participants were presented with compound letters in which an array of small (local) letters was arranged into the shape of a large (global) letter (Figure 1). All stimuli were orthogonal compounds of the letters “H” and “S.” All of the local letters were the same letter. Two sets of displays were used to represent either high global or high local saliency. In the high local salience stimulus display, the compound letters were made of alternating red (RGB color coordinates; [255 0 0]) and white local letters ([255 255 255]). The size of the local letters was $.933^\circ \times 1.17^\circ$ of visual angle (in width and height, respectively), with an inter-item distance of 0.32° . The total width and height of the global letters was $4.43^\circ \times 6.756^\circ$ of visual angle, respectively. In the high global salience stimulus display, the local stimuli consisted of red blurred letters (Fig. 1, bottom row). The width and height of the local letters were the same as reported previously, respectively, resulting in a global letter subtending $3.96^\circ \times 6.29^\circ$ of visual angle (in width and height, respectively). These images were additionally blurred in MATLAB using a Gaussian low-pass filter (with a Gaussian kernel of full width at half-maximum of 1.56 mm). Due to the blurring effect, the adjacent letters blend into each other, albeit on a gradient, so there is no clear inter-letter distance for these stimuli. Moreover, the blurring obscured the edges of the global letter, which is why the global letter was measured as slightly smaller in this condition. To reduce strategic focusing on a local area of the screen and to encourage a diffuse attentional state, the stimuli appeared centrally at a location either 1.098° above or below the center of the screen (Grice et al, 1983).

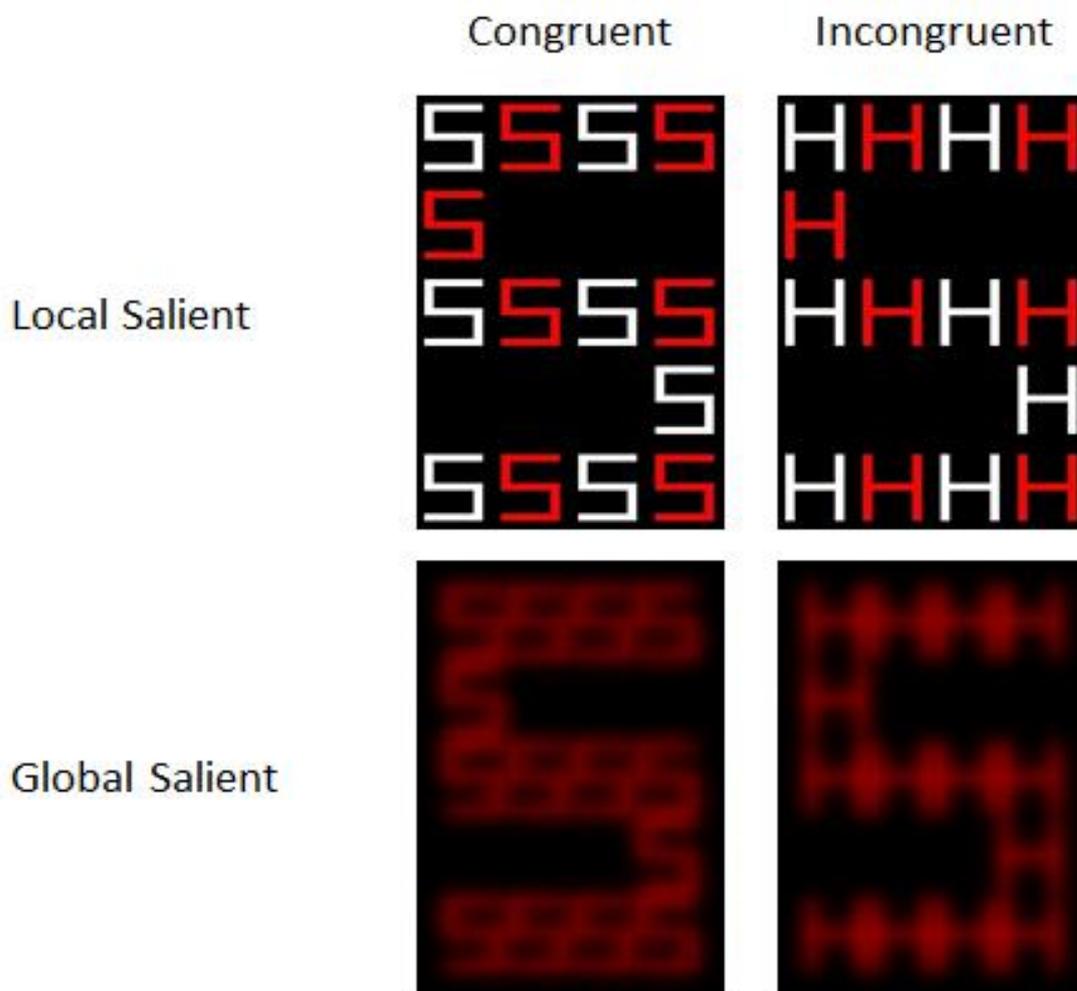


Figure 1. Example of stimuli in the global/local task. The top row shows stimuli where the local letters are more salient than the global letter. The bottom row shows stimuli where the global letter is more salient than the local letter. The left column shows examples where the global and local letters have the same identity, whereas the right column shows examples where they have a different identity.

Procedure

Inside the MRI scanner, stimuli were projected onto a screen ~620mm from the participant's eyes and viewed through a mirror mounted on the MRI head coil. Participants were given a two-button box and instructed that the 'left' button indicated the letter 'S' and that the 'right' button indicated the letter 'H.' Prior to the first block of each experimental scan, participants were presented with a fixation cross for 6 seconds to allow them to adapt to the lower lighting.

Each experimental scan included four block types: global target under global salient displays, global target under local-salient displays, local target under global-salient displays, and local target under local-salient displays. Each block consisted of 12 trials of a single block type and each block was repeated four times. In total, within an experimental scan there were 12 blocks and their presentation order was randomized.

A written instruction (“GLOBAL” or “LOCAL”) appeared at the center of the screen for the first 2 seconds of each block, instructing participants to respond to the identity of the displayed stimulus. This was followed immediately by the experimental trials. Each experimental trial began with the presentation of the compound letter stimuli for 250 msec, followed by a fixation period in which a fixation cross (a plus sign) was displayed for 1750 msec. The next trial would begin immediately after the fixation period ended. Participants could make a response, using the button box, at any time between stimulus onset and the end of the fixation period. If no response was made within the specified time, then the trial was marked as incorrect. On half of the trials, the global and local letters matched (congruent trials), and on the other half the global and local letters differed (incongruent trials). Each block lasted for 26 seconds (2 seconds of instruction and 24 seconds of the task; 2 seconds per trial).

After each block, there was a 2000 msec instruction screen that centrally presented the word ‘REST’ and it was followed by a 24 second rest period in which only a fixation cross was present. This was done to allow the haemodynamic response to reset to baseline levels prior to the next block. The rest instruction was included to facilitate this purpose, so participants didn’t think that the experiment had stopped prematurely or so they didn’t put effort into “figuring out” the reason behind the fixation cross (which might encourage confounding neural activity).

fMRI Data Acquisition

Experiments were conducted at the Birmingham University Imaging Center (BUIC) using a 3T Philips Achieva with a 32-channel head coil. Each scanning session consisted of 6 scans, five functional scans and a T1-weighted anatomical scan (Image Resolution = 1mm isotropic, TR \approx 7.4 ms [shortest], TE = 3.5 ms, Flip Angle = 7°, Slice Orientation = Sagittal, Inversion time = 1100 ms, Bandwidth = 191.5 Hz). During functional scans BOLD fMRI data were acquired using gradient echo EPI (TR = 2000 ms, TE = 35ms, voxel dimensions = 3x3x4 mm, 32 slices, flip angle = 80°, SENSE =2). Three experimental runs of the behavioral task were acquired. These scans lasted for 10min 24sec each (306 volumes). In addition, we acquired a breathhold task scan (lasting 8min 12sec) where participants were visually cued to hold their breath for 12 seconds at a time, followed by a 20 second rest period (14 trials). The data accumulated here were intended to be used to account for intrinsic differences in vascular reactivity between young and older participants. However, after data acquisition, a more effective method was decided on (described below) and the breath hold scan data was not used in this analysis. Finally, a resting state scan was acquired where participants were instructed to relax, lie still and keep their eyes open. The screen was turned off for this scan and there was nothing specific for the participants to fixate on. This scan lasted 12min 12sec.

fMRI Data Analysis

fMRI analysis was performed using FEAT version 6.00 (FMRI Expert Analysis Tool), which is part of FSL version 5.09 (www.fmrib.ox.ac.uk/fsl). A first level analysis was conducted individually on each experimental run (3 per subject). The first three dummy volumes of each scan (6s) were removed to reduce the transient effects of magnetic

stimulation and to allow the BOLD signal to stabilize. The individual scan data was then pre-processed prior to further analysis. A regular-up slice-timing correction using Fourier-space time-series phase-shifting was applied. Head movements were corrected for using MCFLIRT motion correction (Jenkinson et al, 2002). The skull and other nonbrain matter was removed using BET (Smith, 2002). Images were then spatially smoothed using an isotropic Gaussian kernel of full width at half-maximum of 5 mm and all volumes within a scan were mean-based intensity normalized using the grand mean for the time series. Signals within the scan were then high-pass temporally filtered (Gaussian-weighted least-squares straight line fitting, with $\sigma = 52$ s). Each participants' whole-head EPI image was registered to their individual (brain-extracted) structural image. Individual scans were registered to high-resolution standard images in Montreal Neurological Institute space using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

BOLD responses to each of the four conditions of the behavioral task were separately modelled using custom waveform defined by the onset and duration of the experimental blocks (26 seconds; 12 blocks per experimental run). Each waveform was convolved with a gamma haemodynamic response function (Phase: 0, Stdev: 3, Mean lag: 6). The design matrix consisted of four regressors which reflected the modelled haemodynamic response based on the custom waveforms (described above) for each of the four block types in the behavioral task: Respond Global/Global Salient, Respond Global/Local Salient, Respond Local/Global Salient, and Respond Local/Local Salient (The names of the block types have been simplified here for brevity). The temporal derivatives of each regressor were also included and the same temporal filtering was applied to the design matrix as was applied to the data. Four contrasts were calculated to compare BOLD signal change between different task blocks: Global Salient > Local Salient, Local Salient > Global

Salient, Distractor Salient > Target Salient and Target Salient > Distractor Salient. The main contrast of interest is distractor salient > target salient as this is the contrast in which previous research has highlighted left IPS activation in young participants (Mevorach et al, 2008; 2010); moreover, it is a contrast that reflects a top-down control signal associated with the suppression of salient distractors.

Second level analyses were performed to assess average fMRI responses for each individual subject by combining the three first level analyses. A fixed effect analysis was performed to obtain the mean activity within individual participants for each of the contrasts. BOLD Z-statistic images were thresholded using clusters determined by a $Z > 2.3$ and cluster corrected significance of $p < .05$.

Third level analyses were then performed to assess average fMRI responses within and between age groups for each contrast. An analysis was conducted specifically for each of the six contrasts. A mixed effect analysis was performed to obtain the activity within (Flame 1) and between (Flame 1+2; Smith et al, 2004; Woolrich et al, 2009) each age group for each contrast. The analyses included one second-level analysis for each subject as input ($N=15$ for the two within group analyses and $N = 30$ for the between group analysis). BOLD Z-statistic images were thresholded using clusters determined by a $Z > 2.3$ and cluster corrected significance of $p < .05$.

In addition, for the between group analysis, resting state fluctuation amplitude (RSFA; Kannurpatti et al, 2008) was calculated for each voxel using resting state data (see below for details of resting state pre-processing). Voxel-wise matrices for each subject were concatenated to make an additional group-level regressor which was included in the third-level model. To account for three subjects that did not have resting state data (see below), zeros were added to the covariate matrix. The RSFA regressor models between-subject

variability to normalize BOLD responses as a function of the haemodynamic response to regional brain activity. Essentially, it is a way of accounting for and ultimately minimizing variability between different groups due to intrinsic vascular reactivity. RSFA has been shown to be an especially effective regressor for this purpose in the analysis of age-related BOLD data (Kannurpatti et al, 2011; Tsvetanov et al, 2015).

ROI Definitions

Three relevant networks were identified that have been associated with attention, cognitive control, and salience processing: a visuospatial network, an executive control network, and a salience network. Each network consists of multiple individual ROI's and can be analyzed as individual nodes or as a whole network ROI. MNI space ROIs for the whole networks and the individual nodes were obtained from the Stanford FIND lab (Shirer et al, 2012; http://findlab.stanford.edu/functional_ROIs.html).

The executive control network (Figure 2) consisted of 10 individual ROI's. These ROI's reflect the left lateral occipital cortex/angular gyrus, left frontal pole, left middle temporal gyrus, left superior middle frontal gyrus, left thalamus, right frontal pole, right lateral occipital cortex/angular gyrus, right middle frontal gyrus, right superior frontal gyrus, and the right thalamus.

The salience network (Figure 2) consisted of 15 individual ROI's. These ROI's reflect the left precuneus, bilateral cingulate cortex, left frontal pole, left anterior insular, left posterior insular, left middle frontal gyrus, left supramarginal gyrus, left thalamus, right frontal pole, right anterior insular, left anterior insular, right precentral gyrus, right superior parietal lobe, right supramarginal gyrus, and the right thalamus.

The visuospatial network (Figure 2) consisted of 8 individual ROI's. These ROI's reflect the left superior parietal lobe/lateral occipital cortex, left lateral occipital cortex, left middle inferior frontal gyrus, left middle superior frontal gyrus, right inferior temporal gyrus, right middle inferior frontal gyrus, right middle superior frontal gyrus, and the right superior parietal lobe/lateral occipital cortex.

The visuospatial network was selected because it includes the left IPS coordinates from Mevorach et al (2008; Figure 2a) and the left IFG coordinates from DiQuattro and Geng (2011; Figure 2c). The executive control network was selected because it overlaps with the left TPJ and Left IFG coordinates from DiQuattro and Geng (2011; Figure 2b and 2c). However, DiQuattro and Geng (2011) only identified activity in these regions in a young cohort. It is possible that activity is right lateralized or even bilateral in elderly populations, as aging has been associated with both spatial reorganization of networks (Cabeza et al, 2002) and reductions in hemispheric specialization (Cabeza, 2001). Therefore, we considered the FIND labs' 'Left Executive Control Network' and 'Right Executive Control Network' as a single amalgamated network in our analysis consisting of the individual clusters from both networks. The salience network was chosen because we are interested in, and are using a paradigm known to elicit (Tsvetanov et al, 2012), age-related differences in salience suppression. Assessing RSFC in this network will help to determine if aging effects are due to differences in attentional control or salience processing. For the same reasons as before, we considered the FIND labs' 'Posterior Salience Network' and 'Anterior Salience Network' as a single amalgamated network.

In addition, three ROI's were created based on coordinates procured from relevant prior literature. Mevorach et al (2008;2010) identified left IPS coordinates in this region (MNI Coordinates: -30, -68, 34) that were involved in the proactive suppression of salient

distractors. Both the TPJ and IFG coordinates were identified in DiQuattro and Geng (2011; Figure 4b) as part of a reactive control network (MNI coordinates: -46, 50, 34, and -50, 30, 8, for TPJ and IFG, respectively). The ROI's were created using fslmaths by generating a sphere with a diameter of five 1mm voxels centered on the relevant MNI coordinates.

Resting State Functional Connectivity Analysis

Seed-based correlation analysis was used to measure the Pearson correlation coefficient between the BOLD signal time course extracted from regions of interest during resting state scans (van den Heuvel et al, 2009; 2010; Damoiseaux and Greicius, 2009). Resting state data was standardly pre-processed prior to analysis (Fox et al., 2005; Wilson et al, 2015; Goldstone et al, 2016). Data were motion corrected, spatially smoothed (5 mm) and temporally band-pass filtered ($0.009 < \text{Hz} < 0.08$). Due to technical difficulties, the resting state scans of only 12 of the 15 young participants were useable. The following procedures were applied to the data for each individual subject.

To calculate within network connectivity, an individual ROI from each network was chosen as a seed hub and seed based temporal correlations were calculated between the hub and each other individual ROIs within the network. There are no established conventions for which region to use as a seed hub. That being said, Gong et al (2009; Menon and Uddin, 2010) identified the insula and posterior cingulate gyrus as centrally connected regions, independent of age and sex, which suggests ROI's in these regions would be ideal seed hubs. Additionally, as prior literature has implicated the left hemisphere (i.e. Left IPS, Left TPJ, Left IFG) in this task, seed hubs in the left hemisphere were selected. Therefore, the seed hub ROI for the executive control network was the left lateral occipital cortex/angular gyrus, the seed hub for the salience network was the left precuneus, and the

seed hub for the visuospatial network was the left superior parietal lobe/lateral occipital cortex.

Next, the mean of the correlations for each seed-target combination was obtained across participants. To assess the within network connectivity related to the left IPS, left TPJ, and the left IFG nodes, visual inspection was used to assign each node to one of the standardized FIND lab networks (visuospatial for left IPS and left IFG, executive for left TPJ and left IFG; Figure 2). The relevant coordinate-based node was set as the seed and each of the individual nodes from the assigned network was set as the target in a series of seed-based correlations, and the average of those correlations was obtained. Note that the left IFG appears to overlap with both the visuospatial and the executive control network, and therefore it is not clear which network it most “belongs to.” Therefore, the within network connectivity was calculated for both networks with left IFG as a seed. The implications of this are discussed in more detail in the discussion of this chapter. Independent samples t-tests were performed to determine if the within network connectivity was different across age groups (Table 2).

To assess between network connectivity, combinations of the FIND lab whole network ROI's (executive control, salience, and visuospatial network) were set as both seeds and targets. For each combination, two versions of the analyses were performed such that each network was the seed and the target. For example, to assess between network connectivity for the executive control network and the visuospatial network, we calculated RSFC where the executive control network was the seed region and the visuospatial network was the target and vice versa. Then we took the mean pearson r values of the two analyses for each subject. This was repeated for the between network connectivity for the visuospatial network and the salience network, and for the between network connectivity

for the executive control network and the salience network. This procedure was done because the correlation values were different depending on which region was set as the seed and the target, and this should reduce the likelihood of spurious correlation due to random chance. To assess between network connectivity related to the coordinate-based nodes, the coordinate based nodes were set as the seed and the whole network ROI's for networks that the coordinate based nodes were not assigned to were set as the target. Independent samples t-tests were performed to determine if the between network connectivity was different across age groups (Table 2).

The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995; 2000; Benjamini and Yekutieli, 2001; Thissen et al, 2002; McDonald, 2009; Verhoeven et al, 2005; Glickman et al, 2014) controlling for the false discovery rate (FDR) was implemented in order to account for multiple comparisons. This method controls the proportion of significant results that are type I errors (i.e. False Discoveries). Controlling for FDR, rather than family wise error rate (for example, with a Bonferroni correction) increases statistical power while still applying an appropriate correction. To apply the Benjamini-Hochberg procedure (Table 2), the p-values of all of the statistical tests must first be rank ordered from smallest to largest. The smallest p-value is given a rank of 1 and rank increases by 1 with each subsequent p-values. Next, a Benjamini-Hochberg (BH) critical value is calculated for each statistical test using the following formula: $Q(i/m)$, where i = the rank, m = the total number of tests, and Q = the maximum desired false discovery rate. It should be noted that FDR has a different meaning than a p-value. An FDR of .05 means that no more than 5% of the significant findings should be false positives. As there is no set convention for what to set FDR at, this correction was applied with a .05 and .10 FDR in order to assess a range of possible results. Finally, the largest p-value that is smaller than its BH critical value must be identified and all

tests with p-values equal to or less than that p-value are considered significant (even if the BH critical value is larger for some of those smaller p-values). See the papers referenced at the beginning of this paragraph for the mathematical proof of the validity of this method and for more details about its implementation.

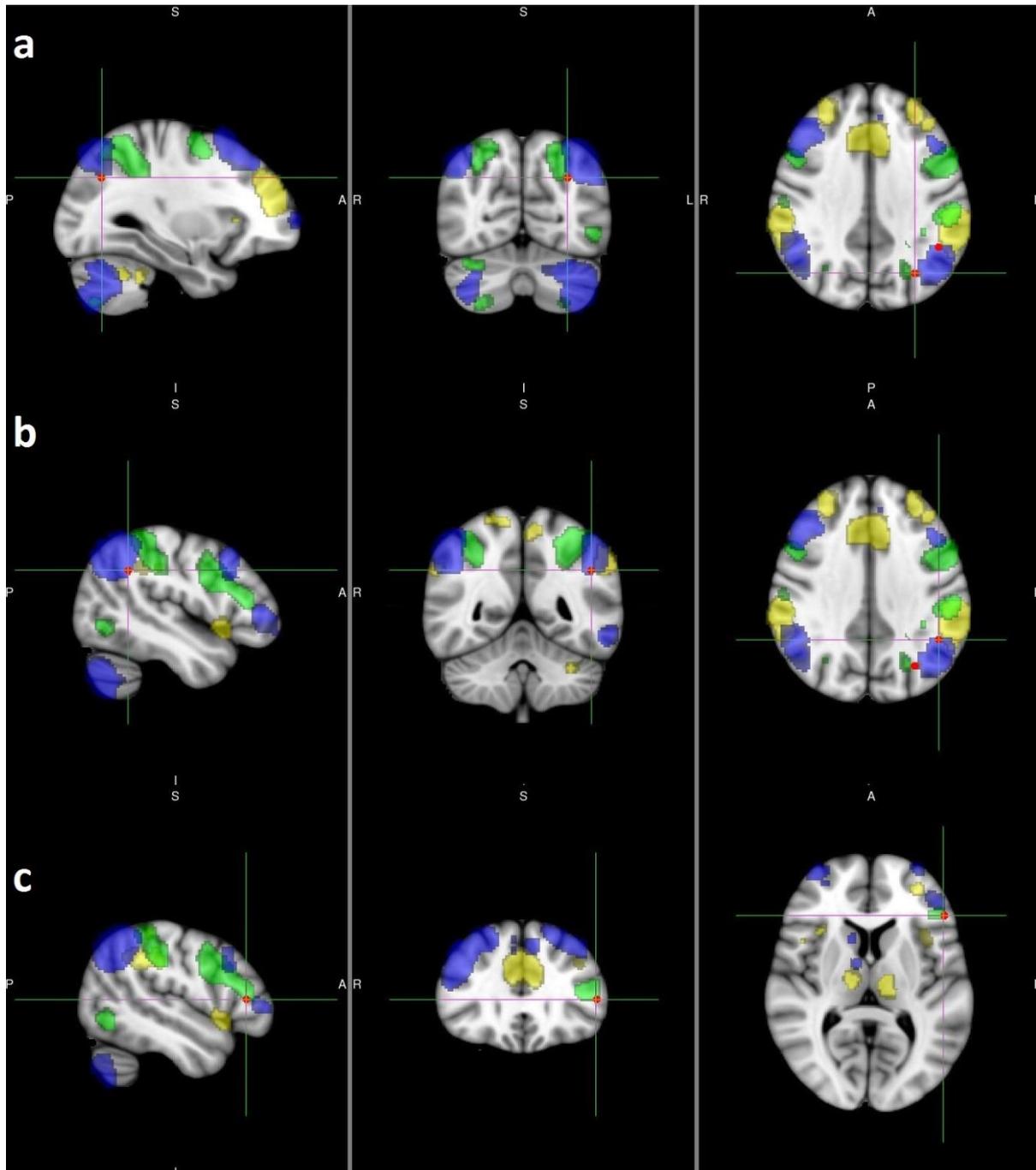


Figure 2. FIND Lab ROI's for the visuospatial network (Green), executive control network (Blue), and the salience network (Yellow). The red dot in the crosshair in the top row reflects the left IPS (a) coordinates from Mevorach et al (2008). The red dots in the crosshair in the second and third row reflect the left TPJ (b) and left IFG (c) coordinates, respectively, from DiQuattro and Geng (2011).

Results

Behavioral Analysis

Response time in msec (RT) and accuracy rate (i.e. proportion of correct responses) were measured as dependent variables. For each subject, the response time data were cleaned to account for outliers by rejecting values that exceeded 2 standard deviations from the mean. This procedure was applied independently to each orthogonal combination of response (Global vs Local), salience (Target Salient vs Distractor Salient) and congruency (Congruent vs Incongruent). This resulted in the loss of a mean of 5.54% (SEM = .2%) of the response time data, per experimental run for the young subjects and 5.09% (SEM = .2%) for the elderly subjects. A two-tailed t-test revealed that these two means were not significantly different from each other, $t(88) = -1.55$, $p = .124$. Additionally, to account for speed/accuracy trade-offs, which are often present in ageing data, the data was converted to adjusted response time (AdjRT; sometimes referred to as an inefficiency measure; Townsend and Ashby, 1983) by dividing the participants' response time by their proportion correct for each orthogonal combination of the within subject variables. This measure was used in Tsventanov et al (2013) using a similar experimental paradigm, as an effective method of accounting for speed/accuracy trade-offs in elderly populations. All values are reported as a mean and standard error of the mean.

A repeated measures ANOVA was conducted with the salient dimension (target vs distractor), the response dimension (global vs local) and congruency (congruent vs incongruent) as within subjects variables and age group (young vs older) as a between subjects variable. The main effect of the response dimension, $F(1,28) = 3.037$, $p = .092$, was not significant. The main effect of salience was not significant, $F(1,28) = .398$, $p = .026$. There was a main effect of congruency, $F(1,28) = 180.75$, $p < .001$, $\eta_p^2 = .866$, driven by faster

adjusted response times for congruent trials (562 ± 11 msec) than incongruent trials (648 ± 13 msec). This is the expected, standard effect of congruency. There was also a main effect of age group, $F(1,28) = 11.37$, $p = .002$, $\eta_p^2 = .289$, driven by younger subjects (566 ± 16 msec) having faster adjRT than older subjects (644 ± 16 msec). This suggests that even after accounting for speed-accuracy trade-offs, older participants are still slower to respond than younger participants.

There was a significant interaction between salience and congruency, $F(1, 28) = 20.497$, $p < .001$, $\eta_p^2 = .423$, showing that the congruency effect (adjRT incongruent – adjRT congruent) was larger during distractor salient trials (136 msec) than target salient trials (38 msec). This confirmed that the salience manipulations were successful at making the non-target element more distracting. Critically, there were no significant interactions with age group (All F 's $< .960$; all p 's $> .336$). This suggests that aside from a generalized slowing in the older subjects, there weren't significant differences in performance in this task between the young and elderly subjects.

A significant interaction between response and congruency, $F(1,28) = 32.626$, $p < .001$, $\eta_p^2 = .538$, confirmed that the congruency effect was stronger when participants had to respond to the global element of the display (130 msec) rather than the local element of the display (43 msec). There was also a significant interaction between response and salience, $F(1,28) = 79.637$, $p < .001$, $\eta_p^2 = .423$, which is common with this paradigm.

Participants responded faster to the response dimension when it was also the salient element in the display (for example, when they had to respond to the global letter which was also the salient letter). However, these interactions are qualified by a significant three-way interaction between salience, response, and congruency, $F(1, 28) = 20.497$, $p < .001$, $\eta_p^2 = .423$ (Figure 3).

To further investigate this interaction, a repeated measures ANOVA was conducted with the congruency effect as the dependent variable, the salient dimension (target vs distractor) and the response dimension (global vs local) as within subjects variables, and age group as a between subjects variable.

There was a significant effect of the salient dimension, $F(1,28) = 65.023$, $p < .001$, $\eta_p^2 = .699$, and the response dimension, $F(1,28) = 32.626$, $p < .001$, $\eta_p^2 = .538$, which are qualified by a significant interaction, $F(1,28) = 20.497$, $p < .001$, $\eta_p^2 = .423$, that appears to be the source of the three-way interaction in the previous analysis. This significant interaction suggests that the difference in congruency effect as a function of salience is more pronounced when subjects have to respond to the global element (congruency effect during target salient trials = 61 msec; during distractor salient trials = 199 msec; congruency effect difference = 138 msec) of the display, rather than the local element (congruency effect during target salient trials = 15 msec; during distractor salient trials = 71 msec; congruency effect difference = 56 msec) of the display. A significant paired samples t-test comparing the congruency effect difference between salience conditions when responding to the local element and the global element confirmed this interpretation, $t(29) = 4.583$, $p < .001$, $d = .99$. These results are consistent with previous literature that have used other versions of this paradigm with young participants (Mevorach et al, 2006a; 2008; see young participant data for Tsvetanov et al, 2013). There was no main effect of age group, $F(1,28) = .428$, $p = .518$, nor any interactions with age group (All F 's $< .725$; all p 's $> .402$).

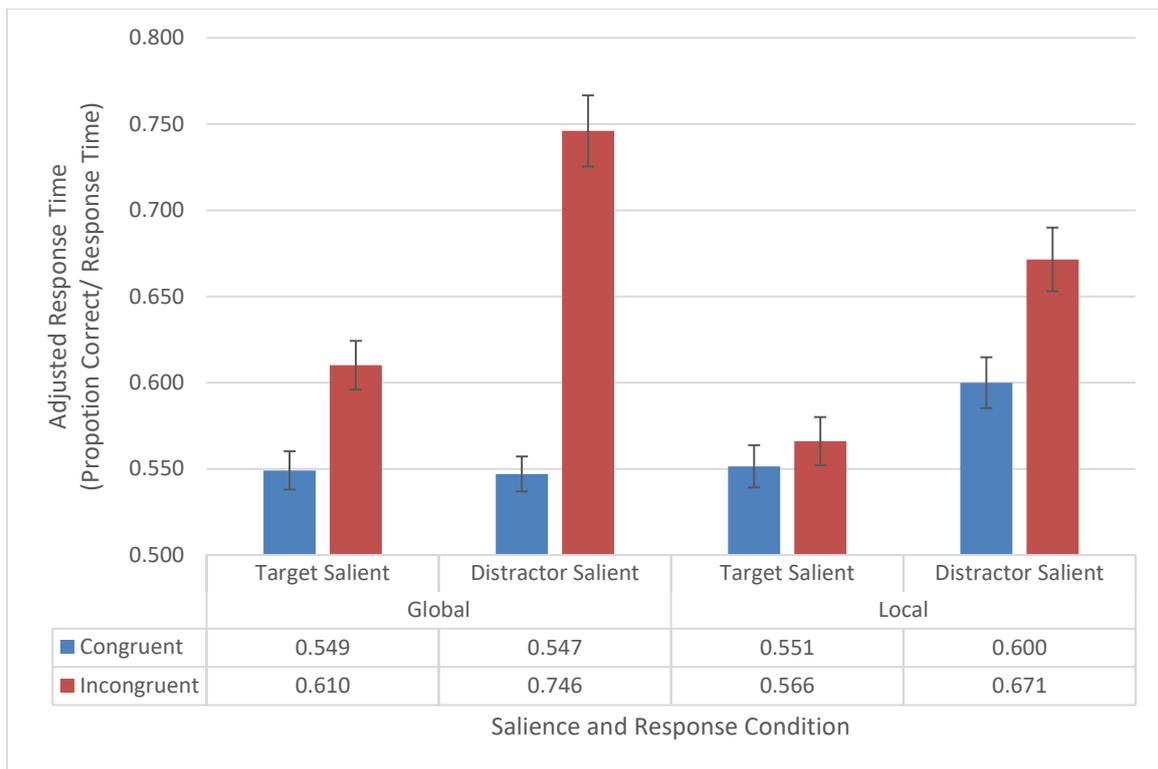


Figure 3. Adjusted Response Time as a function of the salience and response conditions.

fMRI Analysis

GLM Contrasts

For the distractor salient > target salient main effect contrast for young participants alone (see the third level, within age group analysis in the methods) we observed extensive significant bilateral activity (Table 1) throughout dorsal fronto-parietal regions, as well as occipital regions. For the distractor salient > target salient main effect contrast for elderly participants alone there was a more extensive network of bilateral fronto-parietal activations. This included both dorsal fronto-parietal regions and more ventral regions such as the TPJ and IFG. Like the young subjects, the left parietal activity was consistent with Mevorach et al (2008; 2011), however this activity extended further in the inferior and anterior directions in the elderly participants. Notably, brain activity in the older participants included regions of the TPJ as well as inferior/middle frontal regions which were not visible

in younger participants (Figure 4b and 4c). This difference was statistically verified by a between group analysis, but the fact that there is no significant activity in these regions for younger subjects suggests that the left-lateralized ventral fronto-parietal activation, and the engagement of the mechanisms they subserve, is unique to the elderly participants.

Significant group-level BOLD responses were found in the Elderly > Young contrast of Distractor Salient > Target Salient (see the third level, between age group analysis in the methods). Activation maps highlighted left-lateralized ventral fronto-parietal activation, including the TPJ and IFG, which was unique for the elderly subjects (Figure 5). Both the TPJ and IFG, were identified in DiQuattro and Geng (2011; Figure 4b) as part of a reactive control network (MNI coordinates: -46, 50, 34, and -50, 30,8, for TPJ and IFG, respectively). This suggests that elderly subjects rely more on these regions to suppress salience relative to younger participants.

Contrast	Cluster Index	Voxels	p	Local Maxima Z	Local Maxima x	Local Maxima y	Local Maxima z	Activated Brain Regions	
Local Salient > Global Salient Elderly > Young	1	6564	9.00E-04	4.12	-9	-89	36	Cuneus	
				3.95	2	-81	34		
				3.84	3	-83	36		
				3.73	3	-86	34		
				3.59	8	-77	59		
				3.57	-12	-88	43		
Distractor Salient > Target Salient Elderly Only	5	214597	0.00E+00	7.88	-26	-71	39	Both bands of the Left Intra-Parietal Sulcus (Left IPS), including Superior and Inferior Parietal Lobe	
				7.06	35	-68	30		
				6.98	33	-69	28		
				6.72	32	-69	33		
				6.70	-25	-66	35		
					6.61	-28	-58	52	
					6.74	-41	12	28	Left Lateral Prefrontal Cortex, including the Left Inferior Frontal Gyrus (IFG) and Left Middle Frontal Gyrus.
	4	54591	7.73E-19	6.46	-39	13	28		
				6.42	-43	12	27		
				6.39	-44	9	24		
					6.23	-42	8	25	
					6.21	-44	6	24	
	3	37275	2.30E-14	2.30E-14	6.57	57	13	24	Right Lateral Prefrontal Cortex, including the Right IFG and Right Middle Frontal Gyrus
					6.54	47	9	24	
					6.25	47	11	44	
					6.20	45	4	24	
					6.11	43	4	22	
					6.07	45	4	22	
	2	12450	2.38E-06	2.38E-06	6.43	6	22	40	Bilateral Medial Prefrontal Cortex, including the Paracingulate Gyrus
					6.14	4	21	40	
5.66					2	23	40		
5.66					7	18	40		
5.55					3	21	43		
				5.49	7	24	41		
1	3488	4.13E-02	4.13E-02	3.75	16	9	6	Right Caudate Nucleus	
				3.73	14	9	7		
				3.58	18	7	5		
				3.53	16	6	17		
				3.44	17	6	7		
				3.42	11	-7	10		
Distractor Salient > Target Salient Young Only	3	101567	4.72E-29	5.89	-46	-76	-7	Left Lateral Occipital Cortex, extending towards the parietal cortex. Both bands of the Left IPS, including the superior and inferior parietal lobe.	
				5.58	19	-63	67		
				5.57	38	-80	14		
				5.57	-48	-77	-8		
				5.36	-43	-75	-10		
					5.33	-42	-73	-13	
	2	5993	1.74E-03	1.74E-03	5.14	46	7	35	Left Lateral Prefrontal Cortex, including the Left IFG and Left Middle Frontal Gyrus,
					4.95	48	8	36	
					4.93	47	7	32	
					4.39	47	10	35	
					4.32	44	7	32	
					4.10	52	11	24	
	1	3972	2.15E-02	2.15E-02	4.18	-48	8	31	Right Lateral Prefrontal Cortex, including the Right IFG and Right Middle Frontal Gyrus
					4.12	-54	8	32	
					3.90	-49	14	28	
3.87					-56	15	26		
3.86					-47	5	32		
				3.82	-51	10	28		
Distractor Salient > Target Salient Elderly > Young	3	11101	8.34E-06	4.72	-45	-46	38	left TPJ, inferior parietal cortex, extending posteriorly to the inferior bank of the IPS, supramarginal gyrus	
				4.48	-33	-69	44		
				4.37	-36	-62	43		
				4.32	-58	-41	38		
				4.31	-45	-44	35		
					4.23	-61	-45	36	
	2	10847	1.06E-05	1.06E-05	4.37	-48	11	14	Left IFG, Insular Cortex, Frontal Orbital, Frontal Operculum, Middle Frontal Gyrus
					4.28	-45	10	17	
					4.16	-37	22	-4	
					4.07	-52	14	17	
					3.98	-48	14	15	
					3.97	-46	10	12	
	1	4183	1.63E-02	1.63E-02	3.92	-4	-63	-14	Cerebellum
					3.89	4	-76	-19	
					3.70	0	-62	-14	
3.69					-2	-61	-16		
3.57					-3	-60	-14		
				3.56	6	-76	-16		

Table 1. MNI coordinates of local maxima and activated brain regions for significant clusters obtained from the 3rd level between group GLM analysis. The first reported local maxima for each cluster also reflects the peak voxel for the entire cluster.

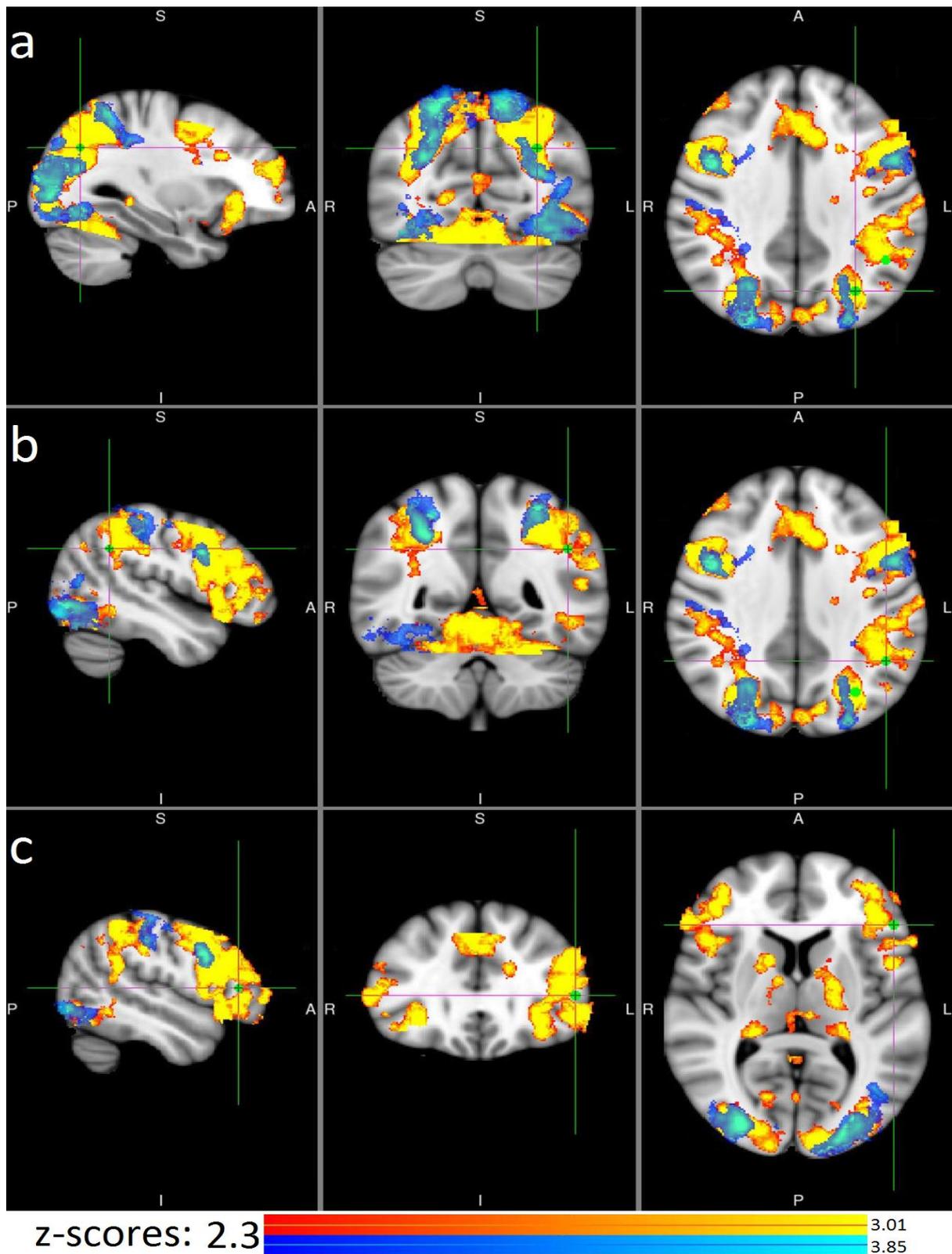


Figure 4. Significant group-level BOLD responses found in the Distractor Salient > Target Salient contrast. Yellow/Red reflects activity for elderly participants and blue/light blue reflects activity for young participants. The green dot in the crosshair in the top row reflects the left IPS (a) coordinates from Mevorach et al (2008). The green dots in the crosshair in the second and third row reflect the left TPJ (b) and left IFG (c) coordinates, respectively, from DiQuattro and Geng (2011).

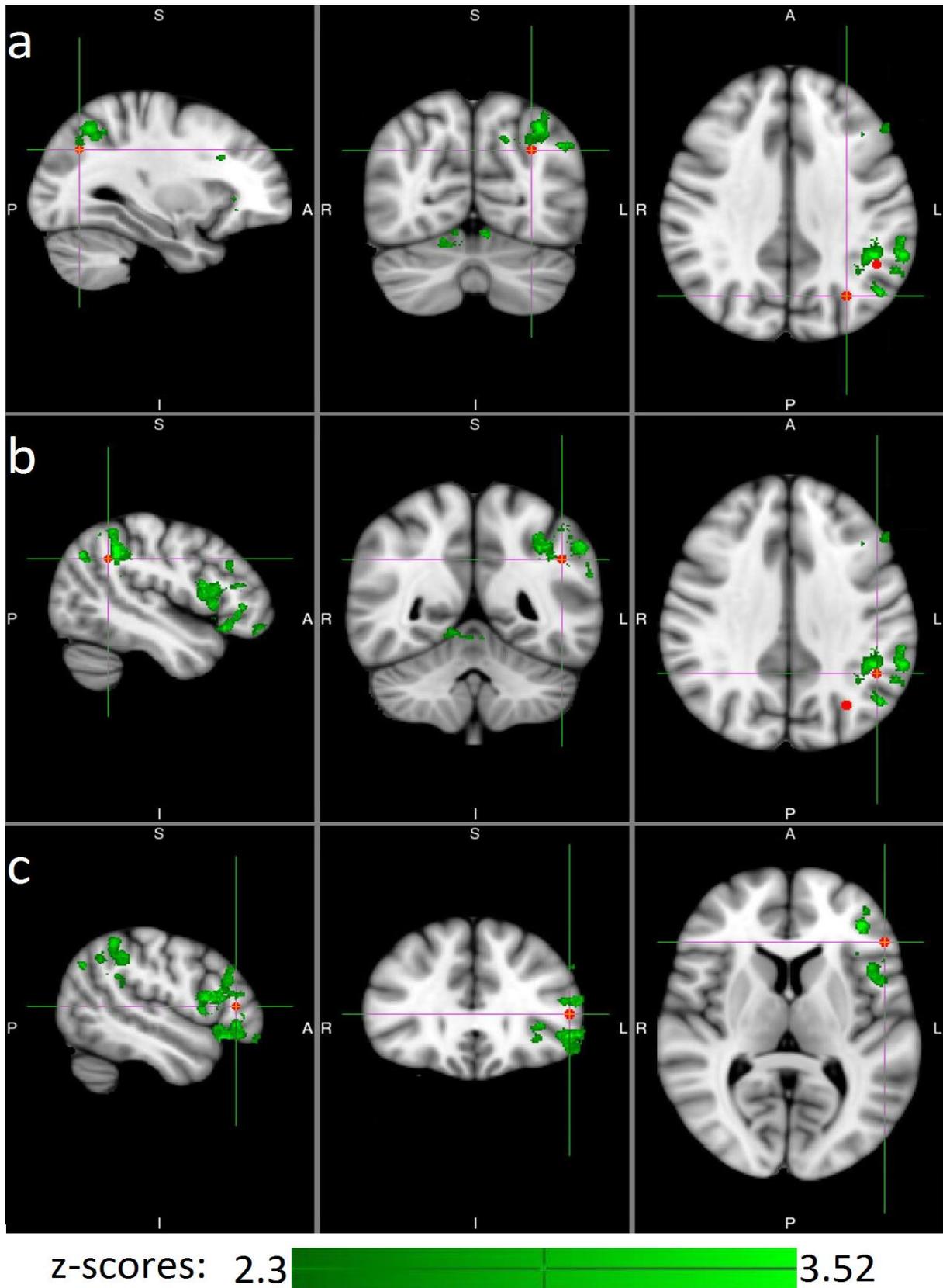


Figure 5. Significant group-level BOLD responses found in the Elderly > Young contrast of Distractor Salient > Target Salient. The red dot in the crosshair in the top row reflects the left IPS (a) coordinates from Mevorach et al (2008). The red dots in the crosshair in the second and third row reflect the left TPJ (b) and left IFG (c) coordinates, respectively, from DiQuattro and Geng (2011).

A group difference analysis was also conducted for the local salient > global salient contrast. The difference in brain activation in these two conditions represents the physical difference in the input regardless of task instruction. As such, it reflects a bottom-up signal, and enables us to identify whether group differences appear in the sensitivity to this signal (regardless of task instruction). This analysis revealed a stronger bilateral activity in the occipital cortex for older compared to younger participants (Figure 6; green clusters). Stronger activity in visual regions for local salient vs global salient displays presumably come from higher contrast and luminance in these displays (compared to the blurred global salient displays). The fact that this difference is greater in elderly participants may indicate that older participants are less effective in modulating this bottom-up signal through top-down control.

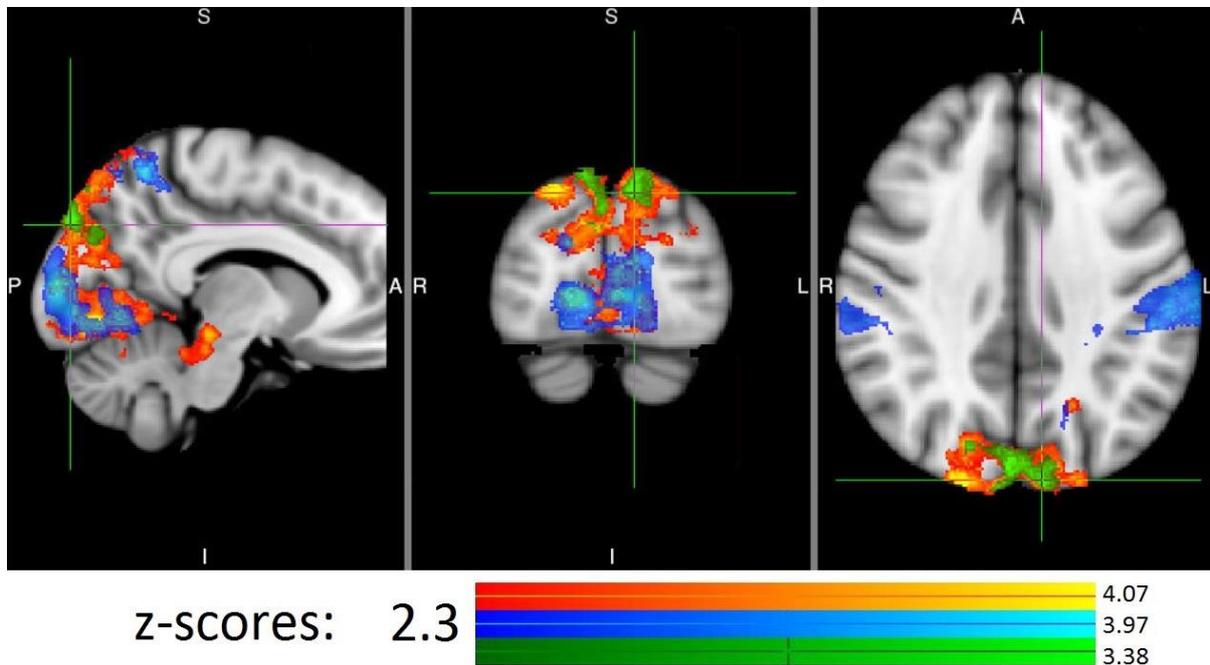


Figure 6. Significant group-level BOLD responses found for the Elderly > Young contrast of Local Salient > Global Salient (green clusters). The cross hair is centered at the maximum intensity voxel for this contrast (-9, -89, 36). The main effect maps for the LS>GS contrast for elderly (red/yellow clusters) and young (blue/light blue clusters) participants alone are also shown.

Regions of Interest

To assess the role of the three ROI's based on coordinates procured from relevant prior literature, we extracted mean BOLD signal change from the left IPS (Mevorach et al, 2008), and the left TPJ and left IFG nodes (DiQuattro and Geng, 2011). Repeated measures ANOVAs were conducted on the mean BOLD signal change for each ROI with salience (Target salient vs distractor salient) as a within subjects variable, and age group as a between subjects variable.

For mean BOLD signal change in the left IPS node (Figure 7a), the main effects of salience, $F(1,28) = 16.590$, $p < .001$, $\eta_p^2 = .372$, and age group, $F(1,28) = 10.049$, $p = .004$, $\eta_p^2 = .264$, were both significant. However, the interaction was not significant, $F(1,28) = 1.120$, $p = .299$. Both elderly and young participants seemed to show greater activity in this area during distractor salient trials (.463; .072% signal change) compared to target salient trials (.348; .066). However, overall elderly participants (.619; .095) engaged this area more than young participants (.192; .095). This supports the notion that both elderly and young participants recruit the left IPS during the global/local task, though elderly participants engage it more robustly.

For mean BOLD signal change in the left TPJ node (Figure 7b), the main effect of salience, $F(1,28) = 2.106$, $p = .158$ was not significant. The main effect of age group was significant, $F(1,28) = 10.708$, $p = .003$, $\eta_p^2 = .277$. The interaction was not significant, $F(1,28) = .581$, $p = .452$. The main effect of age group is driven by deactivation in this region for the younger participants (-.089; .071) and activation in the elderly participants (.238; .071). These findings support the notion the left TPJ was uniquely recruited by older participants in performing the global/local task.

For mean BOLD signal change in the left IFG node (Figure 7c), the main effect of salience, $F(1,28) = 4.012$, $p = .055$ was marginally not significant. The main effect of age group was significant, $F(1,28) = 4.531$, $p = .042$, $\eta_p^2 = .139$. The interaction was not significant, $F(1,28) = .299$, $p = .589$. The main effect of age group is driven by deactivation in this region for the younger participants (-.274; .111) and no activation for the elderly participants (.061; .111). These findings support the notion the left IFG was uniquely recruited by older participants in performing the global/local task.

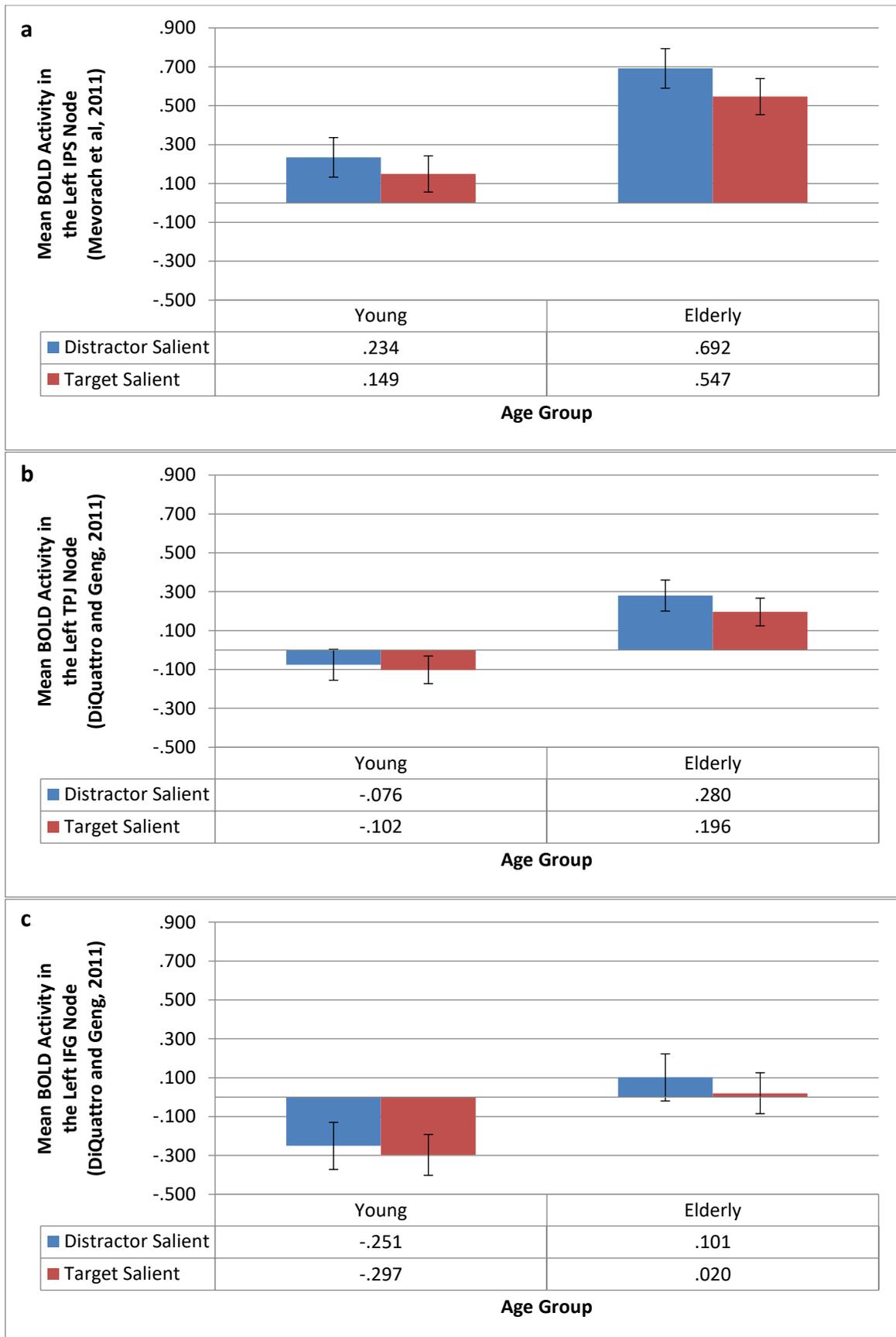


Figure 7. Mean BOLD signal change within the Left IPS (a), Left TPJ (b), and Left IFG (c) node as a function of relative salience and age group.

Brain Activity and Behavior

GLM analysis revealed that elderly subjects showed recruitment of left ventral frontal and parietal regions during distractor salient trials that were not engaged in young participants (Fig 5). To further establish the group differences, we assessed if observed age-related differences in brain activations are associated with individual performance – particularly distractor interference. Thus, a third level within group analysis (Flame 1 + 2) for the Distractor Salient > Target Salient contrast data (reflecting the brain activity associated with suppressing a salient distractor) was conducted for each group using a measure of distractor interference (adjRT congruency effect during distractor salient trials) as a covariate of interest. This analysis asks whether extra engagement of specific brain regions in the distractor salient condition (compared to the target salient ‘baseline’) is explained by the difficulty participants had in ignoring a salient distractor (the congruency effect) and whether such activation is different or shared across the age groups. Depending on the contrast, the activation maps generated reflect the strength of the positive or negative correlations between brain activity and the behavioral data.

For the positive correlation contrast, the activation in figure 8a, 8b, and Table 2 shows, for young participants (in blue), that higher activity in the right posterior IPS (extending superiorly) was associated with increased distractor interference. For Elderly participants (in yellow), similar overlapping right IPS activity (that extends more anteriorly) was also associated with increased distractor interference. In contrast, separate left IPS activation (coinciding with the left IPS node from Mevorach et al., 2009) was also associated with increased distractor interference in this population. For the negative correlation contrast, the activation in figure 8c and Table 2 shows, for young participants (in blue), bilateral activation throughout the orbitofrontal cortex, though the activation is more

extensive in the left hemisphere. Therefore, increased activity in these regions are associated with reduced interference. There was no activation for the elderly participants.

Overall, this data also indicates, that the two groups differed in the activation patterns in parietal and frontal cortices that were associated with increased distractor interference. While some overlap exists (in this case in the right IPS) clear differences are also visible particularly with the association of left IPS recruitment in older participants being associated with increased distractor interference.

Contrast	Cluster Index	Voxels	p	Local Maxima Z	Local Maxima x	Local Maxima y	Local Maxima z	Activated Brain Regions	
Elderly Participants Positive Correlation with AdjRT Compatibility Effect	2	8262	8.50E-05	5.12	33	-70	40	Both bands of the Right Intra-Parietal Sulcus (Right IPS), including Superior and Inferior Parietal Lobe	
				4.96	38	-51	51		
				4.59	37	-47	46		
				4.48	30	-44	46		
				4.35	39	-48	52		
	1	3788	2.13E-02	4.43	-35	-67	41		Both bands of the Left Intra-Parietal Sulcus (Left IPS), including Superior and Inferior Parietal Lobe
				4.33	-29	-43	40		
				4.24	-34	-70	41		
				4.21	-29	-55	45		
				4.19	-30	-43	38		
Young Participants Positive Correlation with AdjRT Compatibility Effect	1	5125	1.10E-02	3.95	25	-78	39	Both bands of the Right Intra-Parietal Sulcus (Right IPS), including Superior and Inferior Parietal Lobe	
				3.86	23	-76	45		
				3.76	24	-79	42		
				3.75	25	-78	48		
				3.74	22	-78	53		
Young Participants Negative Correlation with AdjRT Compatibility Effect	1	4730	1.74E-02	3.77	-26	64	-4	Left Frontal Pole	
				3.58	-28	64	-5		
				3.44	-32	64	-5		
				3.44	-29	58	-4		
				3.43	-23	64	-4		
				3.4	-27	61	-3		

Table 2. MNI coordinates of local maxima and activated brain regions for significant clusters obtained from the 3rd Level within group analyses including the AdjRT congruency effect as a covariate. The first reported local maxima for each cluster also reflects the peak voxel for the entire cluster.

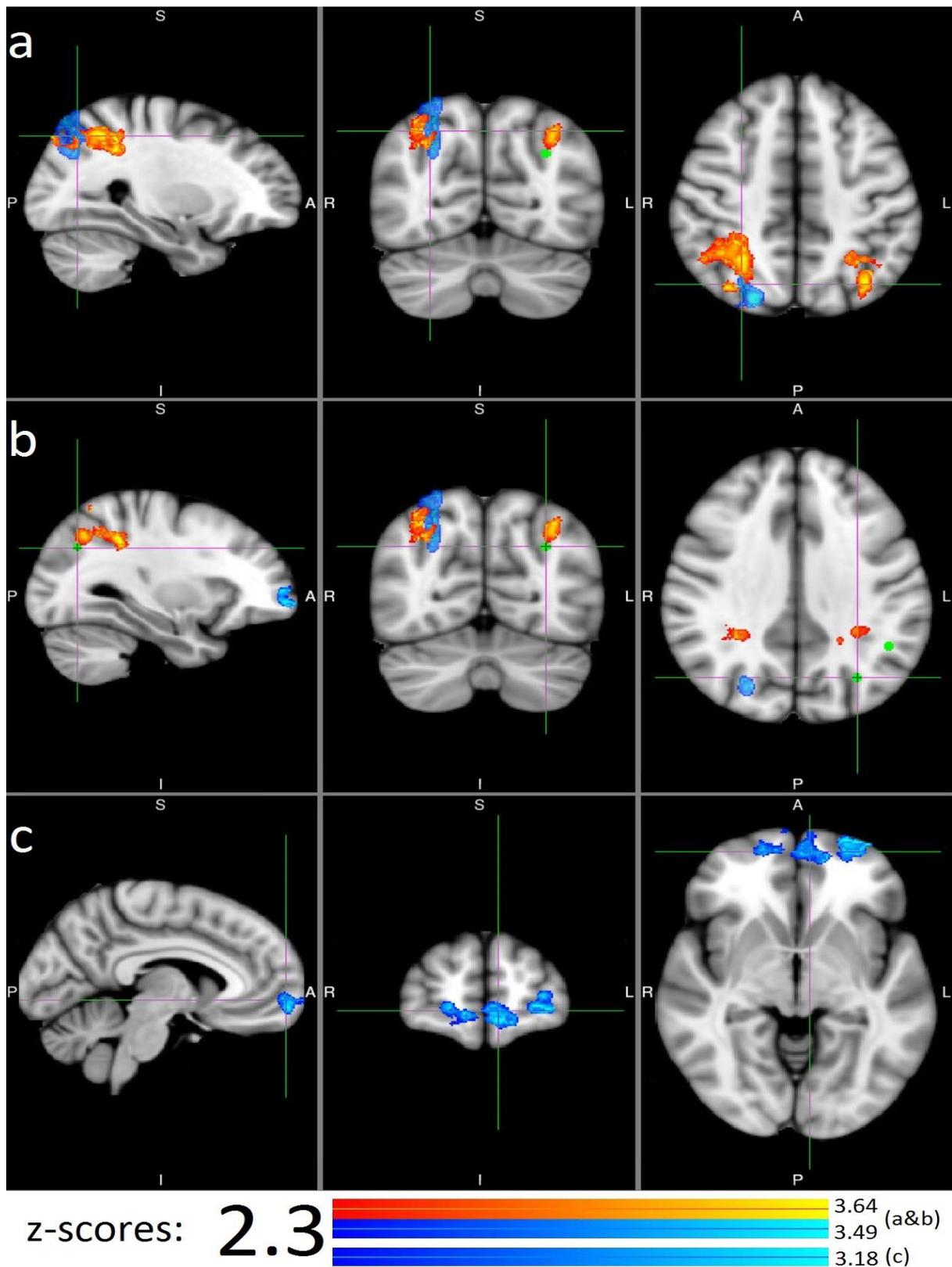


Figure 8. Significant group-level BOLD responses found in the Distractor Salient > Target Salient contrast that correlate positively (a & b) and negatively (c) with the AdjRT congruency effect during distractor salient trials. Red/Yellow reflects activity for elderly participants and blue/light blue reflects activity for young participants. (a) MNI coordinates: [28, -68, 47]; (b) Centered on left IPS ROI from Mevorach et al (2010); (c) MNI coordinates: [-6, 59, -5].

Resting State Functional Connectivity

Within Network Connectivity

Within network RSFC group measures and the statistical comparisons between the groups are presented in Table 2. Within network RSFC for young and elderly participants was not significantly different for the executive control, visuospatial, or salience network ROI's (Table 2). This is in contrast to Onoda et al (2012), who found age related decreases in RSFC in the same salience network (Shirer et al, 2012 and Onoda et al, 2012 both based their salience networks off the work of Seeley et al, 2007). Although, it should be noted that while not significant, the RSFC value for the elderly subjects is always lower than for the young subjects. One possible reason for our different results is that Onoda et al (2012) had 73 participants (43 males; 30 females; Age range: 36 -86 yrs; Mean age: 60.2 ± 12.8 [SD]), whereas we only have 15, so they had more statistical power. Onoda et al (2012) did not report effect sizes, so it's difficult to determine if this could be the reason we don't observe differences in connectivity.

Calculating RSFC using the coordinate based ROI's yielded more interesting results, although only when a more liberal false discovery rate was used ($Q = .10$; See Table 2 for all statistical test details; values in this section always reflect the mean and standard error of the r values). There was reduced RSFC between the left IPS ROI and the visuospatial whole network ROI in elderly participants compared with young ones (elderly participants: .1266; .020; and young participants: .1898; .018) as well as between the left TPJ ROI and the executive control whole network ROI (elderly participants: .0076; .011; and young participants: .0453; .014).

Between Network Connectivity

There was reduced network connectivity between the executive control and visuospatial whole network ROI's for elderly participants, relative to young ones (elderly participants: .0113;.010; and young participants: .0605; .011; Table 2). Moreover, this was significant with the more conservative correction for multiple comparisons (FDR = .05). However, there were no significant differences in connectivity between the executive control and salience whole network ROI's or the visuospatial and salience whole network ROI's.

These results suggest a specific age difference in the connectivity between the executive control network and the visuospatial network. To more precisely investigate the source of this differences we calculated the connectivity between these networks and their associated coordinate based ROI's (the left IPS overlapped with the visuospatial network and the left TPJ overlapped with the executive control network). There was reduced RSFC for elderly participants, relative to young ones, between the left TPJ ROI and the visuospatial whole network ROI (elderly participants: .0803; .019; and young participants: .1748; .021; significant with the more conservative FDR), and between the left IPS ROI and the executive control whole network ROI (elderly participants: .0340; .011; and young participants: .0694; .014; only significant with the more liberal FDR). Both of these analyses were further qualified as there was reduced RSFC for elderly participants between the left IPS ROI and the left TPJ ROI (elderly participants: .0282; .027; and young participants: .1688; .004; significant with the more conservative FDR).

Connectivity with the left IFG

As the left IFG seems to overlap with both the visuospatial and the executive networks, it is hard to assess whether any findings related to it represent within and/or between network connectivity. With that caveat in mind, reduced RSFC for elderly participants was found between the left IFG ROI and the visuospatial whole network ROI (elderly participants: .0600; .015; and young participants: .1180; .020), and between left IFG and the left TPJ (elderly participants: .0304; .03; and young participants: .1401; .047).

General Summary of RSFC Results

Overall, these results suggest that elderly subjects have reduced RSFC between the dorsal visuospatial and more ventral executive control networks, particularly between the left IPS and left TPJ. They also reveal that the elderly participants may have lower within network RSFC in both the dorsal visuospatial network (including the left IPS) and the more ventral executive control network (including the left TPJ). However, the within network results can only be interpreted to a limited extent since these differences were only significant when a more liberal correction ($FDR = .10$) for multiple comparisons was applied.

The results also revealed a reduced RSFC for elderly participants between the left IFG and the visuospatial network, but it is unclear if this reflects a change in between network (Executive Control and Visuospatial) or within network connectivity (Visuospatial). Alternatively, it is possible that the left IFG is part of multiple networks and the observed differences reflect changes in both within and between network connectivity. More research into the function and connectivity of the left IFG will be needed to distinguish between these possibilities.

Within or Between Network Analysis	Network(s) Analyzed	Elderly N = 15	Young N = 12	t-score	t-test p-value	Rank	Benjamini-Hochberg Critical Value (Q = .05)	Is the p-value < BH critical value	Benjamini-Hochberg Critical Value (Q = .10)	Is the p-value < BH critical value	Significant?
Between	Executive Control to Visuospatial Network	.0113 (.010)	.0606 (.011)	3.234	0.003	1	0.004	Yes	0.007	Yes	Yes, at both levels of Q
Between	Left TPJ to Visuospatial Network	.0803 (.019)	.1748 (.021)	3.353	0.003	2	0.007	Yes	0.014	Yes	Yes, at both levels of Q
Between	Left IPS to Left TPJ	.0282 (.027)	.1688 (.004)	3.134	0.004	3	0.011	Yes	0.021	Yes	Yes, at both levels of Q
Within and/or Between	Left IFG to Visuospatial Network	.0600 (.015)	.1180 (.020)	-2.367	0.026	4	0.014	No	0.029	Yes	Yes, but only at Q = .10
Within	Left IPS to Visuospatial Network	.1266 (.020)	.1898 (.018)	2.265	0.032	5	0.018	No	0.036	Yes	Yes, but only at Q = .10
Within	Left TPJ to Executive Control Network	.0076 (.011)	.0453 (.014)	2.113	0.045	6	0.021	No	0.043	No	Yes, but only at Q = .10
Between	Left IPS to Executive Control Network	.0340 (.011)	.0694 (.014)	2.020	0.054	7	0.025	No	0.050	No	Yes, but only at Q = .10
Within and/or Between	Left TPJ to Left IFG	.0304 (.030)	.1401 (.047)	1.990	0.057	8	0.029	No	0.057	Yes	Yes, but only at Q = .10
Within	FIND Lab Visuospatial Network	.2239 (.020)	.2830 (.029)	1.740	0.094	9	0.032	No	0.064	No	No
Within and/or Between	Left IFG to Executive Control Network	.0472 (.014)	.0774 (.012)	-1.615	0.119	10	0.036	No	0.071	No	No
Between	Executive Control to Saliency Network	.0172 (.010)	-.0052 (.015)	-0.806	0.214	11	0.039	No	0.079	No	No
Within	FIND Lab Saliency Network	.0327 (.017)	.0574 (.031)	.710	0.487	12	0.043	No	0.086	No	No
Between	Visuospatial to Saliency Network	.0844 (.016)	.0688 (.017)	.028	0.511	13	0.046	No	0.093	No	No
Within	FIND Lab Executive Control Network	.0812 (.010)	.0961 (.021)	.641	0.531	14	0.050	No	0.100	No	No

Table 3. Age differences in within- and between- network resting state functional connectivity. The df for all t-tests was 25. T-tests are ranked in p-value order from smallest to largest in accordance with the Benjamini-Hochberg correction for multiple comparisons (Benjamini and Hochberg, 1995; 2000; Benjamini and Yekutieli, 2001). The Benjamini-Hochberg (BH) critical value is calculated using the following formula: $Q(i/m)$, where i = the rank, m = the total number of tests, and Q = the maximum desired false discovery rate. Any t-test with a p-value equal to or smaller than the largest p-value where $p < BH$ critical is considered significant.

Analyzing the Link between RSFC, BOLD Activity, and Behavior

In order to better understand how the unique pattern of brain activation and connectivity in old age contributed to performance in this task we ran a stepwise multiple regression analysis with both types of predictors (RSFC and localized BOLD activity) to

predict the AdjRT congruency effect during distractor salient trials (which is the behavioral measure of attention control in our task; higher values reflect more interference). To this end, the analysis was only conducted on the data for the elderly participants.

Earlier we have shown that BOLD activity in the bilateral IPS and superior parietal lobe during distractor salient trials correlates positively with the adjusted response time congruency effect. Therefore, these regions likely contribute to performance in some way; however, it is unclear if both the left and the right lateralized regions contribute equally. Therefore, a left lateralized and a right lateralized ROI was generated from the elderly participants activation maps in Figure 8a and 8b. Mean BOLD activity was extracted for each participant from these ROI's during the four block types: global target under global salient displays, global target under local-salient displays, local target under global-salient displays, and local target under local-salient displays. Next, for each subject, the mean BOLD activity for the distractor salient (global target under local-salient displays and local target under global-salient displays) and target salient (global target under global salient displays and local target under local-salient displays) blocks were averaged. Finally, for each subject a difference score was calculated between the mean BOLD activity during distractor salient trials and target salient trials ($DS - TS$; referred to as the DS-TS BOLD difference). This value reflects the mean activity within an ROI specifically associated with presence of a salient distractor. The DS-TS BOLD difference for the left and right lateralized IPS/SPL ROI's were included as predictors in the analysis.

In the RSFC analysis, elderly participants were found to have reduced RSFC relative to young participants for three between network analyses (at $FDR = .05$ and $FDR = .10$), three within network analyses (at $FDR = .10$ only), and two that may have been between and/or within network analyses (at $FDR = .10$ only). These eight RSFC variables were included as

predictors in the analysis. Overall, ten independent variables were included as predictors in the analysis.

At step 1 of the analysis the DS-TS BOLD difference in the left lateralized IPS/SPL ROI was entered into the model and significantly predicted the DS congruency effect, $F(1,14) = 23.000$, $p < .001$ ($R = .799$; $R^2 = .639$). This is not surprising as it essentially reflects the positive correlation in Figure 8a and 8b for the elderly participants. However, at step 2, the RSFC between the left IPS ROI and the executive control network was also added to the model, and the new model significantly predicted the DS congruency effect, $F(2,12) = 23.405$, $p < .001$ ($R = .892$; $R^2 = .796$), to a significantly greater degree than the first step alone (R^2 change = .157; F change = 9.236; $p = .010$). Based on this model, 79.6% of the variance in the congruency effect could be predicted by the DS-TS BOLD difference in the left lateralized IPS/SPL ROI ($\beta = .285$; all beta weights are unstandardized) and the RSFC between the left IPS and the executive control network ($\beta = -.412$; constant = .106). These results suggest that interference (the congruency effect) is predicted to be higher as a function of increased activity in the left lateralized IPS/SPL ROI, but lower as a function of increased RSFC between the left IPS and the executive control network.

Discussion

The purpose of this study was to investigate the roles of the left intraparietal sulcus (IPS), the left temporoparietal junction (TPJ), and the left inferior frontal gyrus (IFG), as well as their functional connectivity in ageing effects on salience suppression. However, in contrast to previous studies (Tsvetanov et al, 2013; Mevorach et al, 2016), overall salient distractors seemed to affect performance similarly across age groups. For both groups, AdjRT was slower and there was a larger congruency effect when the distractor was salient

relative to when the target was salient, but this effect was equivalent across young and old participants. These results indicated that the salience manipulation was effective at making the distracting item more distracting. This is the standard effect for this paradigm. And, as expected (Verhaeghen and Cerella, 2002; Salthouse, 2000; Verhaeghen and De Meersman, 1998; Verhaeghen and Salthouse, 1997; Salthouse, 1996; Cerella, 1990; Cerella et al, 1980), the elderly participants showed overall slower AdjRT's. Despite this, there was evidence that elderly participants used a qualitatively different brain network compared with younger participants to perform the task. Young participants exhibited bilateral activity throughout dorsal fronto-parietal and occipital regions, including the Left IPS. Elderly participants exhibited similar bilateral dorsal fronto-parietal and occipital activity, but also additional activation in ventral regions – specifically the left TPJ and IFG. The elderly participants also showed lower resting state functional connectivity (RSFC), relative to young participants, between and within the visuospatial (incorporating the IPS) and executive control (incorporating the TPJ) networks. It therefore appears that while young participants rely on regions previously associated with proactive suppression of distractors in this task (such as the left IPS), elderly participants seem to also activate reactive control regions, such as the left TPJ and IFG; this necessitates communication between the proactive and reactive regions, even though the connectivity appears to be impaired.

However, exactly how these regions interact with each other is debatable. A regression model established that, for the elderly participants, interference generated by the salient distractor (i.e. the congruency effect) positively correlated with the DS-TS BOLD difference extracted from a left IPS/Superior Parietal Lobe (SPL) ROI (but not the right IPS, despite the bilateral activity in the correlational analysis; Figure 8a and 8b). This is consistent with previous literature that has highlighted specifically the left IPS (MNI

Coordinates: -30, -68, 34; Mevorach et al, 2008b) as critical in proactive suppression (Mevorach et al, 2008a; 2008b; 2009). While the activation in our overall GLM analysis (Figure 4a, 4b, and 4c) is bilateral, this may be attributed to increased power (block design here vs. event-related in Mevorach et al., 2009). It should also be noted that while the young participants in our study did not show a correlation between BOLD activity in the left IPS and behavioral interference (Figure 8a and 8b), this may be attributed to the fact that the variance in interference may be significantly less in young participants; it may simply be that the magnitude of interference is invariant to left IPS BOLD activity in young participants (or vice versa). Alternatively, it may be that there is a minimum threshold of BOLD activity that must be reached to apply sufficient suppression and young participants reach this threshold easily, after which additional activity has a negligible or no effect. Thus, the left IPS may be critical for young participants while still not showing up in the correlational analysis (Figure 8a and 8b). This may also explain why BOLD activity in the left TPJ did not correlate with interference for neither the young or elderly participants, particularly if the left TPJ plays an indirect supporting role in suppression.

The multiple regression also established that for the elderly subjects increased RSFC between the left IPS and the executive control network was associated with reduced interference. Waites et al (2004) showed that connectivity was affected by prior cognitive states. This suggests that if older participants generally favored a different control mode than younger participants for strategic reasons, it might be reflected in differences in resting state connectivity. However, the fact that variations within RSFC of these ROI's is functionally significant for elderly participants supports the notion that the reduction in RSFC in elderly subjects reflects an impairment in functional connectivity, rather than a generalized shift in strategy in old age. It also increases our confidence in the significant age

group difference in RSFC between these ROI's, despite the fact that it was only significant with a more liberal FDR ($Q = .10$). Ultimately, this suggests that greater connectivity between the executive control and visuospatial networks, particularly the left IPS and left TPJ, supports salience suppression processes in elderly subjects.

The reduced between network RSFC found in this study (Table 2) appears to contradict previous investigations which have highlighted increased between-network RSFC in aging populations (Betz et al, 2014; Salami et al, 2014; Geerlings et al, 2014). This is often referred to as functional dedifferentiation, in which brain activity (Dennis and Cabeza, 2011; Park et al, 2004; Cabeza, 2001) and functional connectivity (Geerlings et al, 2014; Andrews-Hanna, et al, 2007; Madden et al, 2010; Grady et al, 2010) linked to cognitive tasks become less specialized over the lifespan (i.e. brain activity becomes more similar in response to different tasks). However, Chen et al (2016) found that aging affected between and within cortical connectivity in different ways. For example, they found age-related increases in connectivity between the frontal and temporal lobes, but age-related decreases in connectivity between the temporal and parietal lobes. Thus, there is no reason to specifically expect age related increases in between network connectivity, especially considering that most identified brain networks are cross-cortical. Additionally, consistent with our results, they found age related decreases in connectivity within the parietal lobe. Therefore, it's possible that the age-related reduction we found in RSFC between left IPS and left TPJ reflects a reduction in connectivity within the parietal cortex, rather than a general change in between network connectivity. The reduced between network connectivity may also be taken as evidence that the elderly participants are in fact activating both the proactive and reactive control networks, instead of exhibiting dedifferentiation.

Alternatively, the standardized ROI networks used may not have been appropriate for our older subjects. In particular, Goldstone et al (2016) showed evidence of spatial reorganization of elements of resting state networks (notably the anterior cingulate cortex and bilateral anterior insula from a salience network, and the orbitofrontal cortex from a dorsal attention network) in an aging population. Therefore, it's possible that standardized networks for elderly participants would be fundamentally different than the ones we used, which were developed based on healthy young subjects. If this were the case, our RSFC would be invalid for the elderly subjects and this might account the unexpected reduction in between network RSFC. However, the fact that the age-related change in connectivity appears to significantly affect behavioral performance is not consistent with the notion that the standardized networks were inappropriate. Regardless of the nature of the observed impairment (between-network or within-cortical), the regression model suggests that the connectivity observed is functionally relevant for the elderly participants.

It is also worth noting that the within-network reduction of functional connectivity in old age was not limited to the dorsal (proactive) regions but also featured in the ventral (reactive) fronto-parietal network (although these effects were only significant at $Q = .10$, for dorsal and ventral regions). In addition to an age-related reduction in connectivity within the executive control network (TPJ → Executive Control Network), there was also reduced connectivity between the left IFG and the visuospatial network, and the left TPJ and the left IFG (though it's unclear if the effects involving the left IFG reflect between or within network connectivity, or both). This finding is important as it is often assumed that proactive control is uniquely impaired in aging as participants appear to rely more on reactive control. However, our finding that RSFC is impaired in both networks casts doubt on this

assumption, instead suggesting that both proactive and reactive suppression may be impaired.

Overall, this evidence suggests that in old age, the suppression of salient distractors shifts from being mediated by proactive control mechanisms to a combination of proactive and reactive mechanisms. However, it is not clear exactly what role the left TPJ and the reactive control network plays in the suppression processes. It's possible that left IPS mediated proactive suppression is impaired and TPJ/IFG mediated reactive suppression is engaged to compensate for this impairment. This is supported by the reduced RSFC within the visuospatial network for the elderly subjects, particularly between the left IPS node and the executive control network. This may imply a reduced ability for the left IPS to communicate with and ultimately suppress information within the visuospatial network (Mevorach et al., 2010), which could also be interpreted as an impairment within the proactive control network. The additional engagement of TPJ/IFG mediated reactive control mechanisms may therefore support left IPS mediated proactive control mechanisms, rather than supplant them. The multiple regression analysis showed that, for elderly participants, increased RSFC between the Left IPS node and the executive control network (which includes the left TPJ and possibly the left IFG) was associated with decreased interference, supporting the notion that effective communication between the proactive and reactive mechanisms during distractor suppression is beneficial in old age.

The notion that the left reactive mechanisms would supplant the left IPS mediated salient suppression comes from an assumption that the left IPS only engages in a proactive manner. However, while there is evidence that the left IPS engages proactively in young subjects during this task (Mevorach et al, 2008b), being proactive is not necessarily a defining feature of left IPS mediated distractor suppression. It's possible that distractor

suppression requires left IPS engagement, regardless of whether suppression is done proactively or reactively, and that engaging this suppression mechanism is simply temporally delayed in older participants. According to Grady (2012), the shift towards favoring reactive control in old age may simply reflect a change in the time required to engage proactive control due to the need to accumulate greater neural resources in older participants. In this case, the young participants would engage the left IPS within a proactive suppression context, while in elderly subjects, who are biased toward reactive control (see Chapter 1), the left IPS would only be triggered after the left TPJ/IFG recruited it reactively; or proactive mechanisms may take so long to engage that they are ineffective and reactive control mechanisms are necessary to trigger suppression. Essentially, older participants either won't or can't engage suppression proactively because of the additional time it takes to do so. DiQuattro and Geng (2011) suggested that the left TPJ (as part of the ventral attention network; Corbetta and Shulman, 2002) sends reactive control signals to the dorsal attention network (which includes the left IPS) as a kind of update in response to behaviorally relevant visual stimuli, which is consistent with the idea of TPJ triggering left IPS mediated suppression. This explanation can also account for the results of the multiple regression analysis, as it relies on significant communication between the left IPS and the reactive network. Moreover, it helps explain why left TPJ activity did not correlate with interference. If triggering the left IPS is an all or nothing job, the magnitude of activity would be irrelevant as long as it hit a minimum threshold.

A secondary finding is the stronger bottom-up related signal we documented in the occipital cortex of old compared to young participants. Essentially, this suggests that activation in visual cortex in old age is more sensitive to the bottom-up signal than in younger participants. Since the physical stimulus presented to the young and elderly

participants were the same, the increased bottom-up signal can be attributed to reduced top-down modulation over the bottom-up signals. This supports the notion that top-down salience suppression is in fact impaired in older participants. The impairment in top-down modulation could have multiple possible sources. First, the left IPS has been shown to suppress salience through the downregulation of activity within the visual cortex, and any impairment to this region would cascade through the information processing stream and result in generally higher activity within the visual cortex. Second, it is possible that general processing speed deficits could impair early visual function because if the suppression process is slowed, information could be sent on to higher-order processing prior to suppression mechanisms engaging. A third possibility is that functional dedifferentiation could impair the ability to distinguish between targets and distractors. According to Goh et al (2011), dedifferentiation in ventral visual areas leads to difficulty in discriminating differences in visual information. This could make it difficult to determine what information to suppress, which in turn would lead to higher overall activity within the visual cortex.

One question that arises from this data is why there were no distractor interference related behavioral differences across age groups. Using a similar paradigm, Tsvetanov et al (2013) showed that elderly participants showed higher congruency effects than young participants during distractor salient trials (though it's noted that the effect size is small), but not target salient trials. On the other hand, Mevorach et al (2016) showed increased congruency effects for older participants in both response time and accuracy, however, they did not find a difference as a function of distractor or target salience. There are three differences between our study and these studies which may have influenced the results. First, in this study and in Mevorach et al (2016) the hierarchical letter stimuli was presented for 250 msec, where as in Tsvetanov et al (2013) it was presented for 150 msec. Extending

the perception time may allow for enough time for elderly subjects to suppress the distractor more effectively, albeit via compensatory brain mechanisms. Second, there were age differences among the elderly subjects across studies. For Tsvetanov et al (2013) the mean age of subjects was 74 (N = 19; 65 – 84; 10 males), for Mevorach et al (2016) it was 71 (N = 19; 63 – 85; 10 males), and for this study it was 66 (N = 15; 59 – 77; 8 males). Of the three studies, we have the youngest elderly cohort and still found differences in brain function, which we have argued may be compensatory in nature (Cabeza et al, 2004; Persson et al, 2006). However, compensatory brain activity can only offset neurological impairments to a limited degree. Over time behavioral deficits should eventually emerge, as are seen in the other studies with older subjects, assuming impairments in brain function progressively worsen with age. And third, we had a smaller N than the previous studies (15 elderly subjects vs 19 and 20, in Tsvetanov et al, 2013 and Mevorach et al, 2016, respectively), reducing the likelihood of detecting weak effects. Although, in our study, we had many more trials per subject (432 vs 192 and 144), so that would make up for some of the lost power.

Conclusion

The purpose of this study was to investigate how healthy aging mediates the roles of the left IPS, the left TPJ, and the left IFG, as well as their functional connectivity, on salience suppression. Despite no age-related differences in behavioral performance, elderly participants engaged qualitatively different brain regions to complete the task. Young participants engaged only proactive control regions (including the left IPS), whereas elderly participants engaged both proactive and reactive (including the left TPJ and left IFG) regions. Critically, only DS-TS BOLD activity in the left IPS positively correlated with interference,

suggesting that it is directly involved in proactive salience suppression. Moreover, elderly subjects showed reduced resting state functional connectivity between and within these regions.

It was proposed that proactive control may be impaired in aging populations due to processing delays or functional impairments to the left IPS and, in order to compensate for this, the TPJ and the reactive control network may support this process by triggering left IPS mediated suppression faster or more effectively. Importantly, this explanation highlights the involvement of dorsal and ventral control networks in old age and the benefit to performance when they interact. However, the question remains whether this is a solely compensatory activation of the reactive network or if a strategic bias towards reactive control may also play a role.

Overall, this data suggests that while both proactive and reactive brain regions, particularly the left IPS and left TPJ, are involved in proactive suppression in aging populations, they both exhibit functional impairments in connectivity and BOLD activity.

Chapter 3:

Is Reactive Inhibition Impaired in Aging Populations?

Introduction

It is generally accepted that as we age, declines in cognitive performance may occur (Braver and Barch, 2002; Craik and Salithouse, 2011; Andrews-Hannah et al, 2007; Geerligs et al, 2014; Grady, 2012; Larson et al, 2016; Li et al, 2001; 2016; Persson et al, 2006; Zanto et al, 2010). More specifically, there is a plethora of evidence highlighting impairments in inhibition mechanisms (Hasher and Zacks, 1988; Bauer et al, 2012; Mayas et al, 2012; Gazzaley et al, 2005). The focus on inhibitory processes in old age is especially relevant because there is evidence that distractor inhibition, in particular, is crucial in mediating cognitive control in general (Darowski et al., 2008). One of the early examples for inhibition deficits was reported by Hasher et al (1991) in a study measuring inhibitory function in young and elderly participants using a negative priming task (assessing the persistence of inhibition of a distractor by switching its role to a target on subsequent trials). Hasher et al (1991) found that young participants showed persistence of inhibition from one trial to the next, but older participants showed no effects, suggesting impaired inhibitory function. They argued that this reflected impairment in a central inhibition mechanism. Age-related inhibition deficits have also been identified with stop signal tasks (Anguera and Gazzaley, 2012), Ax-CPT tasks (Rush et al, 2006), global/local tasks (Tsvetanov et al, 2013), reading with distractor tasks (Darowski et al, 2008), and task switching tasks (Jimura and Braver, 2010). Moreover, many studies, including the one in Chapter 2, have identified unique brain activation in older participants during inhibition tasks, even when behavioral performance is equivalent to young participants (Park and Reuter Lorenz, 2009; Vallesi et al, 2011). This suggests that participants may be compensating for inhibition impairments, making them less obvious in behavioral measures.

The notion that an all-encompassing inhibition impairment is associated with age has been challenged by studies showing impairments only on subsets of inhibition tasks. For instance, Kramer et al (1994) found age related inhibition deficits in a stop-signal task, but not in a response competition or spatial pre-cueing task. Furthermore, even when inhibition impairment occurs across tasks, evidence suggests it may be independent. For instance, Anguera and Gazzaley (2012) assessed motor inhibition and sensory filtering within the context of a stop-signal task in young and old participants. Critically, they showed that these inhibitory modalities were independently impaired as a function of aging. More recent studies have built upon this conclusion, establishing that impairments in different cognitive inhibitory functions that correlate with age have distinct behavioral and neural correlates (Vadaga et al, 2015; Sebastian et al, 2013; Bloemendaal et al, 2016).

While it appears that only some inhibitory functions are impaired, it is not clear why certain functions are impaired and others are not or if there is some general inhibition deficit that only affects specific inhibitory functions. The dual mechanisms theory of proactive and reactive cognitive control (Braver, 2012) suggests a potential explanation for the failure to identify a general inhibition impairment in old age. Rather than a single inhibition mechanism, the DMC differentiates between two modes of control: Proactive, which allows one to prepare a behavioral response to a given stimulus in advance; and reactive, which is a “late correction” mechanism that allows one to alter behavioral plans in the moment when suddenly presented with new and relevant information. It is possible that only one of these inhibition mechanisms is impaired, or that they are impaired to different degrees. Indeed, current research suggests that older participants tend to rely more on reactive control strategies (Paxton et al, 2008; Jimura and Braver, 2010) due to impairments

in proactive control mechanisms, though proactive control strategies are still possible (Braver et al, 2009).

Braver et al (2005; Paxton et al, 2008) assessed context updating and maintenance in ageing using the AxCPT task. With respect to DMC, the AxCPT task can be arguably completed using either proactive or reactive control mechanisms. Studies utilising the AxCPT tasks have generally demonstrated that young participants performed better on “Ay” than “Bx” cue-probe pairs, a proactive pattern of results, but the elderly participants performed better on the “Bx” pairs, a reactive pattern of results. In a different aging cohort that showed no behavioral differences in AxCPT performance, Paxton et al (2008; study 1) still found brain activity that was consistent with increased reliance on reactive control. The lack of behavioral differences, but presence of differences in functional brain activity also supports the notion that aging participants are compensating for inhibition impairments. In another study, Jimura and Braver (2010) assessed the temporal dynamics of brain activity during a task switching paradigm which required the maintenance and updating of goal related information. They found that elderly participants (relative to younger participants) showed reduced sustained activation in general and increased transient activation during switch trials in the anterior prefrontal cortex. They also found that younger participants demonstrated cue-related activity in the posterior parietal cortex on all trials, whereas older participants only showed that activity on switch trials. These findings are consistent with the idea that older participants show more reactive control related- and less proactive control related activity than younger participants.

While such findings suggest a tendency to utilise reactive processes in old age, these seem to be limited to scenarios where both proactive and reactive control modes may be appropriate for the task and so may reflect a strategic preference rather than impairment.

In fact, even in the context of the negative priming paradigm (e.g., Hasher et al., 1991) the lack of the effect in old age may represent a benefit of using reactive control. In contrast, Tsvetanov et al., (2013) provided evidence of an age-related decline in performance related to the non-spatial inhibition of salient distractors that is specifically linked with proactive processes. Participants were presented with a compound letter task designed so that either the global or local form could be more salient. Older participants (Mean age = 74 yrs; Age range: 65 – 84 yrs) showed larger distractor interference compared to younger participants (18-22 yrs) when the distractor was higher in salience than the target (despite knowing in advance, with 100% validity, which element of the display was the target and which was the distractor). Critically, Mevorach et al (2008a; 2008b; 2010) has shown that the ability to ignore salient distractors in this paradigm relies on a preparatory (proactive) process mediated by the left IPS. Thus, unlike the AxCPT task where there is a performance trade-off between 'Ay' and 'Bx' trials for switching between proactive and reactive strategies, there is no trade-off or benefit for engaging reactive control mechanisms in this task. Therefore, it is unlikely that these results are simply due to a change in strategy and can be interpreted as the result of an impairment in proactive suppression mechanisms in the older participants.

The above evidence points to a selective impairment in inhibition in old age – proactive processes appear to decline with age, while reactive processes may be intact. However, while findings highlight the activation of reactive processes in old age this is not when reactive processes are engaged in young participants. For example, in both Paxton et al (2008) and Jimura and Braver (2010), the tasks are designed in such a way that they tap into proactive control mechanisms for young participants, but not reactive control mechanisms. Since the young participants do not show evidence of engaging reactive control mechanisms, there is no point of comparison for performance or brain activity for

the elderly participants. In order to verify that reactive processes are not affected by age, a comparison of performance is needed using tasks in which young participants also primarily rely on reactive processes. It is possible that older participants are shifting to an impaired, but still strategically better than proactive, reactive control mechanism.

Here, we describe a task which arguably engages reactive control mechanisms specifically. DiQuattro and Geng (2011) investigated the brain mechanisms that are involved in processing contextually relevant, but not task relevant stimuli. While in an fMRI scanner, they had participants (Mean age = 23.8; Age Range: 18 – 39 yrs) perform a visual search task for a low contrast target in the presence of either a high or low contrast non-target (50% predictability), each of which would appear in one of two pre-defined locations. Despite being task irrelevant, the salient non-target was contextually relevant as the presence of a high contrast non-target informed the participant that the target was in the other location. They found that participants were both faster and more accurate on trials with a salient distractor, compared to a similar (to the target) distractor. This confirmed that participants were using the distractor as anti-cue and benefiting from its presence. The fMRI analysis revealed that the left TPJ and left inferior frontal gyrus (IFG) were significantly more active when there was a high salience non-target compared to a low salience non-target. Dynamic causal modelling revealed a network in which left TPJ projects to left IFG that, in turn projects to the frontal eye fields (FEF). The authors interpreted this to mean that the ventral attention network (TPJ and IFG in this study) that is typically associated with bottom up attention (Corbetta and Shulman, 2002), updates control signals to the dorsal attentional network (FEF in this study). Importantly, they further suggest that the TPJ and IFG are effectively generating a “reactive” control signal as a consequence of the stimulus presentation (Braver, 2009; 2012). In this paradigm, participants could not predict the next

stimulus so they could not meaningfully engage proactive control. Therefore, engaging left TPJ and left IFG mediated reactive control is the most strategically appropriate behavior in this task.

To further investigate the role of aging in cognitive control and distractor inhibition, we explicitly assessed the function of reactive inhibition in older (60 -82 years) participants and healthy young controls (18 – 22 years). We used the task from DiQuattro and Geng (2011) for two reasons. First, the use of reactive inhibition of distractors appears to provide a measurable strategic benefit (as compared to proactive inhibition mechanisms) suggesting that impairments in task performance can be reasonably attributed to impairments in reactive control. Second, this task does not emphasize response inhibition and is primarily reliant on sensory inhibition. This will allow us to assess the functionality of reactive suppression in elderly populations more confidently than in previous studies, without the potential confounds of motor suppression. If in older participants reactive cognitive control is indeed intact, it is expected they will derive a similar benefit from the presence of the salient distractor compared with younger participants. Conversely, if older participants have impaired reactive control, it is expected that they will derive less of a benefit than younger participants.

Methods

Participants

25 young participants (Mean Age: 18.8 yrs, SEM of Age: .18, Age Range: 18 -21 yrs; 24 Females) and 26 elderly participants (Mean Age: 69.5 yrs, SEM of Age: 1.16, Age Range: 60 – 82 yrs; 13 Females) participated in three successive behavioral experiments. The order of the tasks was counterbalanced to account for possible fatigue and order effects. Young participants were recruited from the undergraduate population in the school of psychology

at the University of Birmingham, UK. They were compensated for their participation with course credits. The elderly participants were recruited from a volunteer pool maintained by the School of Psychology at the University of Birmingham. They were compensated for 1.5 hours of their time with a one-time payment of £7. All participants had to sign an informed consent form prior to the study. Participants' were healthy with no history of head injury, mental health issues or neurological disorders. The old participants were screened for decline in cognitive functions using the Montreal Cognitive Assessment (MoCA). All of the elderly participants scored within the normal range (Mean Score: 27.5, SEM of Score: .23).

Stimuli and Procedure

Participants were presented with five blocks of 46 trials each. Color was defined using RGB color coordinates. The background color of the display was grey [100 100 100]. On all trials, target and non-target stimuli were displayed. Each stimulus' was a square whose center was 6.5 degrees of visual angle (horizontally 6.3 degrees; vertically 1 degree) diagonally left or right and below the center of the screen. Each square subtended 1.8 degrees of visual angle. The target square was dark grey [120 120 120]. In the target square, an 8 pixel wide vertical line bisected the square. A second horizontal line also appeared to create a 'T'-like shape (Figure 1). These lines were a dark grey [80 80 80]. On half of trials, the horizontal line was 10 pixels above the center of the square, creating an 'Upright' T (Figure 1) and on the other half, the horizontal line was 10 pixels below the center of the square creating an 'Inverted' T. The color of the non-target square depended on the trial type. On 'Similar' trials, the color was the same as the non-target square. On 'Salient' trials, the non-target square was white [255 255 255]. In the non-target square, an 8 pixel wide horizontal line bisected the square. A second vertical line also appeared to create a sideways 'T'-like shape (Figure 1). On 'Similar' trials, the line color was the same as inside

the target square. On 'Salient' trials, the line color was black [0 0 0]. On 50% of trials, the vertical line was 10 pixels right of the center of the square, creating a clockwise rotated "T". On 50% of the trials, the vertical line was 10 pixels left of the center of the square creating a counter-clockwise rotated "T".

In each block there were 50% "Salient" trials and 50% "Similar" trials, randomly intermixed. On any given trial there was a 50% chance that the target would appear in the left square and 50% chance that it would appear in the right square. Participants had to identify if there was an upright or inverted "T" stimulus on each trial. They pressed the "H" key to indicate an upright "T" was present and the "B" key to indicate that an inverted "T" was present. These buttons were chosen because the "H" key is positioned above the "B" key on the keyboard, mimicking the spatial orientation of the target stimuli, where the upright "T" stimulus has a horizontal line above the center of the stimulus square and the inverted "T" stimulus has a horizontal line below the center of the stimulus square.

Every trial began with a black [0 0 0] fixation cross presented at the center of the screen, which persisted throughout the trial (including during 'blank' screens). Each trial began with blank screen. The "fixation" time was randomly selected based on a uniform distribution of times between 1500 – 2000 msec (Figure 1). Next, the appropriate stimulus (depending on the trial) was displayed for 200 msec. Participants could respond starting when the stimulus was presented. After the stimulus was removed, the participant was presented with blank screen until they made a response. Once a response was made, the next trial would begin. Participants were given the chance to take short breaks in between blocks (< 5 min). Each session began with 20 practice trials. During the practice, participants received visual feedback such that if they made an identification error, the fixation cross changed to red for 250 msec before turning back to black for the rest of the fixation time.

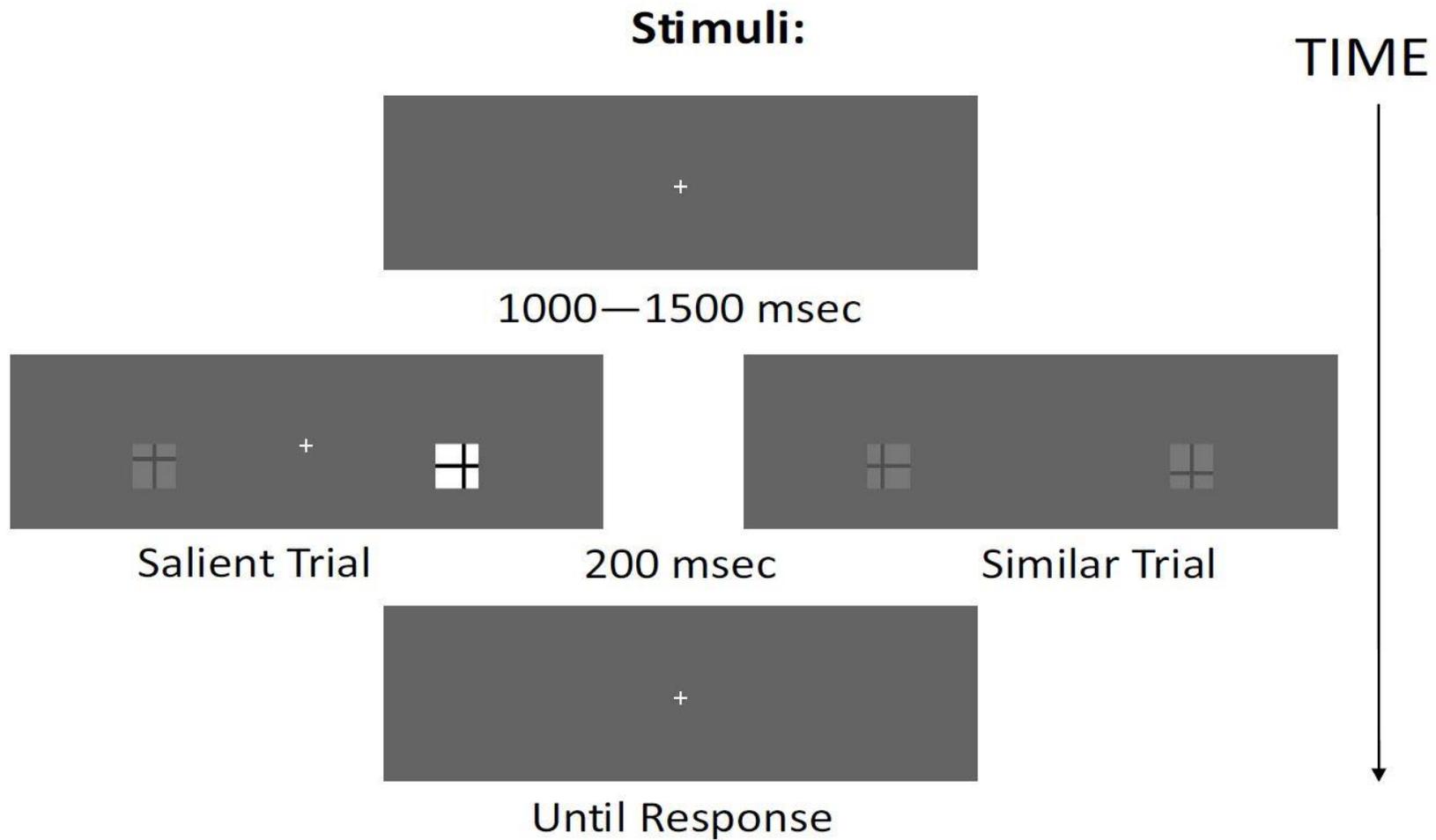


Figure 1. Diagram of the reactive control task. Participants were presented with either a salient or similar stimulus on any give trial. In the salient example the correct response would be to press the H-key to indicate an upright target. In the similar example the correct response would be to press the B-key to indicated an inverted target

Results

Response time in msec (RT) and accuracy rate (i.e. proportion of correct responses) were measured as dependent variables. The response time data was cleaned to account for outliers. For each participant, response time data that was greater than and less than 2 standard deviations from the mean was excluded from all analyses. The mean response time was calculated separately for each salience condition (salient trials and similar trials). This resulted in the loss of an average of 4.33% (SEM = .21%) of the response time data, per elderly participant and 3.79% (SEM = .23%) per young participant. An independent samples t-test revealed that these values were not significantly different, $t(49) = -1.73$, $p = .090$. All values are presented as mean \pm standard error of the mean.

Response time in msec (RT) and accuracy rates were analysed using a repeated measures ANOVA with Saliency (salient distractor vs similar distractor) as within subject factor and participants age group (Young vs Elderly) as a between subject factor. For accuracy (Figure 2), the main effects of salience ($F(1,49) = .591$, $p = .446$) and age group ($F(1,59) = .013$, $p = .449$), were not significant, but there was a significant interaction between salience and age group ($F(1,49) = 8.32$, $p = .006$, $\eta_p^2 = .145$). Planned comparisons comparing performance in the salient and similar conditions within each age group revealed no significant difference ($t(25) = -1.44$, $p = .162$) in accuracy for salient (84.42% \pm .07%) and similar (86.35% \pm .06%) for the older participants. In contrast, young participants were more accurate on salient trials (89.28% \pm .06%) than on similar trials (85.96% \pm .07%; $t(24) = 2.70$, $p = .012$).

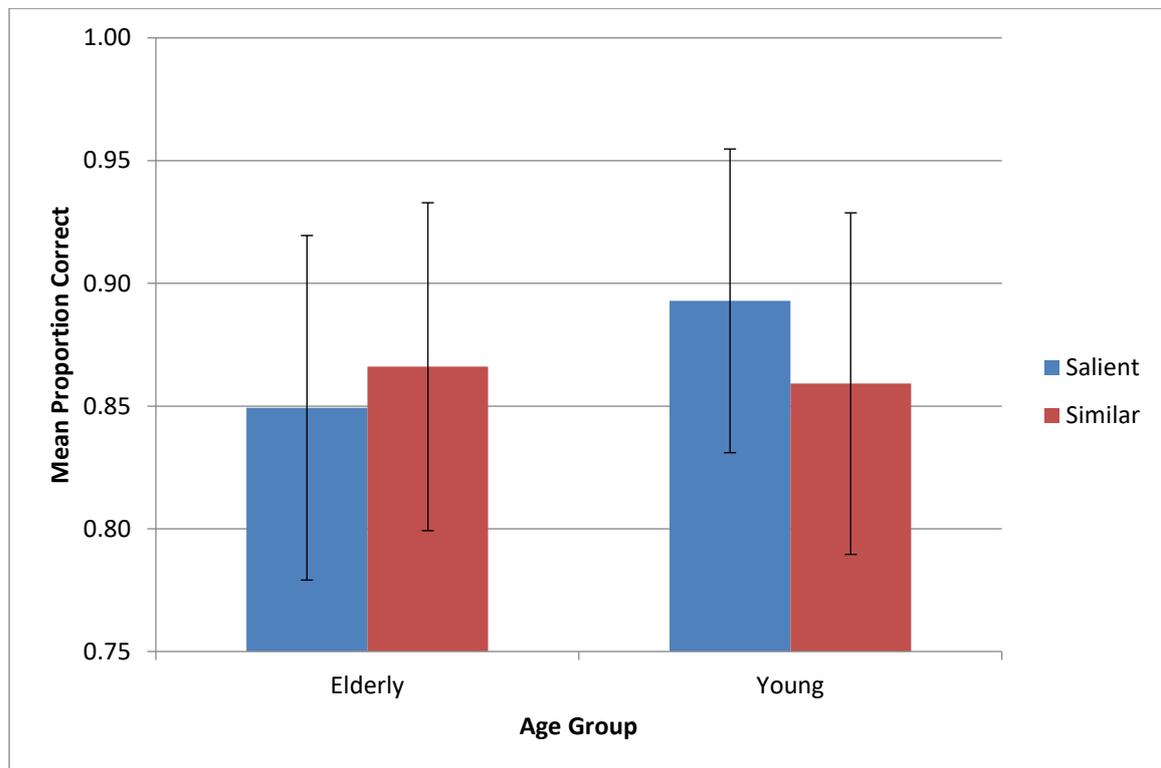


Figure 2. Graph reflecting mean proportion of correct responses for salient and similar conditions across age groups.

To assess the possibility that, the benefit gained (or rather the lack of benefit) from the presence of the salient distractor may be mediated by age, a Pearson r correlation was conducted comparing a benefit score (Salient – Similar: Higher values indicate higher accuracy in the salient condition) to the participants' age. The correlation between age and the benefit score, $r(24) = -.208$, $p = .308$, was not significant.

For the RTs (Figure 3), the analysis revealed a main effect of saliency ($F(1,49) = 4.52$, $p = .039$, $\eta_p^2 = .084$), where participants were quicker to respond to salient trials (848 +/- 22 msec) than to similar trials (872 +/- 22 msec). This benefit effect is a typical result for this paradigm and supports the notion that participants are engaged in reactive cognitive control in order to use the salient distractor as an anti-cue (DiQuattro and

Geng, 2011; Geng and DiQuattro, 2010). There was also a main effect of age group ($F(1,49) = 48.07, p < .001, \eta_p^2 = .495$) as younger participants (715 +/- 30 msec) responded overall faster than the older ones (1005 +/- 29 msec). This was expected as elderly participants typically have slower response times than young participants. Interestingly, there was once again an interaction between saliency and age group, $F(1,49) = 4.62, p .036, \eta_p^2 = .086$. Planned comparisons contrasting RTs in the two salience conditions in each group revealed no significant difference in performance for the older participants ($t(25) = .014, p = .989$; Salient: 1005 +/- 34 msec; Similar: 1004 +/- 35 msec). On the other hand, younger participants responded significantly quicker ($t(24) = -4.04, p < .001$) in the salient condition (691 +/- 25.8 msec) compared with the similar condition (739 +/- 24.9 msec). These results suggest that the main effect of saliency was primarily driven by the younger participants.

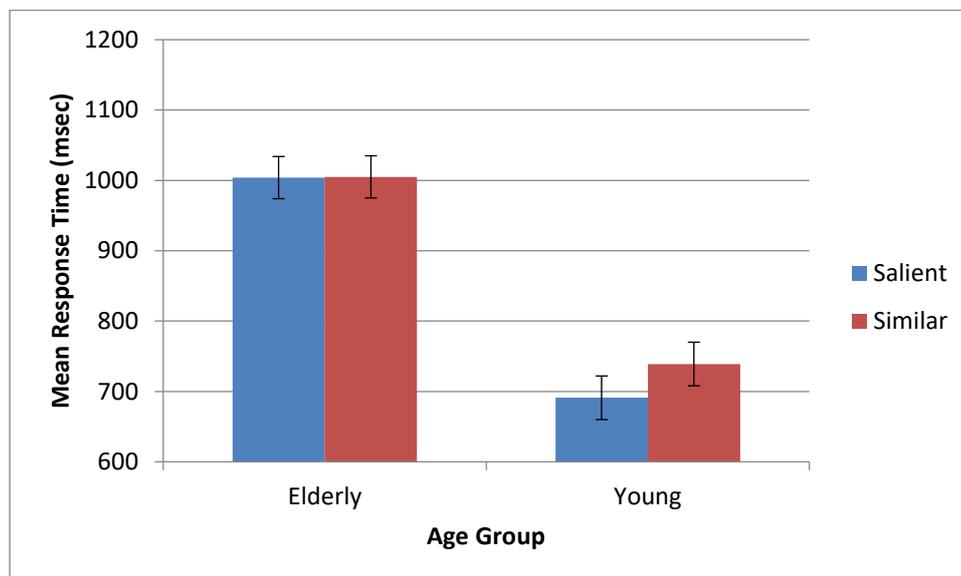


Figure 3. Graph reflecting response time data (msec) for salient and similar conditions across age groups.

To further establish the link between age and reduced benefit from the salient distractor we assessed the correlation between a benefit score (subtracting the response time for the similar condition from the salient condition) and age in the older participants group. The Pearson r correlation was significant, $r(24) = -.552$, $p = .003$, $R^2 = .304$, (Figure 4) supporting the conjecture that old age was associated with a reduced ability to benefit from the salient distractor in this task. As age may also correlate with overall RTs (Verhaeghen and Cerella, 2002; Salthouse, 2000; Verhaeghen and De Meersman, 1998; Verhaeghen and Salthouse, 1997; Salthouse, 1996; Cerella, 1990; Cerella et al, 1980; Zanto et al, 2010), we tested whether the significant correlation we report was simply due to slow responses in this task. To rule this out we assessed, for the elderly participants, the correlation between age and RT ($r(26) = .217$, $p = .287$) and between overall response time and RT benefit ($r(26) = .049$, $p = .812$) which did not show a significant link. Therefore, it is reasonable to attribute the source of the previous correlation to an inhibition deficit in response time for the elderly participants that is associated with the participant's age.

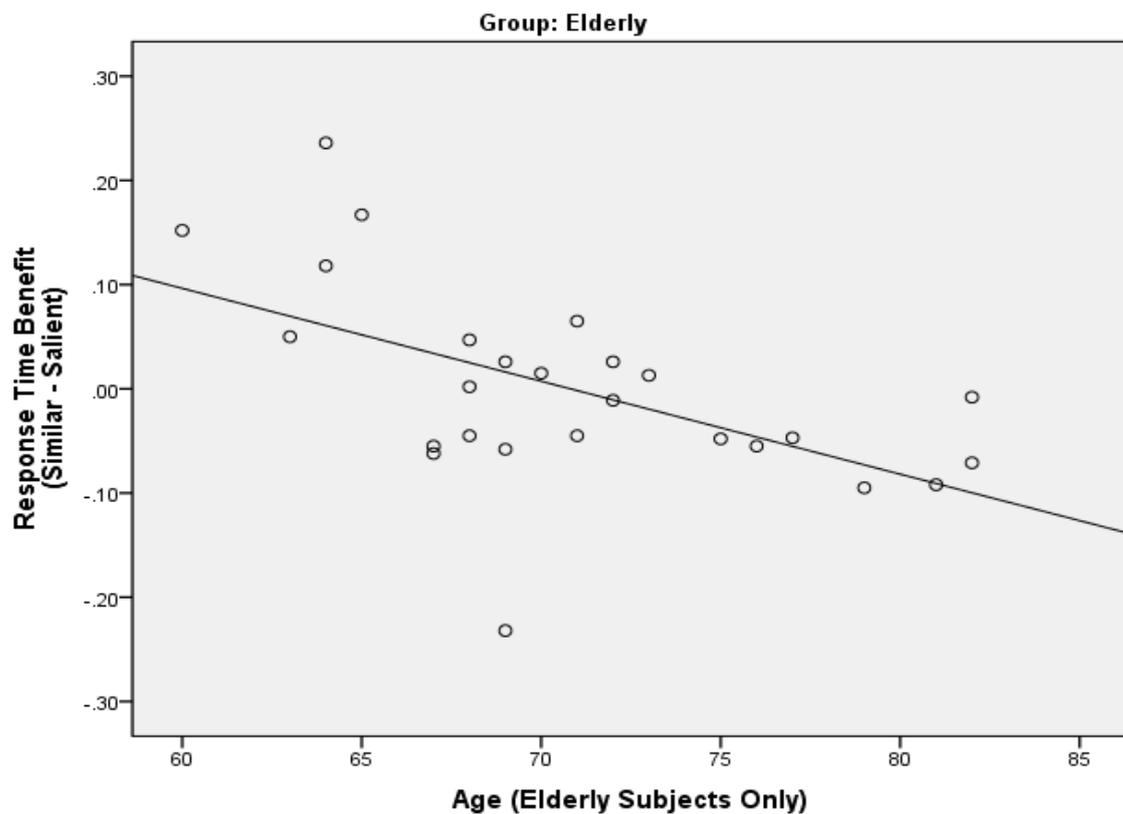


Figure 4. Scatterplot comparing age and RT benefit score for the elderly participants

Discussion

The purpose of this study was to assess the effect of aging on reactive suppression in elderly populations by comparing performance in a task that relies on reactive suppression in young participants too. We found that older participants exhibited an impairment in the reactive inhibition task compared to young participants. Specifically, young participants were able to effectively use a salient distractor as an anti-cue to benefit performance in terms of both accuracy and response. Older participants on the other hand showed no change in performance when the salient distractor was present in the display. Not only that, the response time benefit attributed to the

presence of the salient distractor scaled as function of age for the older participants; the older the participant, the lower the response time benefit. This particular task was selected because there was no strategic benefit to engaging proactive inhibition, suggesting that reactive mechanisms would be required to engage in this task. Therefore, these results cannot be attributed to a simple shift in processing strategy. To the authors knowledge, this is the first instance of apparent reactive control deficits being reported in an aging population. It has significant implications because it challenges the implicit assumption present in much of the literature that older participants shift from proactive to reactive mechanisms because proactive mechanisms are impaired and reactive mechanisms are intact.

One concern for this type of research in general is that inhibition deficits may in fact be attributed to a generalized deficit in processing speed (Salthouse and Meintz, 1995; Salthouse, 2000; Verhaeghen and De Meersman; 1998). Since most studies that identify inhibition deficits measure response time, it could appear as if there were impaired response times in a specific inhibition task for older participants, when in fact they are simply overall slower. However, even after accounting for this possibility, inhibition deficits still persist in many inhibition tasks (Verhaeghen and Cerella, 2002). In our study, the negative correlation we report between age and the size of the benefit might allude to such an issue if longer RTs within the old participants were associated with reduced benefit in the task. Critically, however, we found no correlation between overall RT and the size of the benefit and also no correlation between age and overall RT (within the older participants). As such, we would argue that the age-related lack of a

benefit we report cannot be attributed to general speed of processing deficits and is more likely associated with reduced reactive processes specifically.

A second concern with respect to this specific study is that the deficit observed may in fact be completely or partially due to age-related impairments in attentional orienting rather than reactive inhibition. The nature of orienting attention is complex and there are many variables to consider, particularly with respect to aging (see Erel and Levy, 2016 for a comprehensive review), but the most relevant aspects in the context of our study are covert and overt orienting, and exogenous and endogenous orienting. Participants in the current study were instructed to keep their eyes focused on the fixation point throughout the trials ostensibly to encourage covert attention (no eye movements), however eye tracking was not employed so the use of covert attention cannot be ruled out. Regardless, research shows that older participants typically do not have impairments in covert attentional orienting (Jennings et al, 2007), and that while deficits in overt attention tasks have been reported (Kingstone et al, 2002), it has been argued that they can be attributed to deficits in motor control over eye movements (Chen and Machado, 2016; Dowiasc et al, 2015; Warren et al, 2013; Crawford et al, 2012; Klein et al, 2000, Ross et al, 1999) rather than attentional control (Erel and Levy, 2016).

With regard to exogenous and endogenous orienting during trials with a salient distractor, it is arguable that this study engages both. Geng and DiQuattro (2010) showed that the response time benefit in a similar paradigm was facilitated by rapid rejection when the first saccade was directed towards the salient distractor. The orienting of eye movements towards the salient distractor is a classic example of overt exogenous orienting. However, rapid rejection necessitates a reorienting of attention away from the

distractor and towards the target. Furthermore, the rapid rejection process only begins because the participants recognize the distractor for what it is and therefore the target is no longer in an unpredictable location. This suggests that the reorienting of attention towards the target after rapid rejection is facilitated by endogenous orienting mechanisms. According to Erel and Levy (2016), exogenous orienting is typically reported as intact (Waszak et al, 2010; Iarocci et al, 2009; Jennings et al, 2007; Folk and Hoyer, 1992; Craik and Byrd, 1982) or even enhanced (Langley et al, 2011a; 2011b; Mahoney et al, 2010) in older populations, while endogenous attention is reportedly impaired (Olik and Kingstone, 2009; Bojko et al, 2004; Brodeur and Enns, 1997; Greenwood et al, 1993). However, it is not clear whether such impairments are likely to be due to difficulties in the ability to interpret the more complex endogenous cues (relative to exogenous cues), rather than an impairment in spatial orienting (Swan et al, 2015; Erel and Levy, 2016). Taken together, these findings suggest that spatial orienting or reorienting per se is not unequivocally impaired in old age and while it can be regarded as an integral part of reactive suppression processes it is less likely that ageing impairments in reactive suppression can be attributed to impaired spatial orienting

While we highlight the current task in the context of reactive suppression, an alternative explanation is that these results may still be attributed to deficits in proactive control mechanisms. Assessing brain activation for a similar task, DiQuattro and Geng (2011) proposed that the left TPJ generates reactive control signals that project through the frontal eye field to the IPS. This may be interpreted as a combination of the reactive control network (TPJ/FEF) and the proactive network (IPS) in order to suppress non-target signals. Furthermore, in Chapter 2 it was proposed that left IPS mediated salience

suppression may be necessary even in reactive suppression, albeit triggered by the reactive control network. Therefore, it is possible that the effects of age we report here are a consequence of such impaired left IPS functioning if indeed reactive suppression relies on both reactive and proactive brain mechanisms. In other words, it is also plausible that the reactive control network in the brain is functioning properly, but it is unable to effectively interact with a dysfunctional left IPS. Chapter 4 will investigate this possibility.

If both proactive and reactive inhibition are impaired in ageing, then why is there a shift towards reactive control? There are two possibilities. First, it may be that proactive control is simply impaired to a greater degree than reactive control, necessitating the primary use of reactive control. It is difficult to directly compare deficits within each control mode. Different tasks are generally needed in order to be sure participants are engaging in a specific control mode. For example, the global/local paradigm was ideal for engaging proactive control, whereas DiQuattro and Geng's (2011) t-task was ideal for engaging reactive control. Even if one were to convert the cognitive control deficits to effect sizes or z-scores, there are differences in the visual stimuli and in the presentation times that would not be equivalent across studies. The ideal paradigm to test this idea would be to use a single task where the participant could be biased toward proactive or reactive control. This would allow a more direct comparison of inhibition deficits. Currently, our lab is working on developing such a paradigm.

A second possibility is that proactive control is particularly difficult to engage in aging populations due to deficits in processing speed and resources, necessitating a compensatory shift towards reactive control mechanisms (Grady, 2012; Reuter-Lorentz

et al, 2008). Indeed, the results of Chapter 2 suggest that in old age reactive control regions (e.g., TPJ) are recruited to support proactive control regions in a possibly compensatory manner, rather than completing taking over responsibility for the task. Despite partially engaging reactive inhibition mechanisms in the global/local task in Chapter 2 (which is less strategically beneficial than using proactive inhibition), performance in the older participants was equivalent to that of the younger participants. The results of Chapter 2 support this explanation, though it should be noted that the two explanations described here for a shift to reactive control in aging are not mutually exclusive.

Conclusion

This study suggests that older participants exhibit an impairment in reactive control mechanisms, in addition to the impairments typically observed in proactive control. This impairment cannot not be attributed to speed of processing or attentional orienting deficits. However, if reactive control relies on both reactive and proactive mechanisms, as suggested by DiQuattro and Geng (2010) and in Chapter 2, it is possible that reactive control is not impaired, but rather it is unable to effectively engage with impaired proactive mechanisms. Chapter 4 will examine the specific role of proactive and reactive mechanisms during this kind of reactive task.

Chapter 4:

The Role of the Left IPS and Left TPJ during Reactive Salience Suppression

Introduction

According to the dual mechanisms of cognitive control framework, cognitive control is mediated by a proactive and reactive mechanism (Braver, 2012; Braver et al, 2002; 2005; 2009). The proactive mechanism is an “early selection” mechanism which allows people to prepare responses in advance to stimuli, before the presentation of an expected stimulus. Reactive control, on the other hand is a “late correction” mechanism, allowing people to make last second changes to a behavior in response to new information, and thus is activated after the presentation of some, often unexpected, stimulus. In chapter 2, a proactive control task – a global/local task that orthogonally manipulated target and distractor salience (Mevorach et al, 2008; 2010a; 2010b; Tsvetanov et al, 2013) – was administered to a cohort of young (18-30) and elderly (59-77) participants while fMRI data was recorded. It was found that, despite similar behavioral measures of distractor interference, the elderly participants engaged both proactive (left IPS) and reactive (left TPJ) control regions to complete the task, whereas younger participants only engaged proactive regions. It was concluded that left TPJ mediated reactive suppression mechanisms are recruited in old age to support left IPS mediated proactive suppression mechanisms. One proposed explanation for these results was that the left IPS was necessary for both proactive and reactive distractor suppression in old age and, during reactive distractor suppression, the left TPJ would reactively trigger the left IPS to carry out suppression. Moreover, age related reduced functional connectivity to the IPS and TPJ suggested that there may be an impairment to both of these mechanisms.

While behavioral evidence of age related impairments to proactive control are well established in the literature, chapter 3 was the first study to directly test for age related impairments in reactive control. In chapter 3, a cohort of young (18 - 21) and elderly (60 - 82) participants were presented with a task that inherently encouraged reactive control and in which there was no strategic trade-off for engaging proactive control instead. Participants had to make an orientation discrimination judgement on a target while in the presence of a salient or non-salient (referred to as the similar condition) distractor. Typically, participants are faster and more accurate in the presence of the salient distractor, which they presumably use reactively as an anti-cue (DiQuattro and Geng, 2011). In Chapter 3, it was found that the younger participants showed this standard effect, but the elderly participants showed no difference in performance in the presence of the salient and non-salient distractor. This was argued to reflect a deficit in the ability to reactively use the salient target as an anti-cue, and it was interpreted as evidence of age related impairments in reactive control.

While both chapter 2 and 3 both identify impairments in reactive control, there is no explicit evidence that the functional impairments reported in chapter 2 directly lead to the behavioral deficits observed in older participants reported in chapter 3. In this chapter, we will use rTMS to assess if the age-related impairments in reactive suppression observed in chapter 3 can be attributed to a dysfunction in the left TPJ, left IPS, both, or neither. As previous literature has implicated the left TPJ in reactive suppression in young participants, it's inclusion as a stimulation region is obvious. The left IPS was chosen because in chapters 2 and 3 it was noted that being proactive is not necessarily a defining feature of left IPS mediated distractor suppression, though this has

never been tested. Mevorach et al (2006b) applied rTMS to the left posterior parietal cortex, in which effects were later localized to the left IPS (Mevorach et al, 2008a), and found it disrupted distractor suppression during a proactive task (a variation on the hierarchical letter task from chapter 2). It was further established that online stimulation to the left IPS only affected distractor suppression during the same proactive task if the stimulation occurred prior to the stimulus presentation (Mevorach et al, 2008b).

However, the task in both of these studies were designed in such a way that proactive suppression was strategically advantageous and therefore may have inherently biased participants to use the left IPS proactively. Therefore, stimulating the left IPS will assess if this region plays a role during reactive suppression and will help establish the temporal profile of left IPS mediated distractor suppression (i.e. only proactive or both proactive and reactive).

By applying rTMS to healthy young participants prior to engaging in a reactive suppression task (the same one as in chapter 3 and DiQuattro and Geng, 2011), we will determine if stimulating these brain regions produces results similar to those seen in older participants in chapter 3. If the left TPJ or IPS is causally involved in facilitating reactive suppression in young participants, then we would expect stimulation to reduce the performance benefit gained from the presence of a salient distractor. If the left TPJ does not facilitate reactive suppression, stimulation may increase or not affect the performance benefit. DiQuattro and Geng (2001) argued that the left TPJ was involved in generating reactive control signals, but they specifically identified its role as a hub to integrate contextual information which would then be passed along to the left frontal eye fields, which in turn generated an orienting signal. Therefore, while the left TPJ may

help expedite the process of reactively disengaging and reorienting away from salient distractor, it is not necessarily required for the process. Alternatively, the left TPJ may have a yet unidentified role in reactive control, unrelated to salience suppression. Indeed, this could be consistent with the idea that the left IPS mediates even reactive distractor suppression (depending on the results of IPS stimulation).

Similarly, if the left IPS does not facilitate reactive suppression, there are two possible outcomes. First, stimulating left IPS may increase the performance benefit. As discussed in chapter 3, participants can use either proactive or reactive control to engage with any task, even if it's counter-productive, and certain tasks inherently encourage the use of one control mode over the other. However, stimulating a region associated with a specific control mode may encourage the use of the "other" control mode because it is unimpaired. Therefore, stimulating left IPS (i.e. inhibiting a proactive region) may encourage the use of reactive control, even in participants who would be predisposed to proactive control, resulting in a greater performance benefit. And second, if Left IPS activity is completely independent from reactive control, stimulating it will simply have no effect on the performance benefit.

Methods

In this study, we explicitly tested if the left TPJ and left IPS are involved in reactive salience suppression. In three separate conditions, participants will have 1 Hz offline rTMS applied to the left TPJ, left IPS, or Cz (a control region) for 10 minutes, immediately prior to engaging in a slightly modified version of the DiQuattro and Geng (2011) task. In this task, participants will have to identify the orientation of a "t" shape randomly

presented at one of two locations along the horizontal meridian. At the other location, either a salient or non-salient distractor will be presented. Response time and accuracy will be recorded and our critical measure will be the performance benefit gained when a salient, contextually relevant distractor is present in the display.

Participants

32 participants were recruited from the undergraduate population in the school of psychology at the University of Birmingham, UK, who had previously participated in an fMRI experiment with a researcher within this department. However, due to technical problems viable data was only collected from 27 participants (Mean Age = 22.6 yrs; Median Age = 20 yrs; Age Range = 18 -36 yrs). One further participant was removed from the analysis due to poor performance (< 80% accuracy). Overall, the data consists of 26 participants. They were compensated for their participation with course credits. All participants were healthy with no history of head injury, mental health issues, or neurological disorders. Participating in the experiment was only allowed if none of the contraindication criteria were met based on Rossi et al (2009; also see Wasserman et al, 1998). This study was approved by the institutional ethics committee and conformed with the Declaration of Helsinki. All participants gave informed consent after a full explanation of the experiment and possible side effects of TMS.

TMS

A 70 mm figure-of-eight coil connected to a MagStim Rapid stimulator (MagStim) was positioned over either Cz (the control site: 10-20 EEG coordinate system), the left intraparietal sulcus (MNI coordinates: -30 -68 34), or the left temporo-parietal junction

(MNI coordinates: -46 -50 34). The position of the coil was identified using the Brainsight TMS-MRI co-registration system. Copies of the participant's T1 structural scans (1mm isotropic; for more information see Anatomical T1 details at https://www.buic.bham.ac.uk/wiki/index.php/Standard_sequence_parameters) were obtained with the participants' consent from the previous researchers who conducted their fMRI scan. MNI coordinates for the left IPS (Mevorach et al, 2009) and left TPJ (DiQuattro and Geng, 2011) were obtained from previous studies which have shown relevant activation in the critical regions. Prior to the behavioral experiment, offline rTMS was applied at a frequency of 1hz and 60% of the stimulators maximum intensity for 10 minutes. This type of stimulation protocol typically results in extended cortical inhibition at the stimulation site (Stewart et al, 2001; Hilgetag et al, 2001; Mevorach et al, 2005). Intensity was not determined based on motor threshold because it has been shown that this may not necessarily be a good indicator of cortical excitability (Stewart, Walsh, and Rothwell, 2001). Additionally, previous studies have shown that using a constant intensity across participants is an effective method of rTMS stimulation (Mevorach et al, 2008; 2010; Sack et al, 2007). The rTMS frequency, intensity, and duration were all within appropriate safety limits (Wasserman, 1998; Rossi et al, 2009).

Stimuli and Procedure

Participants performed three experimental sessions on different days. In the first session, participants completed 20 practice trials of the behavioral task (before stimulation). In the second and third session, participants were given the option to re-do the practice blocks (before stimulation), based on how well they remembered the task.

Next, rTMS was applied to the appropriate brain region. rTMS stimulation occurred only once per experimental session. The order of stimulation across sessions was counterbalanced to account for possible effects of TMS on learning, resulting in 6 possible order conditions. Finally, they were presented with the main version of the behavioral task immediately after the rTMS finished. The behavioral task took approximately 7.5 minutes to complete. The second and third sessions worked the same way, except there was not practice of the behavioral task prior to rTMS.

In the behavioral task, participants were presented with five blocks of 46 trials each. Color was defined using RGB color coordinates. The background color of the display was grey [100 100 100]. On all trials, target and non-target stimuli were displayed. Each stimulus was a square whose center was 6.5 degrees of visual angle (horizontally 6.3 degrees; vertically 1 degree) diagonally left or right and below the center of the screen. Each square subtended 1.8 degrees of visual angle. The target square was dark grey [120 120 120]. In the target square, an 8 pixel wide vertical line bisected the square. A second horizontal line also appeared to create a 'T'-like shape (Figure 1). These lines were a dark grey [80 80 80]. On 50% of trials, the horizontal line was 10 pixels above the center of the square, creating an 'Upright' T (Figure 1). On 50% of the trials, the horizontal line was 10 pixels below the center of the square creating an 'Inverted' T. The color of the non-target square depended on the trial type. On 'Similar' trials, the color was the same as the non-target square. On 'Salient' trials, the non-target square was white [255 255 255]. In the non-target square, an 8 pixel wide horizontal line bisected the square. A second vertical line also appeared to create a sideways 'T'-like shape (Figure 1). On 'Similar' trials, the line color was the same as inside the target square. On 'Salient' trials, the line color was

black [0 0 0]. On 50% of trials, the vertical line was 10 pixels left of the center of the square, creating a clockwise rotated “T”. On 50% of the trials, the vertical line was 10 pixels right of the center of the square creating a counter-clockwise rotated “T”.

In each block there were 50% “Salient” trials and 50% “Similar” trials, randomly intermixed. On any given trial there was a 50% chance that the target would appear in the left square and 50% chance that it would appear in the right square. Participants had to identify if there was an upright or inverted “T” stimulus on each trial. They pressed the “H” key to indicate an upright “T” was present and the “B” key to indicate that an inverted “T” was present. These buttons were chosen because the “H” key is positioned above the “B” key on the keyboard, mimicking the spatial orientation of the target stimuli, where the upright “T” stimulus has a horizontal line above the center of the stimulus square and the inverted “T” stimulus has a horizontal line below the center of the stimulus square.

Every trial began with a black [0 0 0] fixation cross presented at the center of the screen, which persisted throughout the trial (including during ‘blank’ screens). Each trial began with blank screen. The “fixation” time was randomly selected based on a uniform distribution of times between 1500 – 2000 msec. Next, the appropriate stimulus (depending on the trial) was displayed for 200 msec. Participants could respond starting when the stimulus was presented. After the stimulus was removed, the participant was presented with blank screen until they made a response. Once a response was made, the next trial would begin. Participants were given the chance to take short breaks in between blocks. During the practice trials, participants received visual feedback such that

if they made an identification error, the fixation cross changed to red for 250 msec before turning back to black for the rest of the fixation time.

Results

Response time in msec (RT) and accuracy rate (i.e. proportion of correct responses) were measured as dependent variables. Only response time for correct responses was analysed. Any participant who performed below 80% accuracy within any salience condition, during any TMS condition was removed from the analysis. One participant was removed based on this criterion. Therefore, the data for 26 participants was analysed. The response time data was cleaned to account for outliers. For each participant, response time data that was greater than and less than 2 standard deviations from their individual mean was excluded from all analyses. The mean response time was calculated separately for each salience condition (salient trials and similar trials). This resulted in the loss of an average of 3.84% (SEM = .24%) of the response time data, per participant. All values are reported as mean and standard error of the mean. For both the response time and accuracy data, a repeated measures ANOVA was conducted with salience (Salient trials and similar trials), TMS (Cz, Left IPS, and Left TPJ), and block (1 – 5; a discrete interval measure of time) as within subjects variables. For any tests where sphericity was violated, a Greenhouse-Geisser (GG) correction was applied.

Response Time Analysis

For the response time data (Figure 7), there was a significant main effect of salience, $F(1,25) = 49.538$, $p < .001$, $\eta_p^2 = .665$. This was driven by faster responses during salient (551 msec; 14 msec; all data reported is mean and standard error of the mean) relative to similar (602 msec; 14 msec) trials. The main effect of TMS was not significant,

$F(2, 50) = .375, p = .643$ (GG corrected; $\chi^2(2) = 7.02, p = .030; \epsilon=.798$), but the main effect of block was significant, $F(1.516, 21.221) = 1.516, p = .036, \eta_p^2 = .234$ (GG corrected; $\chi^2(9) = 44.451, p < .001, \epsilon=.379$). A significant linear contrast for the main effect of block, $F(1,25) = 14.017, p = .001, \eta_p^2 = .359$, suggested that response times decreased over the course of the blocks. All of the two-way interactions were not significant (all p 's $> .584$). The three-way interaction (Figure 1), however, was significant, $F(8, 200) = 2.356, p = .019, \eta_p^2 = .086$. This suggests the interaction between TMS and Salience changes as a function of block.

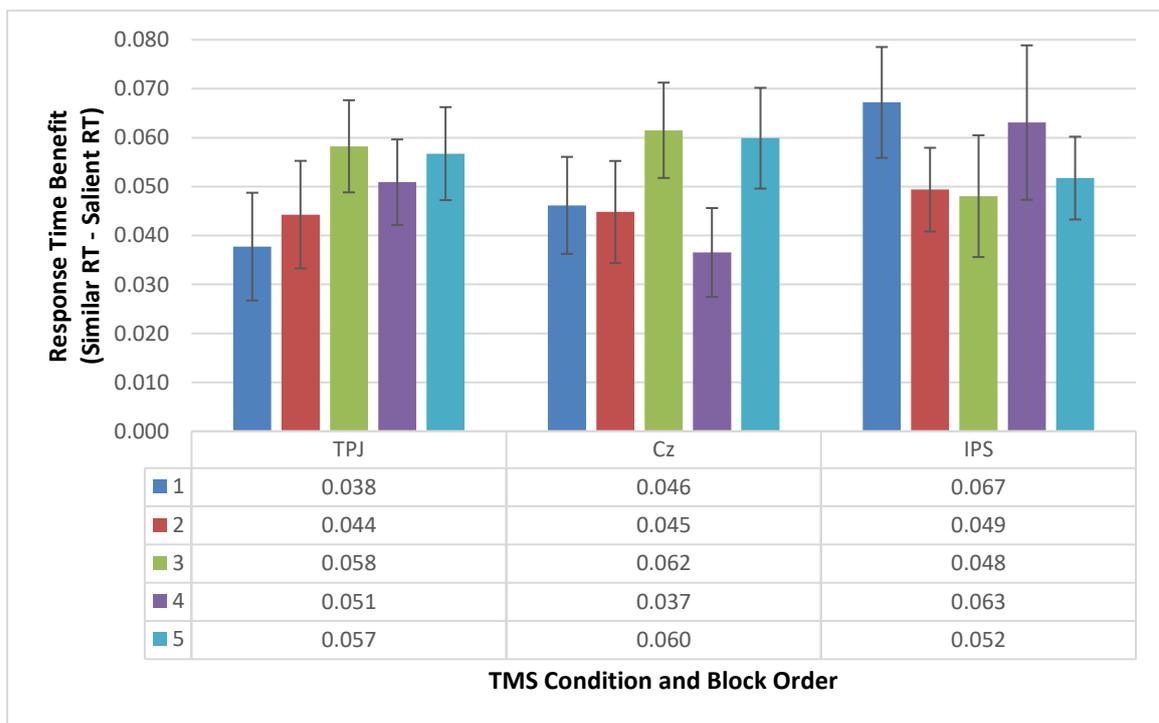


Figure 1. The response time benefit as a function of TMS and block.

Previous research has shown that the effects of rTMS diminish fairly rapidly over time (Eisenecker et al, 2008) and it is therefore possible that the interaction we report represents such a reduction of the effect of TMS with every block. To account for this,

and to further unpack the three-way interaction, the data were analysed for each block independently using a repeated measures ANOVA with TMS and salience as within subjects variables. For block 1, the main effect of salience was significant, $F(1,25) = 35.591$, $p < .001$, $\eta_p^2 = .587$. This was driven by faster responses during the salient trials (576 msec; 19 msec) relative to the similar trials (626 msec; 20 msec). The main effect of TMS was not significant, $F(1.193, 29.830) = .287$, $p = .637$ (GG corrected; $X^2(2) = 27.058$, $p < .001$; $\epsilon = .597$). Critically though, the interaction between salience and TMS was significant, $F(2,50) = 3.434$, $p = .040$, $\eta_p^2 = .121$ (Figure 2). Simple main effects revealed that the performance benefit during Cz stimulation was not significantly different than during TPJ or IPS stimulation ($p = .455$ and $.129$, respectively), but the difference between TPJ and IPS stimulation ($p = .007$; Cohen's $d = -.518$) was significant. This reflects a classic stepwise pattern where performance benefit in the Cz stimulation condition falls in between the performance benefit in the TPJ and IPS conditions (Figure 3). This suggests that TPJ stimulation reduces the performance benefit, whereas IPS stimulation increases it. Moreover, performance during salient trials (all p 's $> .128$) or similar trials (all p 's $> .593$) alone were not significantly different in each TMS condition, suggesting that difference in the performance benefit cannot be attributed to a specific change in either salient or similar performance.

The interaction between salience and TMS was not significant for block 2, $F(2,50) = .123$, $p = .885$, block 3, $F(2,50) = .899$, $p = .413$, block 4, $F(2,50) = 2.443$, $p = .097$, or block 5, $F(2,50) = .461$, $p = .633$.

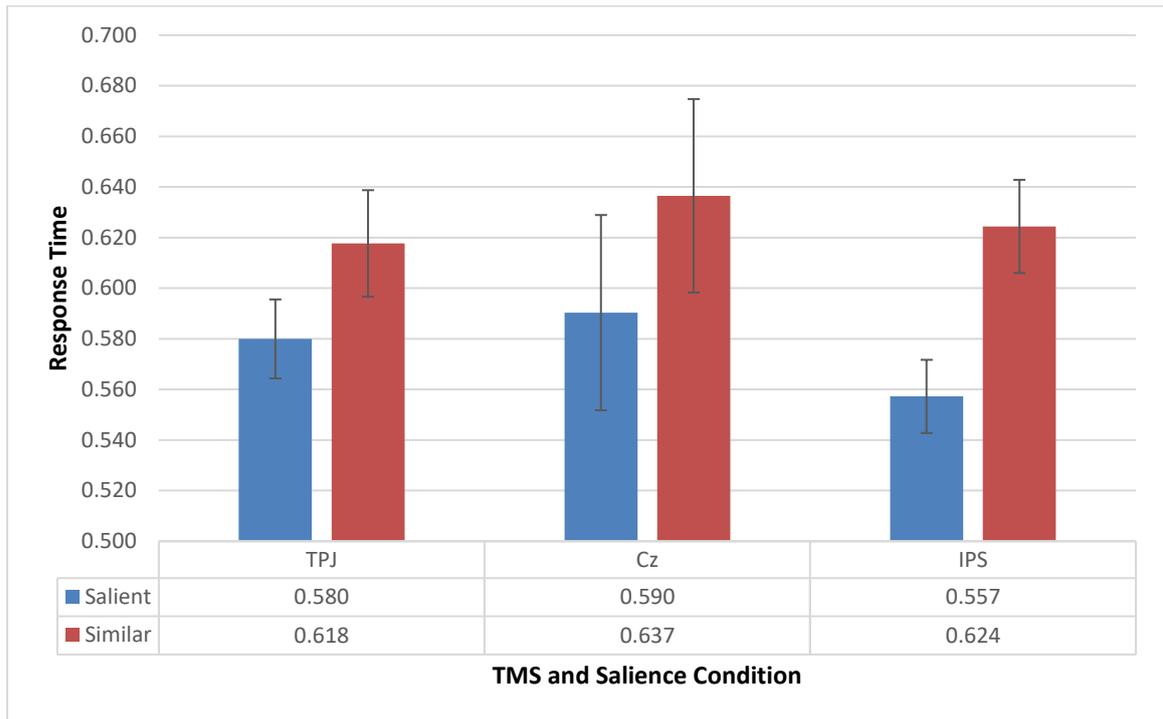


Figure 2. Response time during block 1 as a function of TMS and salience.

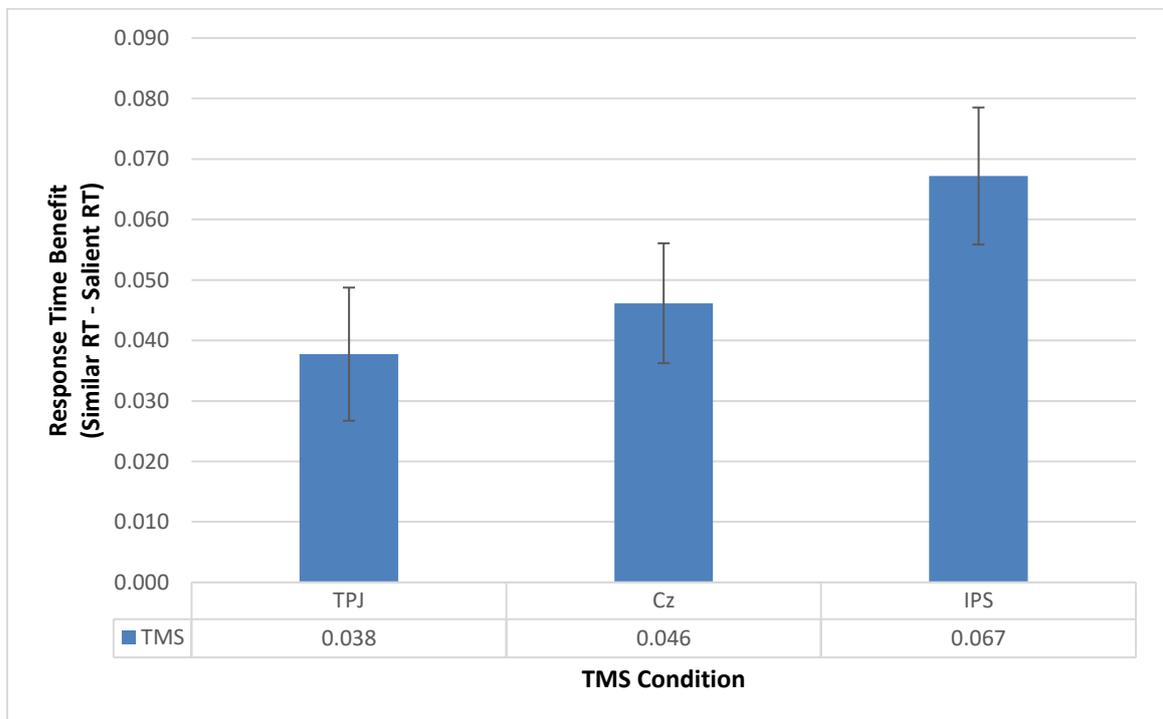


Figure 3. Response Time based performance benefit (Similar RT – Salient RT) during block 1 as a function of TMS condition. It should be noted that this is the same data from Figure 1, just simplified for explanatory purposes.

Accuracy Analysis

For the accuracy data (Figure 8), there was a significant main effect of salience, $F(1,25) = 19.899$, $p < .001$, $\eta_p^2 = .443$. This was driven by more accurate responses during salient (95.7%; 0.7%) relative to similar (93.4%; 1.0%) trials. The main effect of TMS was not significant, $F(1.5819, 39.521) = .021$, $p = .959$ (GG corrected; $X^2(2) = 7.395$, $p = .025$; $\epsilon = .790$). The main effect of block was significant, $F(3.164, 70.090) = 3.339$, $p = .013$, $\eta_p^2 = .118$ (GG corrected; $X^2(9) = 19.883$, $p = .019$; $\epsilon = .791$). A significant linear contrast for the main effect of block, $F(1,25) = 13.946$, $p = .001$, $\eta_p^2 = .358$, suggested that accuracy increased over the course of the blocks. None of the two-way interactions (p 's $> .188$) were significant. The three-way interaction (Figure 4) trended towards, but did not reach, significance, $F(8, 200) = 1.863$, $p = .068$.

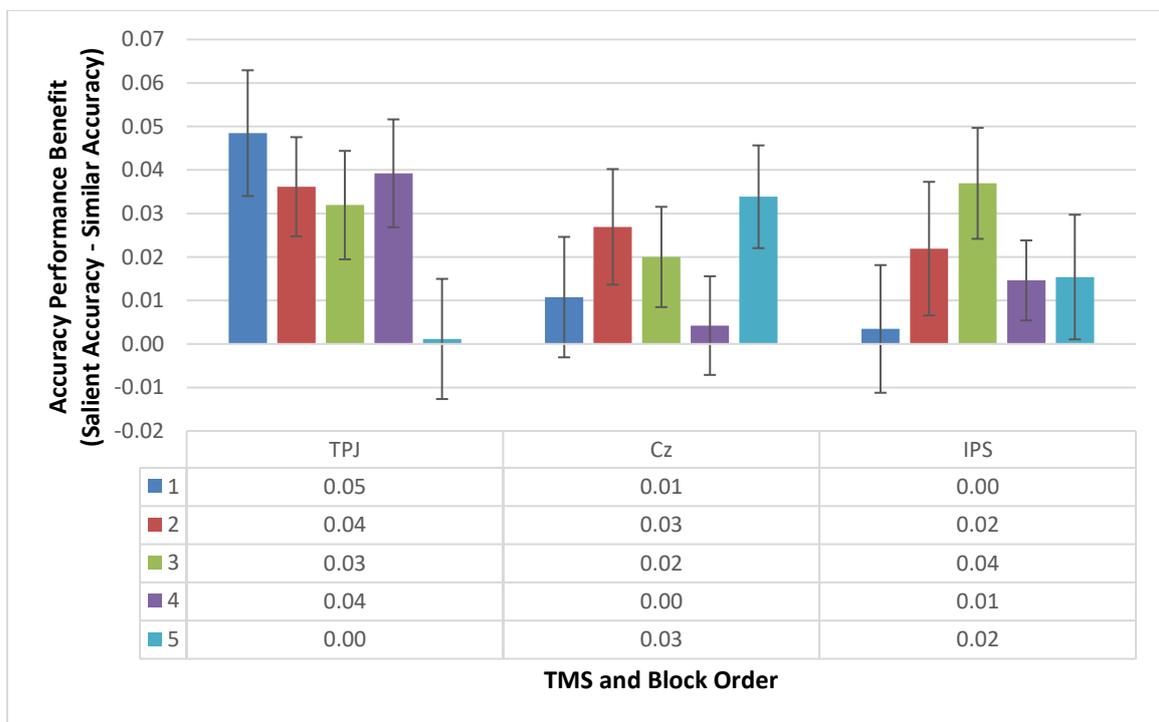


Figure 4. The accuracy benefit as a function of TMS and block

While the interaction did not reach significance, in order to have a reasonable comparison for the blocked response time data, the accuracy data was also analysed by individual block. For block 1, the main effect of salience, $F(1,25) = 4.345$, $p = .047$, $\eta_p^2 = .148$, was significant. This was driven by more accurate performance during salient trials (94.3%; 1.0%) than similar trials (92.2%; 1.1%). The main effect of TMS was not significant, $F(2,50) = .663$, $p = .520$. However, the interaction was significant, $F(2,50) = 3.707$, $p = .032$, $\eta_p^2 = .129$ (Figure 5). Simple main effects (Figure 6) revealed that this was driven by an increased performance benefit during TPJ stimulation relative to IPS stimulation ($p = .016$; $d = .612$). Similarly, the performance benefit during TPJ stimulation trended towards being larger than during Cz stimulation, but the difference was marginally not significant ($p = .051$). There was no difference in performance between Cz and IPS stimulation ($p = .679$). Moreover, performance during salient trials alone were not significantly different in each condition (all p 's $> .519$). However, performance did change during similar trials. In particular, performance during TPJ stimulation was significantly different than during Cz ($p = .034$; $d = -.420$) and IPS ($p = .021$; $d = -.530$) stimulation, and there was no difference during Cz and IPS ($p = .796$). This suggests that the increase in the performance benefit during TPJ stimulation was specifically driven by a decrease in accuracy in similar trials.

The interaction between salience and TMS was not significant for block 2, $F(2,50) = .324$, $p = .725$, block 3, $F(2,50) = .568$, $p = .571$, block 4, $F(2,50) = 2.634$, $p = .082$, or block 5, $F(2,50) = 1.975$, $p = .149$.

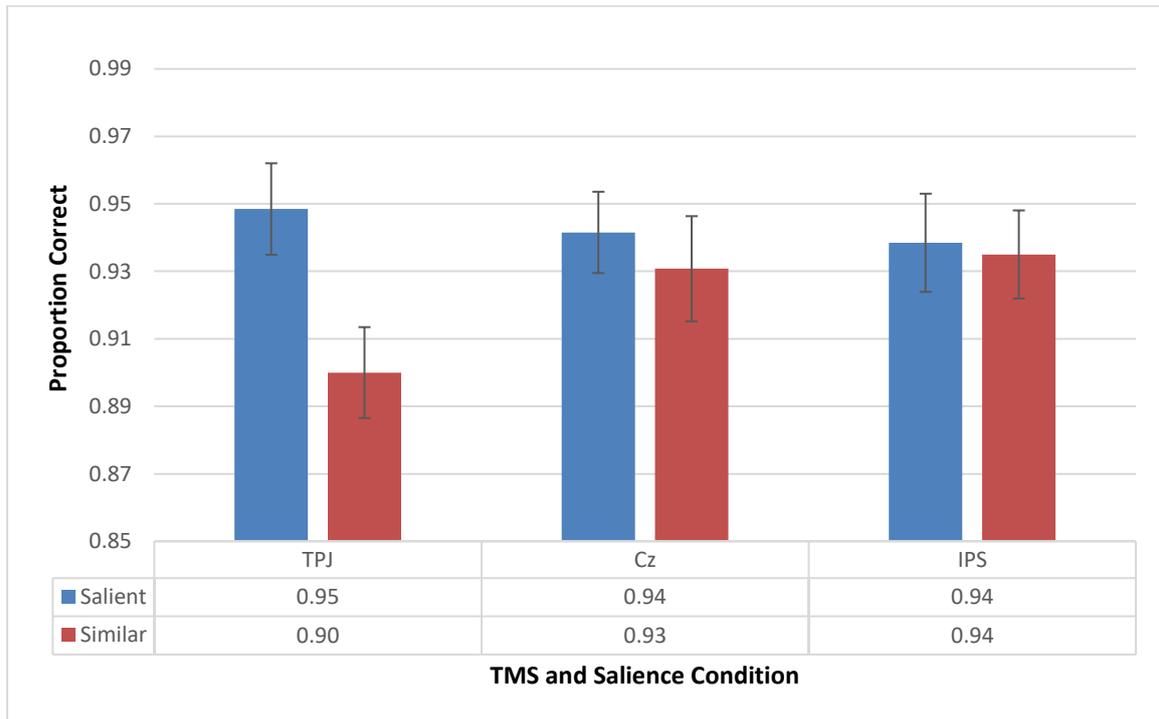


Figure 5. Proportion of correct responses during block 1 as a function of TMS and salience

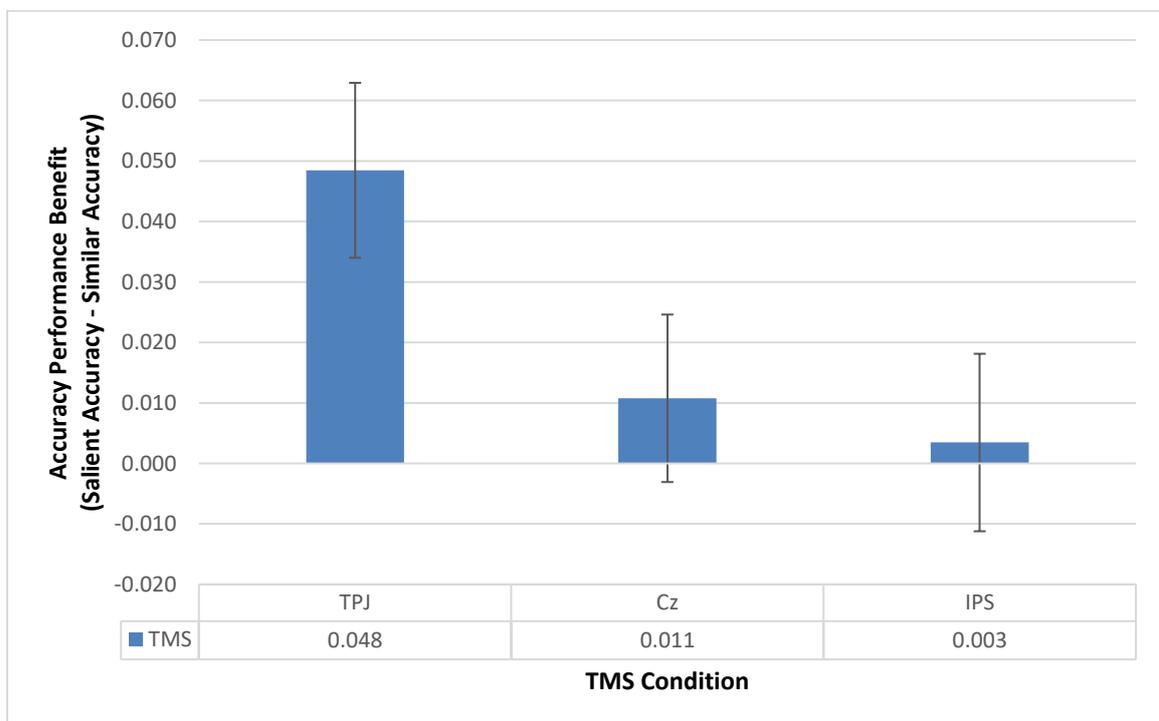


Figure 6. Accuracy based performance benefit (Salient Performance Correct – Similar Performance Correct) during block 1 as a function of TMS condition. It should be noted that this is the same data from Figure 2, just simplified for explanatory purposes.

Speed/Accuracy Trade-off Analysis

One concern with this type of data is that a speed-accuracy trade off may be masking or artificially enhancing differences between groups. To assess this possibility, six correlations between accuracy and response time during block 1 were conducted; one correlation for each combination of the salience and TMS conditions. The correlation between response time and accuracy for salient trials during Cz stimulation was significant, $r(26) = -.508$, $p = .008$, and approached significance during IPS stimulation, $r(26) = -.365$, $p = .067$. The remaining four correlations were all not significant (all p 's $> .207$). As the one significant correlation was negative and the rest are not significant, these correlations suggest that speed-accuracy trade-offs are not influencing the results of the study. The fact that TPJ stimulation, and to a lesser extent IPS stimulation, during salient trials appears to eliminate the significant correlation found for the Cz stimulation condition (the control condition) further supports the notion that these regions are both involved in reactive suppression, at least during salient trials.

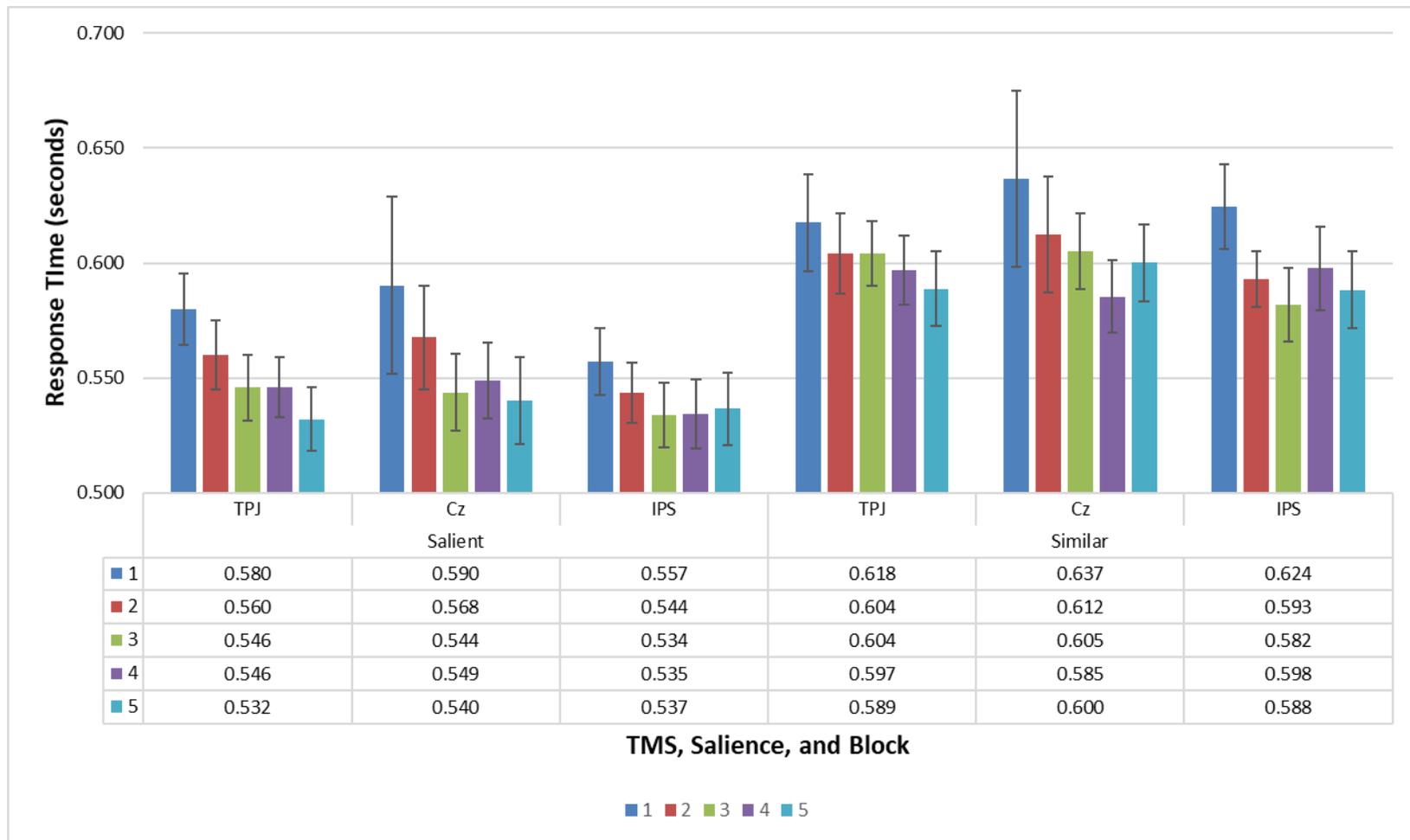


Figure 7. Raw response time data as a function of TMS, Salience, and Block

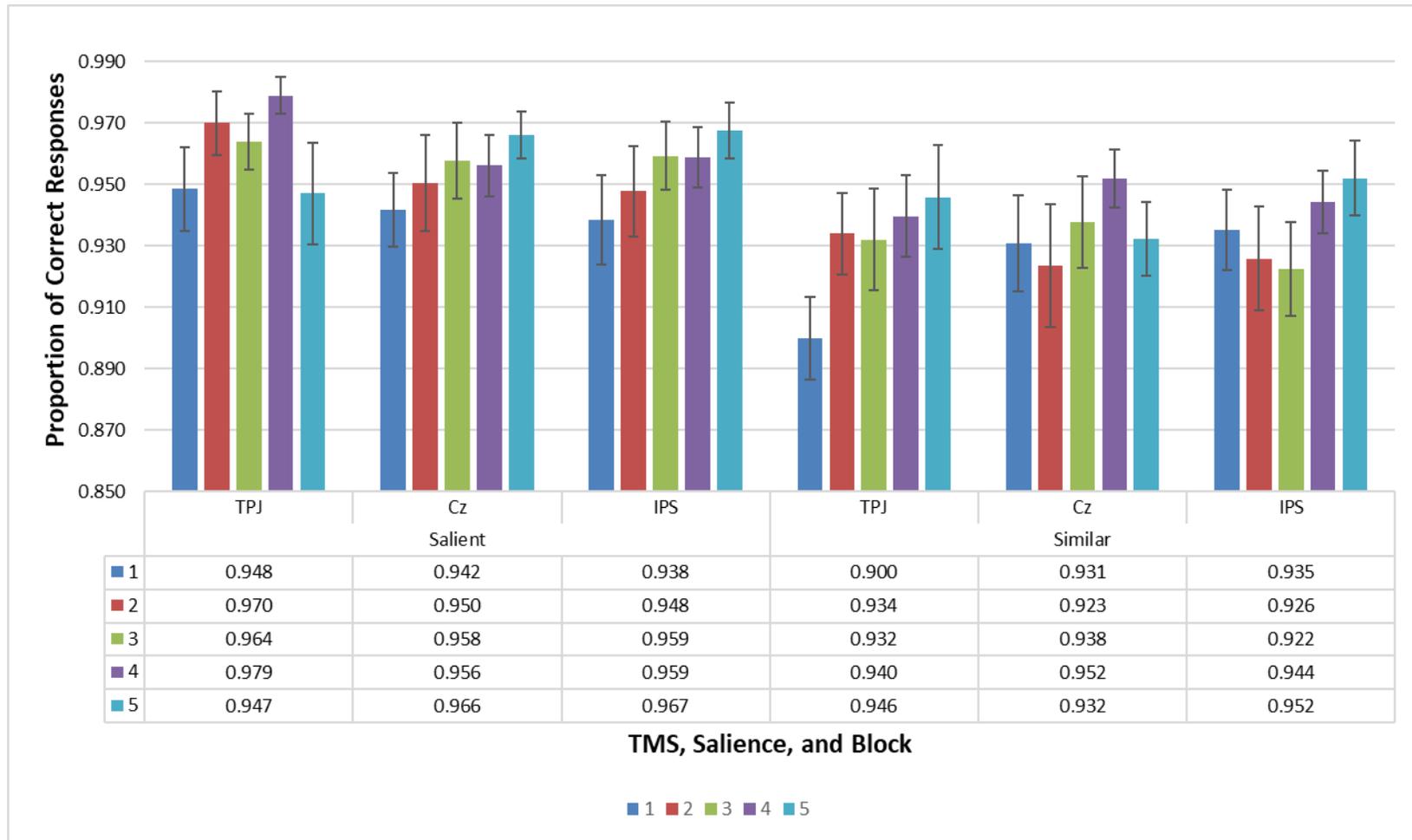


Figure 8. Raw accuracy data as a function of TMS, Salience, and Block

Discussion

The purpose of this study was to determine if there was a causal link between left TPJ and/or left IPS activity and reactive salience suppression. An analysis of the data by individual blocks revealed that during block 1, which should reflect the strongest effect of TMS, stimulating TPJ reduced the response time performance benefit in general and had a tendency to decrease accuracy on similar trials. Stimulating IPS, on the other hand, increased the response time benefit in general. After block 1, the effects of TMS appeared to dissipate.

Stimulating the left TPJ

In chapter 3, it was argued that the task used in this study, developed by DiQuattro and Geng (2011), specifically engaged reactive control mechanisms. In the original study, participants were faster and more accurate on trials with a salient distractor, compared to a similar distractor, presumably by using the salient distractor as an anti-cue. It was argued that the anti-cue was utilized by engaging TPJ mediated reactive suppression to direct attention away from the distractor. Therefore, if the TPJ were directly involved in stimulus suppression, stimulation should have impaired the ability to properly respond to the salient distractor. It was predicted that this would result in a decrease in both the response time and accuracy performance benefit, similar to the performance of the elderly participants in chapter 3. Indeed, as expected, stimulation to TPJ decreased the response time performance benefit in such a way that this effect could not be attributed to independent changes in either the salient or similar condition (during block 1 only); but unexpectedly, stimulation to TPJ reduced accuracy only during similar trials (during block 1 only; though it should be noted that the 3-way

interaction of salience x TMS x block approached, but did not reach, significance for the accuracy data). Moreover, the impaired accuracy during similar trials could not be attributed to a speed accuracy trade-off. It should also be noted that while the RT performance benefit was significantly reduced, it wasn't eliminated like it was for the elderly participants in chapter 3.

Contrary to previous literature, these results, suggest that the left TPJ may facilitate reactive suppression during both salient and similar trials. DiQuattro and Geng (2011) argued that the role of the left TPJ was to integrate contextual knowledge (i.e., the fact that the salient item in the display is never the target) and send that information to brain regions induce an orienting response to bias attention away from salient distractors. It was also suggested that this was effectively suppressed during similar trials. In fact, while participants completed a similar variation of the task described in this paper, DiQuattro and Geng (2011) identified BOLD differences in the left TPJ that were primarily driven by deactivation in the left TPJ during similar trials. However, based on the results of this study, it is possible that the TPJ is involved in contributing to the suppression of any distractor, contextually relevant or otherwise, and that in the salient trials the process simply happens more often and/or faster.

During the salient trials, the presence of the salient distractor makes the use of TPJ mediated suppression relevant on every trial in order to avoid attending to, or to quickly disengage from (Geng and DiQuattro, 2010), the distractor in the first place. On the other hand, for similar trials, participants would only need to engage reactive suppression on the ~50% of trials where they attend to the distractor first, because there is nothing stopping them from doing so. Stimulating TPJ may extend the time needed to

switch to the target enough that by the time attention reaches the location of the target it is already gone, leading to reduced accuracy on similar trials. This would not have been detected in the RT data because only RT data for correct responses was analysed.

Another consequence of this account is that response times should be slower during similar trials, which was found in this study and in previous ones. One way to test this theory would be to use eye-movement data to parse the similar data into similar-switch and similar-no switch trials. If this account is true, TPJ stimulation should only reduce accuracy during the switch trials.

Another possibility is that the left TPJ plays a different role in spatial attention during salient and similar trials. Macaluso and Doricchi (2013; Doricchi et al, 2010) have shown that just the left TPJ responds to validly cued targets, whereas left and right TPJ respond to invalidly cued targets. They argue that left TPJ activation is often missed in fMRI studies of spatial attention because the typical comparison in activation is between valid and invalid cues, rather than valid/invalid and neutral cues which effectively masks that the left TPJ is playing a critical role. This is relevant because the idea that the left TPJ is involved in reactive suppression is largely motivated by DiQuattro and Geng's (2010) finding of significant left TPJ activation when comparing salient and similar trials.

However, the salient trials arguably reflect a valid cue condition due to the use of the distractor as an anti-cue, whereas the similar trials may reflect a neutral cue condition.

Macaluso and Dorricchi (2013) argue that when a participant is presented with validly cued targets the left TPJ specifically codes for the match between the expected and actual target location, whereas for invalidly cued targets (in conjunction with the right TPJ), it codes for the mismatch between the cued and actual target location.

Unfortunately, Macaluso and Dorrriichi (2013) did not test the role of the left TPJ in dealing with neutrally cued targets, and since activation was only reported in comparison to valid/invalid cues, it's not clear if the left TPJ was inactive or just less active during neutral trials than during invalidly or validly cued trials. Future studies will have to assess the role of the left TPJ in the presence of neutrally cued targets.

Overall, the results suggest that left TPJ is causally involved in the reactive suppression of salient, and possibly non-salient, distractors.

Stimulating the left IPS

It was predicted that stimulation to left IPS could increase, decrease, or not affect the performance benefit, all for different reasons. Ultimately, it was found that stimulation to left IPS increased the response time performance benefit. These results support the notion that there is a balance between the use of proactive and reactive control mechanisms, and that stimulating one mechanism predisposes participants towards using the other one if it is not impaired itself. Stimulating the left IPS, a proactive control region predisposed participants to engage reactive control more often (or possibly more strongly), resulting in the observed increase in the response time performance benefit. Overall, the results suggest that the left IPS is causally involved in reactive suppression, though indirectly, possibly by providing an alternative control mechanism.

Conclusion

These results suggest that the left TPJ and left IPS play a facilitatory role and an obstructive role, respectively, during reactive suppression. However, it is not clear why the effect of stimulation only occurs on block 1, especially as state dependent TMS effects have been shown to be consistent over time (Cattaneo and Silvanto, 2008). Nevertheless, while the magnitude of the results in this study did not quite match those of the elderly participants in chapter 3 (who showed no response time benefit, rather than a small one), these results support the notion that the impairments observed in those elderly participants were at least partially due to a reactive control impairment, specifically a dysfunctional left TPJ.

This left IPS results are also the first reported empirical evidence of an apparent balance between proactive and reactive control. In this study, stimulating a presumed proactive region, enhanced the behavioral effect of reactive control (i.e. increasing the performance benefit). In chapter 2, it was proposed that the left IPS may facilitate both proactive and reactive suppression. The results of this study would suggest that this is not the case, but rather that the left IPS obstructs reactive control. It was proposed that stimulating the left IPS encouraged engaging left TPJ mediated reactive control as it was an “unimpaired” mechanism compared to proactive control. In fact, the TPJ results could also be interpreted in this context. Stimulating TPJ, a reactive control region, would predispose participants to proactive control (even if it were counter-productive) and result in the observed reduction in the response time performance benefit. Critically, this “balance” account and the “impaired reactive control” account are not mutually exclusive and may both explain the TPJ results.

Chapter 5: The Allocation of Attention Prior to Suppression Across the Lifespan

Introduction

As we age, many changes take place that alter our cognitive abilities (Grady, 2012; Craik and Salthouse, 2011; Persson et al, 2006; Hedden and Gabrieli, 2004). These include age-related structural changes, like cerebral atrophy (Rusinek et al, 2003; Good et al, 2002; Raz et al, 2005; Fox and Schott, 2004; Devanand et al, 2007; Apostolova et al, 2010; Barkhof et al, 2007), and functional changes, such as changes in cortical connectivity (Geerligs et al, 2014; Andrews-Hannah et al, 2007), neuromodulation (Braver and Barch, 2002; Li et al, 2001), and cognitive engagement (Larson et al, 2016; Li et al, 2016; Zanto et al, 2010). Several researchers have argued that a prominent aspect of cognitive aging is the decline in the ability to ignore distracting information (Hasher and Zacks, 1998; Hasher et al, 1991; Kramer et al, 1994; Braver et al, 2012; Lustig et al, 2007). The inhibition deficit theory of cognitive aging, for example, states that the ability to ignore distracting and irrelevant information becomes progressively impaired over the lifespan (Lustig, 2007). For example, Tsvetanov (2013) showed an age-related decline in performance related to the non-spatial inhibition of salient distractors. In a global/local task with an orthogonal saliency manipulation, older participants (>60 yrs) showed larger distractor interference compared to younger participants (18-22 yrs) when the non-target stimulus level was higher in salience than the target stimulus level. However, previous studies have highlighted that only a subset of inhibitory functions are susceptible to the effects of aging (Kramer et al, 1994; Anguera and Gazzaley, 2012; Vadaga et al, 2015; Sebastian et al, 2013; Bloemendaal et al, 2016). Kramer et al (1994) found age related inhibition deficits in a stop-signal task, but not in a response competition or

spatial pre-cueing task. Thus, it is possible that age-related inhibition deficits are specific rather than general.

The dual mechanisms theory of proactive and reactive control (DMC; Braver, 2012) provides a possible theoretical explanation for these differences. The DMC argues that cognitive control is driven by two primary mechanisms: Proactive and reactive control. Proactive control is an “early selection” mechanism that allows one to select and maintain goal-relevant information prior to stimulus presentation in order to prepare a response to a given stimulus based on prior knowledge. Reactive control is a “late correction” mechanism that allows one to alter behavioral plans in the moment when suddenly presented with new and relevant information. Critically, each of these control modes can engage the ability to allocate or inhibit attention as necessary. It is therefore possible that aging effects on inhibition are specific to one mode of control and not the other. Indeed, recent research has shown that older participants tend to favor reactive over proactive control strategies (Paxton et al, 2008; Jimura and Braver, 2010) and that impaired performance may be particularly evident during proactive inhibition tasks (Tsvetanov et al, 2013) –where all relevant information about distractors is known in advance of stimulus presentation.

However, regardless of the question whether inhibition occurs proactively or reactively, certain accounts suggest that initial attention allocation to distractors is necessary for their inhibition. Consider preview search paradigms: participants have to search for a pre-defined target among distractors, but a subset of the distractors is presented (the preview display) at least 400 msec prior to the target display. Typically, it is found that participants are able to inhibit the preview array, so that search is restricted

to the new items presented later (as if the new items were presented on their own). However, using dot probes, Humphreys et al (2004; Olivers et al, 2006) demonstrated that attention is initially allocated to the previewed distractors (a probe dot presented 200ms after the onset of the preview display at a preview item location was more detectable than one at an empty location). Suppression of the previewed distractors followed the initial allocation of attention; this was evident when the dot probe was presented later on in the trial, as at this point in time dots appearing at a preview item location were less detectable than those appearing at an empty location. The authors argued that the preview search allowed for the relevant to-be-ignored locations to be initially attended to and identified (which facilitated probe dot detection early on in the trial)– a process called visual marking – prior to proactively adopting an inhibitory bias against the locations of the previewed distractors (which impaired probe dot detection later on in the trial; Humphreys et al, 2004). Visual ERP studies have provided converging evidence, showing that participants initially attend to the previewed items (increased P1 and N1 amplitudes during a preview search task relative to a control condition; Belopolsky et al, 2005) and subsequently inhibited them over time (sustained negativity in a preview search relative to a control condition from 350 to 750 msec after onset of the preview display; Jacobson et al, 2002).

This concept of initial allocation of attention to distractors was further demonstrated by the Attentional White Bear (AWB) effect (Tsal and Makovski, 2006), which suggests that the initial allocation of attention to distractors is mandatory and can occur even before distractors appear (i.e., at an expected distractor position). In Tsal & Makovsky (2006), participants primarily engaged in a flanker task (identifying a central

letter among three vertically and diagonally oriented letters). However, on a small minority of trials (20%), a temporal order judgment task appeared instead of the flankers' display, in which participants had to indicate which of two horizontally oriented dots appeared first. The critical finding was a tendency to identify the dot that appeared at an expected distractor position as appearing first – referred to as the attentional white bear effect. This effect was only visible when the flankers' arrangement was blocked so that the position of the imminent flankers was known to the participants (i.e. allowing for proactive inhibition). Crucially, the white bear effect seems to occur at the same magnitude even when significant perceptual, memory, and sensory constraints are placed on the flanker task (Lahav et al, 2012). Based on this, Lahav et al (2012) argued that advanced knowledge of distractor location results in a “mandatory attentional allocation...always of a fixed minimal amount.”

Other studies also provide converging evidence for the existence of “allocation first” inhibition mechanisms. For example, Moher and Egeth (2012; Munneke et al, 2008; Jollie et al, 2016; Cepeda et al, 1998) showed that cueing non-target (i.e. distractor) features (i.e. IGNORE RED) also resulted in the allocation of attention towards a to-be ignored item prior to inhibition in a visual search task (like the visual marking studies). And, in a particularly unique study, Max and Tsai (2015) characterized the temporal dynamics of “allocation first” inhibition mechanisms. Participants were presented with a flanker task which began with identical target and distractor items. However, at a random interval during the trial, the distractor items would mutate into incongruent or neutral distractors. They found that performance was impaired if the distractor mutation occurred within the first 50 msec of stimulus presentation, suggesting that at least some

attention was allocated towards them early on. If the mutation occurred after 50 msec, the new identities of the flanker items were successfully inhibited and had no effect on task performance. While these results generally support the notion that inhibition follows a period of attentional allocation, Max and Tsal (2015) do note that in their paradigm the process characterized might be pre-attentive or reflective of an attentional 'zoom lens' contracting around the target, rather than a shift from allocation to inhibition.

This may have important implication for inhibition deficit theories of cognitive ageing (e.g., Lustig et al, 2013) because impairments in attentional allocation prior to inhibition could result in cascading effects that would appear as inhibition deficits. For example, in the preview search paradigms, if participants had an allocation impairment they would be less efficient at inhibiting distractors because they wouldn't be able to mark them as effectively. This also complicates the assumed roles of proactive and reactive inhibition. It is possible that suppression always follows initial allocation of attention to the distractors, but in proactive control the process can start earlier, as attention allocation could take place even before the presentation of the input so that suppression is quickly achieved following its presentation. Alternatively, it is possible that attention allocation to distractors is mandatory (as in Lahav et al., 2012) but in proactive control this allocation is kept to a minimum while in reactive control there is no such limit. To begin to understand these issues and how they may be affected by age, we must first determine whether the reported inhibition deficits in ageing might also be associated with impaired initial allocation of attention to expected distractors.

There is already some evidence that older participants show comparable visual marking effects to young participants (Watson et al 2002, 2003), but that this may depend on the type of stimuli. For instance, Watson et al (2002) showed that elderly participants produced standard visual marking effects for static displays (see also Allen et al, 2008), but that there was no preview benefit for moving displays. While this points to a possible difference in how older participants search dynamic displays (also see Becic et al, 2007), it is unclear if this is related at all to the initial allocation of attention to the preview items. To test for aging effects on attention allocation prior to inhibition, we used the fixed-block attentional white bear paradigm (Tsal and Makovski, 2006), which provides distinct measures of proactive allocation of attention to expected distractor locations. The magnitude of the white bear effect (proportion of responses identifying the dot appearing in the expected distractor location as appearing first in time) arguably reflects the magnitude of the resources proactively allocated to the distractor location.

There are two ways in which age-related allocation impairments would lead to apparent impairments in inhibition. One way is that older participants might be less effective at allocating attention which would make it harder to apply an inhibitory effect to specific targets. Alternatively, older participants might allocate attention too strongly which would make it so a greater amount of effort is required to inhibit a target. In this study, these possibilities can be distinguished because ineffective allocation would result in a reduced white bear effect, whereas overactive allocation would result in an exaggerated white bear effect. However, if older participants' ability to proactively allocate attention is intact, then it is expected that a similar magnitude of the white bear effect will be observed for old and young participants. Performance in the flanker task,

on the other hand, provides a measure of inhibition. This will allow us to measure the effect of proactive allocation on inhibition processes.

To further assess the changes in the white bear effect across the lifespan, we have to also consider the effect of task difficulty. Lahav et al (2012) argued that allocation of attention to distractors was mandatory and to a minimum magnitude, regardless of task difficulty. One possibility is that this mandatory minimum magnitude is not consistent across age groups. Therefore, two versions of this task were developed. In one, the flanker distractors are equal in contrast to the target letters. In the second version, the flanker distractors are a significantly lower contrast than the target letters. To be consistent with Lahav et al (2012), the white bear effect in the low and equal contrast condition would have to be consistent across each age group.

Methods

Participants

25 young and 26 elderly participants took part in this study, however, due to technical issues during a couple of experiment sessions we had to exclude 2 young and 2 elderly participants resulting with 23 young (Mean Age: 18.7 yrs, SEM of Age: .17, Age Range: 18 -21 yrs; 22 Females) and 24 elderly (Mean Age: 70.8 yrs, SEM of Age: 1.26, Age Range: 60 -82 yrs; 13 Females). The two groups participated in three successive behavioral experiments. The order of the tasks was counterbalanced to account for possible fatigue and order effects. Young participants were recruited from the undergraduate population in the school of psychology at the University of Birmingham, UK. They were compensated for their participation with course credits. The elderly participants were recruited from a volunteer pool maintained by the School of

Psychology at the University of Birmingham. They were compensated for 1.5 hours of their time with a one-time payment of £7. All participants had to sign an informed consent form prior to the study. Participants' were healthy with no history of head injury, mental health issues or neurological disorders. The old participants were screened for decline in cognitive functions using the Montreal Cognitive Assessment (MoCA). All of the elderly participants scored within the normal range (Mean Score: 27.5, SEM of Score: .23).

Stimuli and Procedure

Two versions of the attentional "white bear" task (Tsal and Makovski, 2006; Lahav et al, 2012) were used. These versions were the same except where indicated below. Color was defined using RGB color coordinates. The background color of the screen thorough the experiment was grey [100 100 100]. Participants were presented with four blocks of 180 trials each. Each block consisted of 80% (144) flanker displays (Figure 1a and 1b) and 20% (36) two-dot displays trials (Figure 1c). These displays were randomly intermixed with the exception that two-dot displays could not appear consecutively. Flanker trials consisted of three letters oriented along a diagonal through the center of the screen. Upon being presented with a flanker display, participants had to identify the central letter and respond based on its identity. The central letter was randomly drawn from "H", "K", "C", or "S." Participants were required to press the "A" key if the central letter was an "H" or a "K", and the "L" key if the central letter was a "C" or an "S". The two flanking letters were also drawn from the same group of four letters, though both distractor letters were always the same within a trial. Therefore, on each trial the distractor letter could be congruent or incongruent with the correct response to the

central letter. Since there are 4 possible central letters and 4 possible distractor letters, there are 16 possible combinations of central and distractor letters and each combination appeared an equal number of times in each block (9 repetitions yielding 144 flanker trials per block).

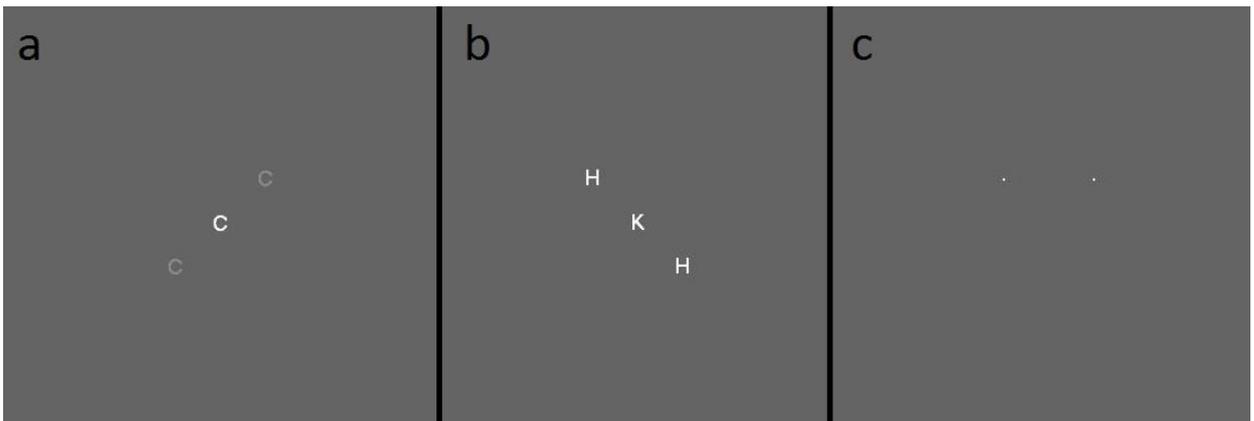


Figure 1a. Illustrates the low contrast display with distractors in the upper right/lower left flanker configuration. 1b illustrates the equal contrast display with distractors in the upper left/lower right flanker configuration. 1c illustrates the dot display.

On two of the four blocks, the distractors were located towards the upper left and bottom right of the central letter and on the other two blocks the distractors were located towards the upper right and lower left. The center of the distractors was 1.58 (1.122 1.112 degrees of vertical visual angle) degrees of visual angle from the center of the central letter. Critically, within a block the distractor locations never changed. Letters were displayed in 14 point Arial font. The central letter was white [255 255 255]. As mentioned earlier, there were two versions of this task. In each version the contrast of the distractor letters relative to the background were different. In the equal contrast version, the distractor letters were white [255 255 255], the same color as the central target. In the low contrast version, the distractor letters were a light grey that was

defined as 25% of the difference (rounded up) between the background color and white [139 139 139]. The phenomenological effect is that in the low contrast version of the task, the distractors are harder to see because they blend in more with the background.

The two-dot displays consisted of two white dots (one pixel wide) that, during the main experiment, appeared simultaneously at the two possible top distractor positions (1.58 degrees of visual angle from the center of the screen to the top-left or the top-right). Thus, one of the dots appeared in the same location as the “upper” distractor letters in the flanker task in that block. Participants were instructed to judge which dot they perceived to appear first. To indicate that the left dot appeared first, they would press the “S” key. To indicate that the right dot appeared first, they would press the “K” key. To enhance the likelihood participants will make a genuine attempt to judge the temporal order, during the practice trials one of the two dots would appear 50 msec prior to the second dot. However, during the actual experimental run the two dots appeared simultaneously.

Every trial began with 500 msec of a fixation cross presented at the center of the screen. The fixation cross was black [0 0 0]. Next, there was a 500 msec blank interval. Finally, the appropriate stimulus (flanker display or dots depending on the trial) was displayed until a response was made. Participants were given the chance to rest in between blocks for as long as they wanted, though no participant took a break for more than a few minutes (< 5 min). Each session began with 20 practice trials consisting of 16 flanker trials and 4 dot trials. During the practice, participants received visual feedback such that if they made an error on the flanker task, after their response the following

fixation cross would turn red for the first 250 msec it was displayed and turn black for another 250 msec.

Results

Flanker Task Performance

Response time in msec (RT) and accuracy rate (i.e. proportion of correct responses) were measured as dependent variables for the flanker task. The response time data was cleaned to account for outliers ($\pm 2SD$). For the young participants, this resulted in the loss of an average of 4.41% (SEM = .24%) of the equal contrast response time data and 4.39% (.22%) of the low contrast response time data, per participant. For the elderly participants, this resulted in the loss of an average of 4.30% (SEM = .22%) of the equal contrast response time data and 4.30% (.19%) of the low contrast response time data, per participant. All results reported as mean \pm standard error of the mean (SEM).

RT data was analysed using a repeated measures ANOVA with Contrast (Low vs Regular), Distractor Location (Upper Left/Lower Right vs Upper Right/Lower Left), and Congruency (Congruent Vs Incongruent) as within subjects factors and Age Group (Young vs Elderly) as a between subject factor. The analysis revealed a significant main effect of congruency ($F(1,45) = 13.59, p = .001, \eta_p^2 = .232$), as across both groups participants responded faster during congruent trials (746 ± 29 msec) than incongruent trials (764 ± 30 msec). There was also a significant main effect of age group ($F(1,45) = 7.23, p = .01, \eta_p^2 = .138$), as young participants were generally faster (677 ± 42 msec) than the elderly participants (834 ± 41 msec). The main effects of contrast ($F(1,45) = 2.77, p = .103$) and

distractor location ($F(1,45) = .295, p = .590$) were not significant. None of the other 2- 3- or 4-way interactions reached significance (all $P_s > 0.144$).

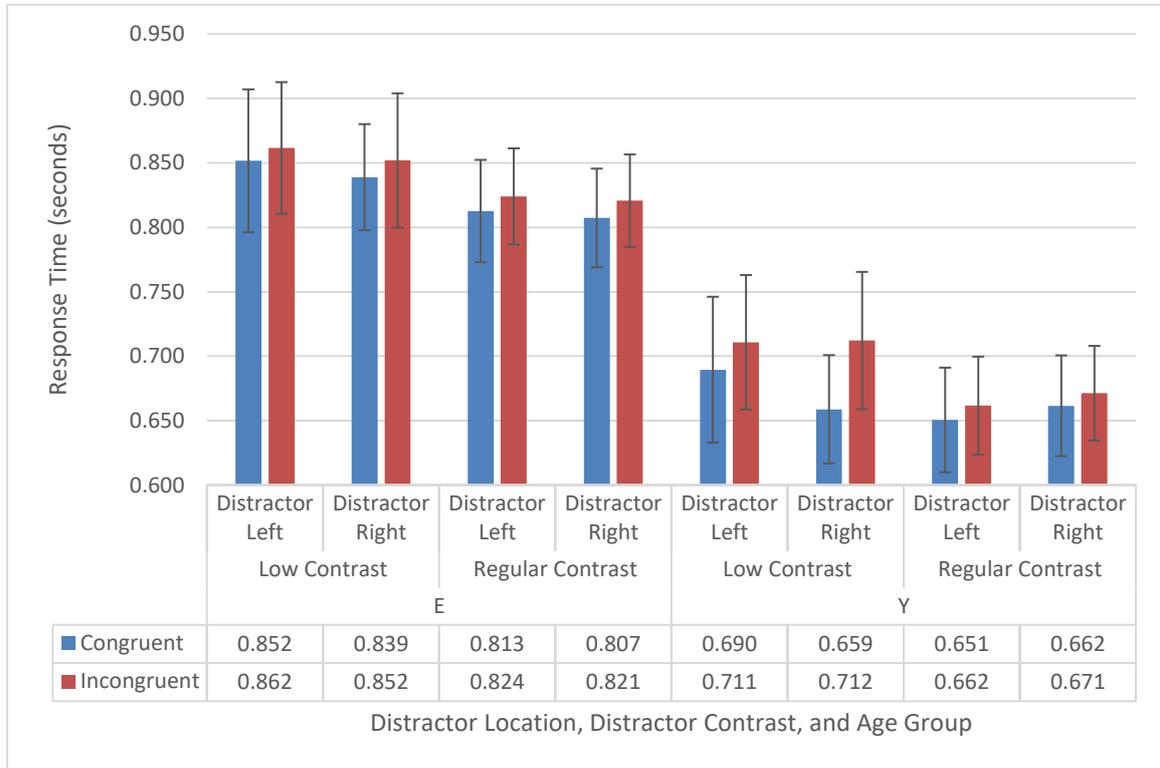


Figure 2. Flanker task response time data as a function of congruency, distractor location, distractor contrast, and age group. Error bars reflect standard error of the mean.

A similar repeated measures ANOVA with the same factors was conducted over accuracy data (Figure 3). As with RT, the ANOVA revealed a significant main effect of congruency ($F(1,45) = 13.56, p = .001, \eta_p^2 = .232$), as participants across both groups were more accurate during congruent trials ($97.6 \pm .3\%$) than incongruent trials ($96.9\% \pm 0.004$). Again, the analysis also revealed a significant main effect of age group ($F(1,45) = 35.69, p < .001, \eta_p^2 = .442$) with the elderly participants performing more accurately ($99.2\% \pm .5\%$) than the young ones ($95.3\% \pm .5\%$). Once again the main effects of contrast, ($F(1,45) = .024, p = .877$) and distractor location, ($F(1,45) = 2.15, p = .150$) were not significant. The

two way interaction between group and congruency approached significance ($F(1,45) = 3.40, p = .072$) as the congruency effect for the young participants (1.17%; .34%) trended towards being larger than that of the old participants (.38%; .19%; $t(35.38) = 2.020, p = .051$; Levine's test indicated unequal variance, $F = 6.249, p = .016$, necessitating an adjustment of the df). None of the other interactions reached significance levels (all $P_s > 0.208$).

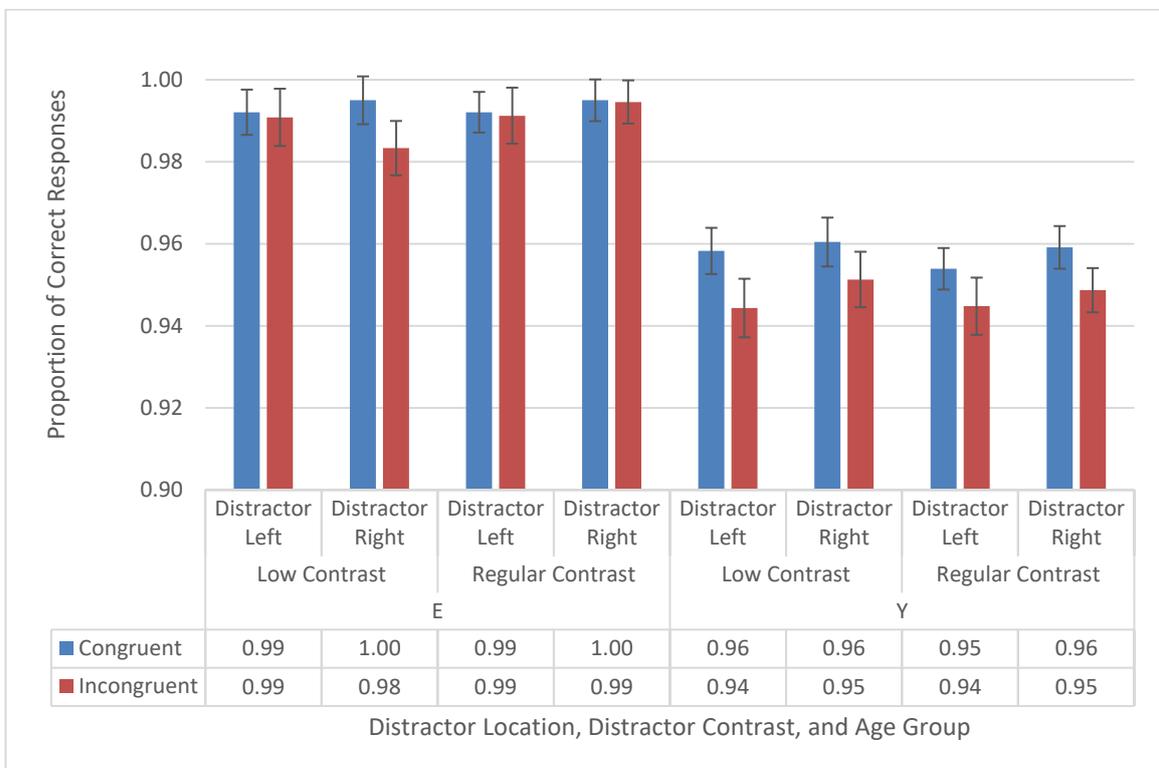


Figure 3. Flanker task accuracy data as a function of congruency, distractor location, distractor contrast, and age group. Error bars reflect standard error of the mean.

As expected, interference from the flankers was observed in both RTs and accuracy (main effect of congruency) for all participants regardless of age. The group difference in RT is also expected with older participants typically responding overall slower. The group difference in accuracy with older participants performing overall more

accurately than young participants is also quite common in the aging literature. These findings may represent a simple speed-accuracy trade-off in the two groups or alternatively, may be attributable to a generalized age-related deficit in processing speed (Salthouse and Meintz, 1995; Salthouse, 2000; Verhaeghen and De Meersman; 1998). Critically, however, the data did not point to increased interference in old age in this task and if anything, the marginally significant interaction between age and congruency reported for the accuracy data suggested more interference in young compared to old participants.

Temporal Order Judgment Task

Next, we assessed the presence and magnitude of the attentional white bear effect (Figure 4). The AWB is indexed by the difference in likelihood of identifying the left or right dots as appearing first as a function of flanker position. Thus, we have used a Repeated Measures ANOVA (similar to Tsal and Makovsky, 2006) on the proportion of 'left' responses with contrast (low vs equal) and flanker configuration (upper left vs upper right) as within subject factors and age group (Young vs Elderly) as a between subject factor. The ANOVA revealed a main effect of flanker configuration ($F(1,45) = 24.62, p < .001, \eta_p^2 = .354$) as participants across both groups had a greater proportion of left responses when a flanker appeared in the upper left position ($63.7\% \pm 3.3\%$) compared to the upper right position ($41.6\% \pm 3.9\%$). This is the standard AWB effect. The main effects of contrast ($F(1,45) = 1.26, p = .268$) and age group ($F(1,45) = .000, p = .986$) were not significant. However, a significant interaction between contrast and age group was also found ($F(1,45) = 4.73, p < .05, \eta_p^2 = .095$). Simple main effects revealed

that this was driven by a lower proportion of left responses in the low contrast condition (49.8%; 4.3%) than in the equal contrast condition (55.5%; 4.1%) for the young participants ($p = .026$), but no difference in proportion of left responses between low (53.6%; 4.3%) and equal (51.8%; 4.0%) contrast conditions for the old participants ($p = .455$). The remaining interactions did not reach significance levels (all $F_s < 1$). This data suggests that both young and elderly participants exhibit the standard white bear effect and that the magnitude of the effect is consistent across age groups. The interaction we report is somewhat intriguing and suggests that young participants were more sensitive to the contrast manipulation. However, since this was not with respect to the flanker configuration it does not reflect AWB related processes. Indeed, two-tailed one-sample t -tests revealed that, for the young participants, the overall proportion of left responses (across both flanker configurations) in the low contrast condition ($t(22) = -.080$, $p = .937$), and the equal contrast condition ($t(22) = 1.289$, $p = .211$) did not differ significantly from .50 (i.e. chance performance). This supports the notion that the increased tendency of the younger participants to respond left during the equal contrast trials cannot account for the white bear effect in that condition.

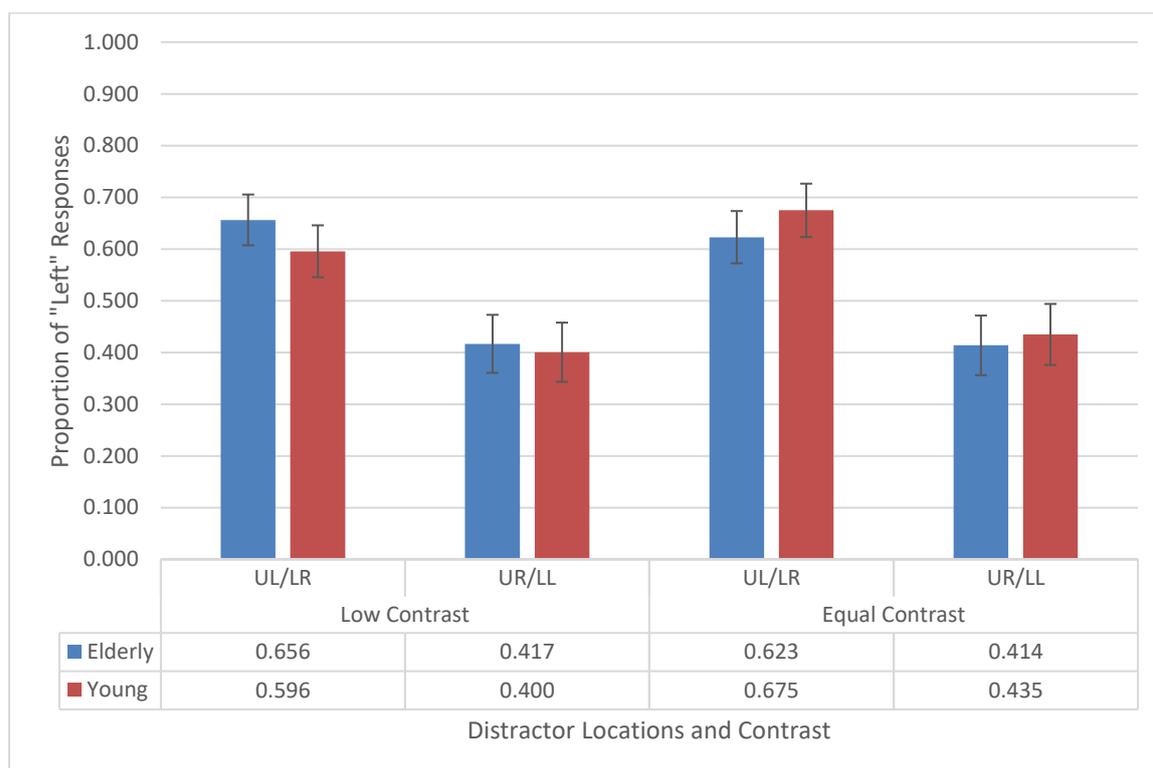


Figure 4. Proportion of “Left” responses on dot task as a function of distractor location, distractor contrast, and age group. UL/LR refers to Upper Left/Lower right and UR/LL refers to Upper Right/Lower Left. Error bars reflect standard error of the mean.

While these results highlight the presence of the AWB for both young and old adults to a similar extent a closer inspection of the data may point to subtle differences. In particular, it appears that the AWB effect was more pronounced for Upper-left flanker configurations than for Upper-right ones (see Figure 4). To establish this, we tested whether the proportion of left responses was significantly different from chance (.5) in both upper-left and upper right flanker configurations. Two-tailed ttests revealed that while this was the case for upper-left configurations ($t(22) = 3.393, p = .003$ and $t(23) = 2.741, p = .012$; for young and old participants, respectively) proportion of left responses did not differ from chance for the upper-right configurations ($t(22) = -1.538, p = .138$ and $t(23) = -1.559, p = .133$; for young and old respectively). Thus, it appears that the white

bear effect was particularly robust when the flanker was positioned in the upper left/lower right configurations.

Therefore, we re-analyzed the proportion of left responses data specifically looking at the upper left flanker configuration (Figure 5). A repeated measures ANOVA was calculated with distractor contrast as a within subjects factor and age group as a between subjects factor. While the main effects of contrast ($F(1,45) = .624, p = .434$) and age group ($F(1,45) = .005, p = .947$) were not significant the interaction between contrast and age group approached significance ($F(1,45) = 3.764, p = .059$). Simple main effects revealed that for the young participants, the difference in performance during low (59.6%; 5.0%) and equal (67.5%; 5.2%) contrast blocks approached significance ($p = .062$), but for elderly participants the difference was not significant ($p = .415$). This data suggests a tendency for the young participants to be sensitive to the contrast manipulation, such that the white bear effect may be stronger for young participants in the equal contrast condition.

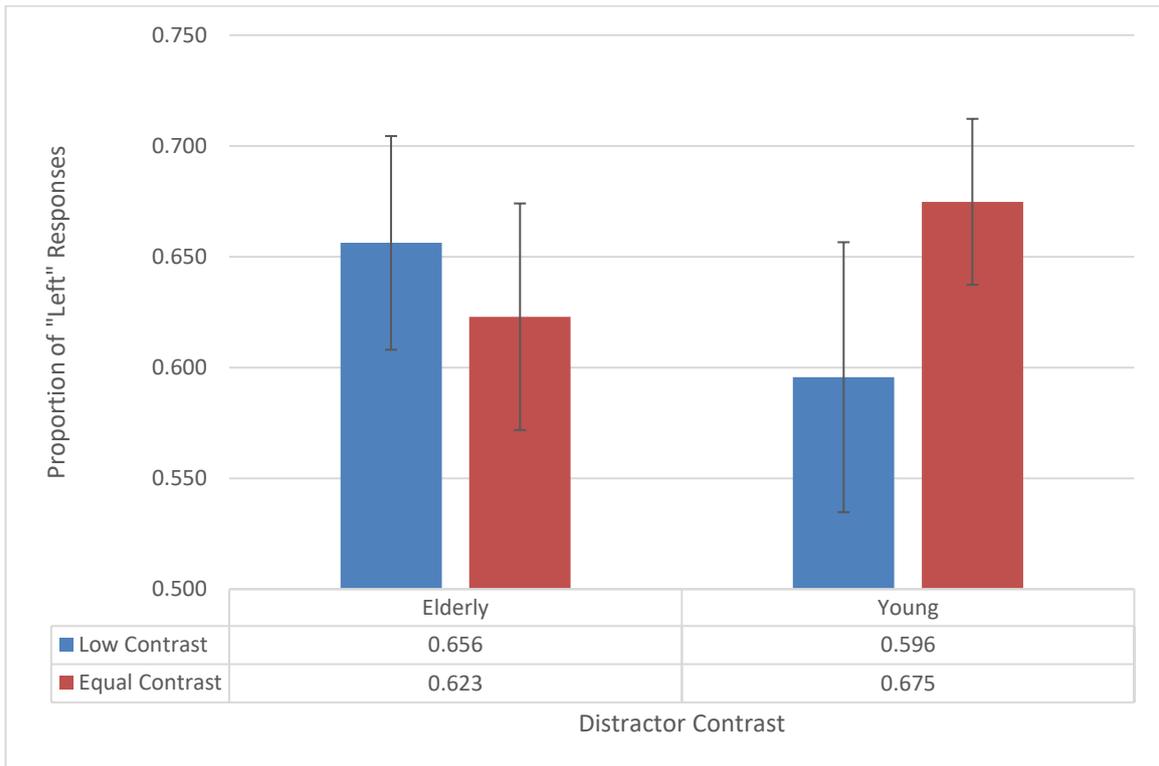


Figure 5. Proportion of “Left” responses on dot task when the distractors were in the upper left/lower right locations as a function of distractor contrast and age group. Error bars reflect standard error of the mean. The interaction was marginally not significant ($p = .059$).

To assess the possible link between age and the white bear effect we also calculated a correlation between participants’ age and a measure of the white bear effect (proportion of left responses in the upper left configuration minus the proportion of left responses in the upper right configuration). However, the correlation between age and distractor location difference score was not significant for the elderly participants, $r(22) = .027$, $p = .90$. Therefore, the white bear effect was not mediated by the age of the elderly participants

Finally, we examined the relationship between proactive allocation and inhibition. The white bear statistic from the previous analysis was used as a measure of proactive allocation. A response time based inhibition statistic was calculated by subtracting the

flanker task response time for the congruent condition from the incongruent condition for each participant, then dividing that number by the participants' individual overall response time mean. This statistic provided normalized congruency score (i.e. measure of inhibition) which was not skewed by overall processing speed differences. Higher values of the congruency ratio reflect reduced inhibition/increased interference, whereas lower values reflect increased inhibition/reduced interference. The white bear statistic and response time congruency ratio was calculated for each age group and distractor contrast combination. To test if flanker inhibition was a function of proactive allocation of attention to the flanker configuration, and if this relationship changed based on age group or task difficulty, hierarchical multiple regression analyses were conducted. This method was chosen to account for the possibility that these relationships may not be linear. Specifically, we tested for linear and quadratic relationships, always adding the linear component to the model first and the quadratic term second. For these models, the white bear effect was entered as the independent variable and the congruency ratio was entered as the dependent variable.

For young participants during low contrast blocks, the model revealed that there was no linear, $F(1,21) = .982$, $p = .333$, or quadratic relationship, $F(2,20) = .789$, $p = .468$, between the white bear statistic and the response time congruency ratio. For the elderly participants, during low contrast blocks (Figure 6), the model revealed that the linear relationship was not significant, $F(1,22) = .083$, $p = .775$, but that the quadratic relationship was significant, $F(2,21) = 4.544$, $p = .023$. For the elderly participants during low contrast trials, the standardized beta coefficient for the linear term was, $\beta = -1.109$ ($t = -2.572$; $p = .018$), and for the quadratic term was, $\beta = 1.291$ ($t = 2.996$; $p = .007$).

Crucially, adding the quadratic term significantly improved the model fit (R^2 change = .298; F change = 8.974; p = .007).

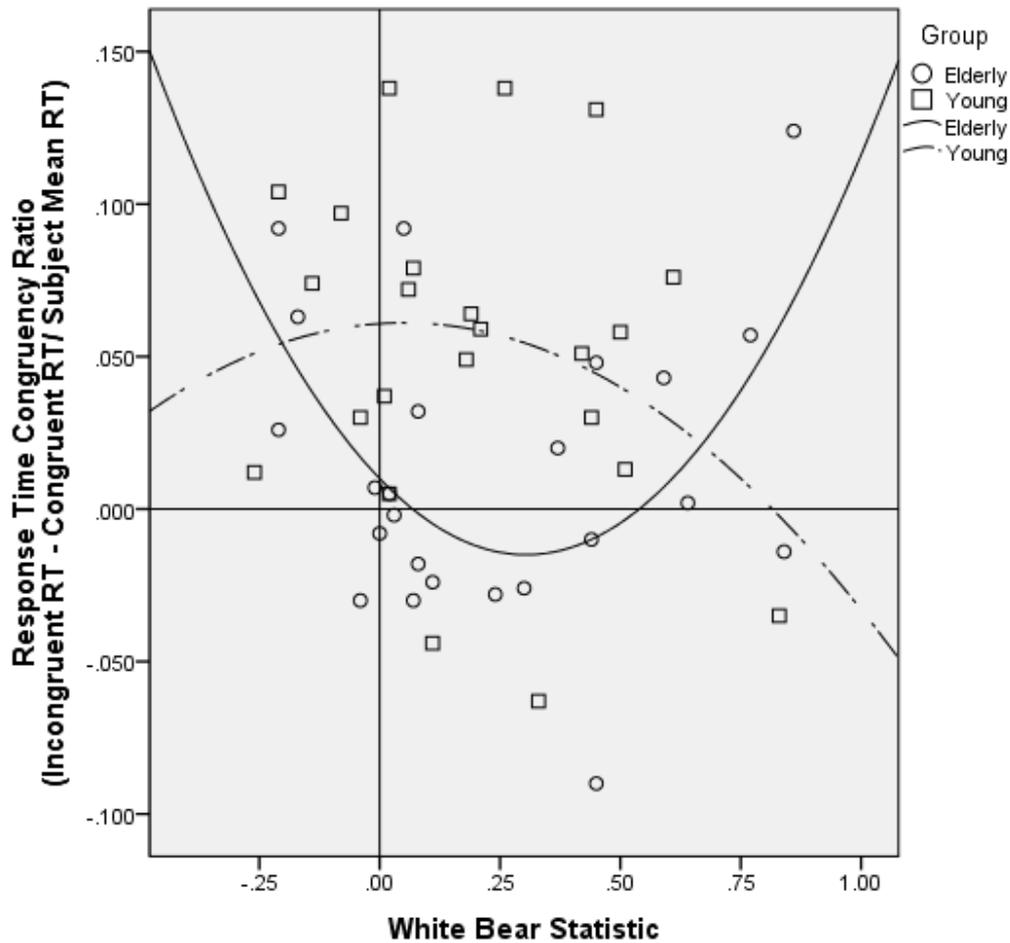


Figure 6. Scatterplot reflecting the data for young and elderly participants during low contrast trials as a function of the white bear statistic and the response time congruency ratio. Higher values of the congruency ratio reflect decreasing inhibition (and more interference). Higher values of the white bear statistic reflect a stronger white bear effect (i.e. stronger or more efficient allocation to the to-be-ignored distractor). The dotted line reflects the quadratic trend line for the young participants and the solid line reflects the quadratic trend line for the elderly participants. The horizontal and vertical reference lines indicate the location of zero on the x and y axis.

For young participants during equal contrast blocks, the model revealed that there was no linear, $F(1,21) = .095$, $p = .761$, or quadratic relationship, $F(2,20) = .132$, $p = .877$, between the white bear statistic and the response time congruency ratio. For elderly participants during equal contrast blocks, the model revealed that there was no linear, $F(1,22) = .501$, $p = .487$, or quadratic relationship, $F(2,21) = 1.940$, $p = .169$, between the white bear statistic and the response time congruency ratio. Although, it should be noted that the quadratic relationship should at least be kept in mind as the R^2 change is approaching significance (R^2 change = .134, F change = 3.326, $p = .082$).

The relationship between accuracy and the white bear effect was also assessed. An accuracy based inhibition statistic was calculated by subtracting the mean accuracy during incongruent trials from congruent trials. This statistic was calculated for each age group and distractor contrast combination. The same series of hierarchical regressions was conducted with the accuracy based congruency effect replacing the response time congruency ratio. For young and elderly participants during the low and equal contrast blocks, the model revealed that there was no linear, or quadratic relationship (All P 's > .176) between the white bear statistic and the accuracy based congruency effect.

Based on these analyses, for young participants there does not appear to be a relationship between proactive allocation of attention and inhibition. However, for the elderly participants there is a quadratic relationship in the low contrast condition (the possibly more distracting condition, for the older participants), but no relationship in the equal contrast condition. In particular, the relationship in the low contrast condition suggests that white bear statistics around .25 are associated with small, close to zero, congruency ratios (i.e. more inhibition/less flanker interference) but as the white bear

statistic deviates from this value, the congruency ratio increases (surprisingly, even when the white bear statistic get weaker). Essentially, when older participants are confronted with a distracting stimulus, paying attention too much or not enough seems to be associated with increased interference.

Discussion

Overall, these data suggest that both the young and elderly participants showed the typical attentional white bear effect and that the magnitude of the effect was generally the same across both groups. In the flanker task, these data suggest that older participants are slower to respond than younger participants, but ultimately achieve the same accuracy. Based on these results there is no evidence that proactive allocation of attention is impaired in elderly participants. It is also notable that there is no between-group evidence that inhibition is impaired in elderly participants.

There was also some limited evidence, based on a near-significant interaction between age group and flanker contrast, that the white bear effect may be stronger for young participants in the equal contrast condition. If this were the case, it may be attributable to distractors in the low contrast condition being easy enough to ignore that inhibition mechanisms were less necessary to complete the task, therefore resulting in a reduced white bear effect relative to the equal contrast condition. However, because elderly participants have more difficulty disengaging from (Crawford et al, 2013; Greenwood and Parasuraman, 1994; but see Lincourt et al, 2007) information outright, they may have processed the distractor more fully, ultimately requiring a similar or even greater (as it's harder to see) amount of attention than in the equal contrast version.

This, in turn, would lead to a similar or a greater white bear effect in the low contrast condition for the elderly participants, which is observed here.

The notion of impaired disengagement in this paradigm is supported by the significant quadratic relationship between attentional allocation and inhibition found for elderly participants specifically during the low contrast trials. A moderate white bear effect (a measure of attentional allocation) was associated with enhanced inhibition (low congruency ratios), but small (and negative) and large white bear effects were associated with reduced inhibition. Impaired disengagement, like described before, can account for the component of the quadratic relationship associated with large white bear effects – participants focused too strongly on the distractor location and were unable to disengage prior to stimulus presentation. Small white bear effects imply that participants were simply not allocating attention enough to the to-be-ignored distractor location, or in the case of negative white bear effects that they were allocating their attention to the wrong location. In this case, it would be difficult to engage “allocation first” inhibition because there would be little to no attentional allocation to the proper stimulus location. This theory is consistent with the Yerkes-Dodson Law (Yerkes and Dodson, 1918) which states that performance is a function of arousal, such that optimal performance is typically found at a moderate level of arousal with relatively decreased performance for low and high arousal.

The fact that a between-group inhibition deficit was not observed was unexpected. As described in the introduction, there is ample evidence that inhibition, in some contexts, is impaired in ageing. Until recently, the evidence seemed to suggest that impairments were specific to proactive inhibition (Paxton et al, 2008; Jimura and Braver,

2010), while reactive inhibition remained relatively intact. Here, the white bear paradigm appears to be a textbook example of inducing proactive inhibition because it allows participants to adopt an inhibitory bias in advance of target presentation since the distractor location is predictable, but this may be a false assumption. It is possible that the proactive allocation of attention to a possible distractor inherently precludes the deployment of proactive inhibition to that same distractor (i.e. you can't inhibit "in advance" something you are actively attending to), thus necessitating the engagement of reactive inhibition, which may be unimpaired. Even if reactive control was impaired, proactive allocation process may be able to support reactive inhibition in such a way that it compensates for any inhibition deficits. Reactive inhibition acts through rapid rejection and enhanced disengagement of distractor stimuli (Geng et al, 2010), so proactive allocation would support it by reducing uncertainty to the location of the distractor and/or by allowing reactive inhibition to begin earlier. Consider, Watson et al (2002) who showed no effects of visual marking in a moving preview search paradigm. A moving display would introduce increased uncertainty into the display and would require greater attentional resources to process which could make it more difficult for proactive allocation to enhance reactive inhibition arguably revealing an underlying inhibition deficit. If there were a reactive control impairment that took the form of delayed disengagement, an earlier start to the inhibition process may mask this impairment in tasks where response time is the primary measure of inhibition, such as in the white bear paradigm. One way to test this would be to have participants engage in a series of blocked versions of the white bear task, where the stimulus onset asynchrony (SOA) was parametrically manipulated between blocks. If there were a delayed disengagement

deficit in elderly participants, we would expect to see increased white bear effects and decreased inhibition at the shorter SOA's, relative to young participants, and similar white bear effects and inhibition at longer SOA's. Alternatively, it's possible that our task was simply too easy and therefore was not sensitive enough to detect group level differences.

While this may provide a possible explanation for the lack of an observable inhibition deficits in our study, it is not clear if these explanations might apply to other paradigms as well. Visual marking studies have argued that, for static displays (and for moving displays under some conditions; see Watson, 2001), the inhibition in the preview search acts via a location-based inhibitory bias against the to-be-ignored distractors (Humphreys et al, 2004; Watson and Humphreys, 2004; Olivers et al, 1999). Critically, Emirich et al (2008) showed that inhibition was limited to the first four fixated items during a preview display and that set size negatively affected the probability of fixating on old items during the search display. They concluded that inhibition of old items in the preview search paradigm is a capacity limited process. Similarly, Moher and Egeth (2012) also noted that the "allocation first" inhibition they observed (in the study described in the introduction) was a serial capacity-limited process. They further argued that participants used feature information to identify non-target locations, but specifically inhibited the non-target locations (rather than engaging feature based inhibition) one item at a time – referred to as the "search and destroy" strategy.

The serial capacity-limited mechanisms described by Moher and Egeth (2012) and Emirich et al (2008) are consistent with each other and with reactive inhibition. This is because they would require participants to determine locations to inhibit based on

feature information and/or to actively shift from one distractor to another after stimulus presentation. DiQuattro and Geng (2011) have shown that this kind of integration of contextual knowledge and active sensory information is a reactive control process. While Tsal and Makovski (2006) do not explicitly refer to the allocation phase in their study as visual marking, the two phenomena are remarkably similar and it is tempting to assume they are part of the same process. However, the “type” of inhibition (i.e. capacity limited) in the white bear studies has not been explicitly tested. If it were shown that a capacity limited mechanism was engaged, it would provide converging support that in the white bear task (and in “allocation first” inhibition tasks in general), proactive attentional allocation precedes reactive inhibition, rather than (as initially expected) proactive inhibition. One way to test this would be to parametrically manipulate the number of flanker distractors between blocks in a white bear paradigm. Future research will have to address this, and the other questions raised by this study.

Chapter 6: Summary and Future Directions

Introduction

The purpose of this dissertation was to investigate which brain mechanisms are involved in proactive and reactive attentional control across the lifespan, how the function of those brain mechanisms is affected by age, and how those functional changes translate to differences in behavior. Chapter 1 reviewed the prior literature regarding the brain mechanisms that sub-serve salience suppression, particularly within the posterior parietal cortex, and their relationship with the dual mechanisms of cognitive control framework (DMC; Braver et al, 2010). It was established that the suppression of physically salient distractors was mediated via left intraparietal sulcus (Left IPS) and left superior parietal lobe (left SPL) mechanisms, that the suppression of distractors that were behaviorally relevant was mediated via left IPS and left temporoparietal junction (Left TPJ) mechanisms, and that the suppression of socially salient distractors was mediated by a left IPS mechanism. These mechanisms were then connected to the DMC framework, which posits that cognitive control is mediated by a proactive and reactive network. Based primarily on the temporal profiles of left IPS and left TPJ mediated suppression, it was argued that they may be involved in proactive and reactive cognitive control, respectively. Moreover, age-related difference in proactive and reactive control have been described in the literature. Based on this, the DMC was identified as an ideal framework to investigate the role of salience suppression mechanisms across the lifespan.

Chapter 2 investigated the brain mechanisms involved during a proactive suppression task – a global/local task where the salience of the target and distractor was orthogonally manipulated. Previous studies of aging using this task have shown the

behavioral correlates of a proactive inhibition impairment (Tsvetanov et al, 2013; Mevorach et al, 2016). However, in our study there were no behavioral differences in non-spatial salience suppression. Despite this, there were significant differences in brain activity between the young and the elderly groups. Young participants engaged proactive control mechanisms (including the left IPS), but elderly participants engaged proactive and reactive control regions (including the left IPS and left TPJ). Critically, this was supported by evidence that between network resting state connectivity decreased for the elderly participants, suggesting that they were in fact engaging two distinct control networks, rather than exhibiting signs of dedifferentiation between the networks. It was generally concluded that left TPJ mediated reactive control mechanisms supported proactive control mechanisms, rather than replaced them, in old age. However, it was not entirely clear how the support manifested. Since proactive control mechanisms have been shown to be temporally delayed in aging populations, it was proposed that the left TPJ triggers supports proactive control by triggering left IPS mediated suppression on time or more efficiently, though confirmation of this requires more research. It was further shown that both the proactive and reactive networks exhibited an age-related reduction in within network resting state functional connectivity (RSFC), supporting the notion that both networks were functionally impaired for the elderly participants. This was surprising because the prior literature had suggested that only proactive control was impaired in aging populations.

Chapter 3 examined the possibility that reactive control was impaired in aging populations. Previous studies had inferred that reactive control was intact in aging populations because there was evidence that proactive control was impaired and the

elderly participants appeared to favor reactive control strategies. However, these studies never directly compared reactive control in young and elderly participants. In our study, subjects engage in a reactive control task where subjects had to discriminate between an upright and inverted t-shape. Each trial had two stimuli: a target and a distractor. On 50% of trials the distractor was more salient than the target. In previous studies using this paradigm (DiQuattro and Geng, 2010) subjects performed better when a salient distractor was present, suggesting that subjects were using the salient distractor as an anti-cue. To do this, reactive control mechanisms would be necessary since subjects could not predict the presence of the salient distractor prior to stimulus presentation. Therefore, the performance benefit gained as a function of the salient distractor is effectively a measure of the engagement of reactive control mechanisms. Greater engagement will lead to higher performance benefits. It was found that, unlike young subjects, older subjects did not show any performance benefit when a salient distractor was present. Not only that, but the magnitude of the impairment scaled positively with age, suggesting that older people had greater impairments. This was interpreted as behavioral evidence that reactive suppression mechanisms were impaired in elderly participants. This is the first known evidence of an age-related impairment to reactive control.

Chapter 4 used TMS to assess if a dysfunction in the left TPJ or left IPS (or both) was causally responsible for the impairments to reactive salience suppression observed in chapter 3. The left TPJ was tested because of the finding in DiQuattro & Geng (2010) showing that the left TPJ feeds into the FEF and IPS during a reactive suppression task (the same one used in Chapter 3). The left IPS was tested because in chapter 2 it was

suggested that even during left TPJ mediated reactive suppression “proactive regions”, specifically the left IPS, may need to engage to suppress salience. In chapter 2 there was some limited evidence for this possibility, notably the fact that the left IPS and left TPJ were both active when elderly participants were presented with a salient distractor. Moreover, the reduced RSFC between the TPJ and IPS in old age reported in chapter 2 supports the notion that communication between these two regions and/or control networks may be impaired in old age. Based on these data, the age-related impairment to reactive salience suppression could be caused by a dysfunction of the left IPS, a dysfunction of the left TPJ, or an impairment in the ability for these regions to communicate with each other. In chapter 4, a young cohort of participants engaged in the same t-task as in chapter 3 and DiQuattro and Geng (2011) but prior to the experiment were exposed to 10 minutes of 1Hz rTMS applied over the left TPJ, the left IPS, or Cz. The results revealed that stimulating the left TPJ impaired participants’ ability to reactively use a salient anti-cue to their benefit. This suggests that the left TPJ facilitates reactive salience suppression and that the behavioral impairments reported in chapter 3 may be at least partially attributable to a dysfunctional left TPJ. The results also surprisingly revealed that stimulating the left IPS actually improved the ability to use the anti-cue. This implies that the left IPS impairs reactive salience suppression, suggesting that engagement of the left IPS is not critical in reactive salience suppression for young participants (though this may be different in an elderly cohort).

Chapter 5 deconstructed the inhibition process and established that in some cases, mostly during arguably proactive tasks, inhibition is preceded by the allocation of attention to the location of the to-be-ignored item. Therefore, it was asked if age-related

deficits in inhibition were in fact just a consequence of impairments to the allocation of attention. In this study, young and elderly participants had to report the identity of a centrally located letter in presence of congruent or incongruent flankers. On some trials, instead of a flanker task, participants were presented with a temporal order judgement and had to report which of two dots appeared on the screen first (it should be noted that the dots both appeared at the same time and appeared in the same location as the “upper” flankers). It was found that both young and elderly participants reported that the dot that appeared in the location of an expected flanker appeared prior to the dot that appeared where no flanker was expected. This was interpreted as both cohorts deploying their attention to the location where they expected to have to inhibit a flanker. Critically, there was no age-group difference in the magnitude of the effect, suggesting that elderly participants did not exhibit an impairment in the allocation of attention prior to inhibition. Although, it should also be noted that in this task, elderly participants also did not exhibit any impairments in inhibition (as measured by response time and accuracy in the flanker task). However, there was some evidence of an age-related impairment in attentional disengagement (based on a significant “inverted-U” quadratic relationship between attentional allocation and inhibition for elderly participants), which is arguably a form of inhibition (Geng and DiQuattro, 2010). Overall, these results suggest that inhibition is specifically impaired in aging populations and attentional allocation mechanisms that precede inhibition are intact.

The next section will consider the implications of the findings reported in this thesis to the broader context of cognitive control in aging.

Proactive and Reactive Cognitive Control in Aging

This dissertation has made several important empirical and theoretical contributions to the field of cognitive control in aging. One of the most pervasive concepts in the literature is that as people get older they shift from preferential use of proactive mechanisms to reactive mechanisms, specifically because proactive mechanisms appear to be impaired and reactive mechanisms appear to be intact. Chapters 2 and 3 challenge this notion in several ways. Due to possible performance trade-offs in previously used paradigms, it was unclear if proactive control was really impaired in aging populations or if participants simply made different strategic choices. More egregiously, the evidence that reactive control was intact was not based on empirical data, but rather circumstantial evidence. Using a task where there was no performance trade-off for switching to reactive control mechanisms, Chapter 2 provided evidence of functional deficits within both the proactive and reactive networks in an elderly cohort. And further, chapter 3 provided direct behavioral evidence that reactive control was impaired in an elderly cohort.

It should be noted there is arguably evidence for reactive control impairments already in the literature that has now become apparent in hindsight. The task switching literature often refers to global and local switch costs. Global costs reflect the resources required to maintain and coordinate multiple task sets, a possibly proactive process, and local costs reflect the resources required to deactivate a task set and implement a new one, a possibly reactive process. Wasylyshyn et al (2011) conducted a meta-analysis and showed that the literature generally showed that global costs are specifically impaired by age but local costs are not, and that both groups show generalized processing deficits.

However, in light of this dissertation, it is reasonable to question if there is some age-related deficit in local costs that was not detected by the original analysis. In particular, the meta-analysis did not compare the magnitude of the global and local processing speed deficits. If it really is a “generalized” deficit, it should affect both costs similarly. Basically, if speed of processing deficits could masquerade as specific inhibition deficits, as discussed in chapter 3, the reverse could also be true. Thus, this dissertation provides evidence that previous analyses may need to be revisited and future analyses may need to update their methods to account for these possibilities.

Overall, this dissertation confirms an age-related impairment in proactive control and explicitly highlights, for the first time, an age-related impairment in reactive control. The fact that both are impaired is critical because calls in question why older participants would tend to favor reactive mechanisms. However, the notion of a shift from one control mode to another inherently implies that people engage only one control mode at a time. Chapter 2 challenges this assumption because we found evidence that both proactive and reactive control mechanisms were engaged in an elderly cohort during a proactive inhibition task. This may explain why most studies do not detect reactive control impairments. It was argued that proactive mechanisms may support reactive mechanisms during a reactive task to compensate for age-related impairments, but it’s unclear if this dual mechanism support would, or even could, occur during a proactive task. Essentially, elderly participants may simply be better at compensating for impairments in reactive control mechanisms than proactive control mechanisms, leading to generally smaller effects and reducing the likelihood of detecting an impairment. Wasylshyn et al (2011) noted in their study that they had relatively low power due to

the number of studies they were able to find for their meta-analysis. In fact, there are some studies which have shown an age-related impairment in local task switch costs (Meiran et al, 2001; Kray et al, 2002), though these results are not typical. Notably, Kray et al (2002) found a specific impairment to local switch costs that scaled as a function of the number of possible task sets. Taken in conjunction with this dissertation, it suggests that age-related impairments to reactive control may be more apparent as uncertainty increases because it would make support from proactive control mechanisms, which require advance knowledge, less effective. Therefore, previous studies of reactive control may have not been sensitive enough or calibrated in such a way to detect impairments.

However, it's also possible that, rather than supporting each other, both control modes simply act simultaneously but independently. This is further complicated by chapter 4, in which it was proposed that there may be a "balance" between proactive and reactive control, where the two control modes effectively take over for each other when one is not functioning properly. Therefore, this dissertation opens up the possibility that, in healthy aging, proactive and reactive control can be engaged simultaneously and support each other, engaged simultaneously and act independently, or engaged alone. Crucially, these possibilities are not mutually exclusive. The manner in which the control modes interact with each other (supporting, supplanting, or independence) may depend on task demands, stimulus properties, or something else entirely. Exploring how the control modes interact with one another in healthy aging will be an important avenue for future research.

Additionally, chapter 5 investigated the possibility that age-related inhibition impairments might have been attributed to impairments to attentional allocation prior to

inhibition. The results revealed that attentional allocation prior to inhibition is intact. However, this is the only study to consider and test for this possibility. Prior to this study, it was simply assumed that allocation was intact in this context.

This dissertation has also made contributions to the literature beyond the context of aging. Chapter 1 argued, for the first time, that the left IPS may mediate the suppression of salient distractors as part of the proactive control network. In chapter 2, young participants specifically engaged the left IPS during a proactive inhibition task when the distractor was more salient than the target. Chapter 1 also argued that the left TPJ may mediate reactive inhibition. In chapter 4, rTMS to the left TPJ significantly impaired performance during a reactive inhibition task. Essentially, chapters 2 and 4 provide the first empirical evidence that the left IPS and left TPJ mediate the suppression of salient distractors in the proactive and reactive control networks, respectively.

A New Paradigm?

At the moment, the literature is ill-equipped to provide a satisfying answer to all of the issues raised in the previous section. A major part of this is because, as mentioned in chapter 3, different tasks are typically necessary in order to be reasonably certain that participants are engaging a specific control mode. However, this means that there are significant differences in the visual stimuli and in the presentation times across studies, complicating our ability to test for and interpret differences between the control modes. To address this problem, our lab has begun pilot testing a new paradigm in which proactive and reactive control can be manipulated and tested within a single task. A spatial and non-spatial variation of the Ax-CPT task were developed in which trial

frequency was actively manipulated to encourage either proactive or reactive control strategies.

In both versions of the task participants are presented with two letters at a time, a cue and probe pair. In the non-spatial version of the task, the cue-probe pair is embedded in a hierarchical letter (Figure 1). In the spatial version of the task, the cue-probe pair are presented in two different locations in the same display (Figure 2). There are four trial types: Ax trials, where the critical letter (i.e. the probe letter) is an X and the other letter (i.e. the cue letter) is an A; Ay trials, where the critical letter is a Y or H and the other letter is an A; Bx trials, where the critical letter is an X, but the other letter is a Y or H; and By trials, where both the critical letter and the other letter are H's or Y's (though they are never the same letter). In order to encourage the use of proactive or reactive control, the frequency of the different types of trials are manipulated. It should be noted that this paradigm is based on the assumption that proactive responders make decisions based on "cues" and reactive responders make decisions based on "probes." The initial studies with this paradigm will help confirm or disprove this assumption. In the proactive frequency condition, 20% of trials are Ax trials, 60% are Bx trials, 10% are Ay trials, and 10% are By trials. In these trials, the X is frequently the critical letter, so the ability to respond based on the other letter (i.e. the cue) should be especially useful. In the baseline frequency condition, 25% of trials are Ax trials, 25% are Bx trials, 25% are Ay trials, and 25% are By trials. In these trials, there should be no reason to focus on the critical or the other letter beyond individual preference. In the reactive frequency condition, 20% of trials are Ax trials, 10% are Bx trials, 60% are Ay trials, and 10% are By trials. In these trials, the A would frequently be the other letter, so the ability to respond

based on the critical letter (i.e. the probe) will be especially useful. The task is to report the presence of the letter X in the target level of the display, but only when the “other” letter (the cue) is an A.

As discussed in chapter 1, proactive responders should perform better during “Bx” trials than “Ay” trials and vice versa for reactive responders. To be a useful paradigm, participants should respond proactively during the proactive frequency condition and reactively during the reactive frequency condition. Participants should theoretically respond to the baseline frequency condition based on their natural inclinations. For example, elderly participants might show a reactive pattern of results. This pilot study will ideally provide a “proof of concept” that these paradigms can manipulate the engagement of proactive and reactive control in both young and elderly cohorts, while holding constant the many other factors that can impact performance in visual attention tasks. These paradigms will allow imaging and brain stimulation studies to get a much clearer picture of brain function during proactive and reactive control. Additionally, they will allow researchers to test how control mode engagement changes in the presence of impairments to one or both control mode. Future research into this area will depend heavily on newer paradigms like the ones described here.

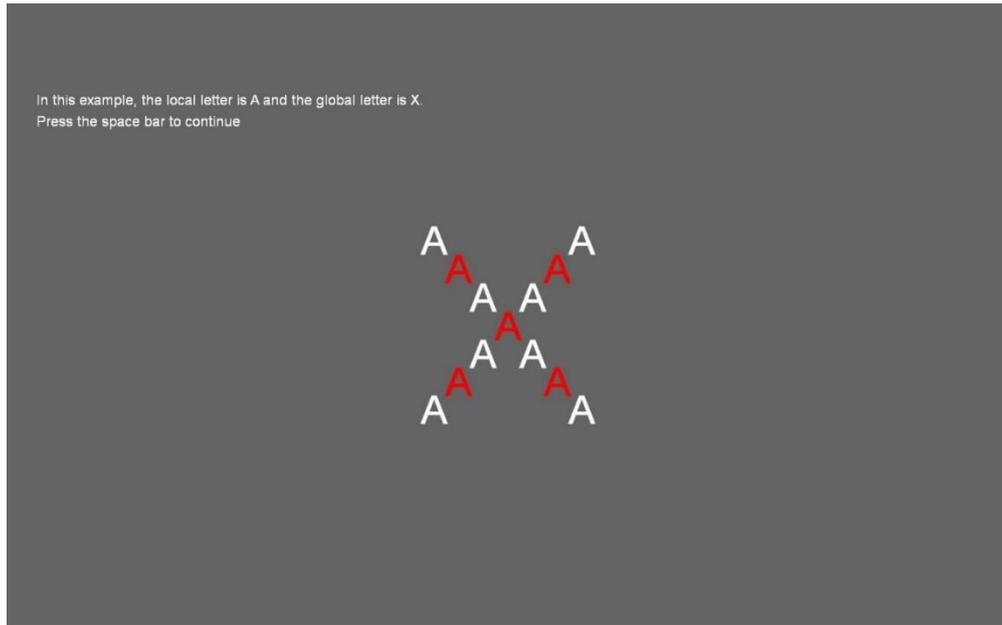


Figure 1. Example of non-spatial task. If the subject were being asked to respond to the local letter, they would respond that the target was not present. If they were being asked to respond to the global letter, then they would respond that the target is present.



Figure 2. Example of a spatial task. In this example, the subject would respond that the target is present.

The DMC Framework and Individual Differences

Throughout this dissertation, it has been mentioned that elderly participants tend to engage reactive control over proactive control. However, the preference of one control mode over the other is not limited to age-related differences. There is evidence that people with autism spectrum disorders show evidence of impaired reactive control mechanisms (Solomon et al, 2014), and therefore favor the use of proactive control. Conversely, people with schizophrenia (and other forms of psychosis) show neurological and functional impairments of proactive control mechanisms (Lesh et al., 2013), and therefore favor the use of reactive control mechanisms. Even in healthy neurotypical subjects who have varying degrees of autistic-like and psychotic-like traits, similar tendencies of using proactive and reactive control have been shown.

Cresipi and Badcock (2008) have argued that psychosis (particularly positive symptoms of schizophrenia) and autism exhibit diametrically opposite patterns of social development, neurological development, and cognitive function. According to Chisholm et al (2015), while there are many possible models of co-expression of these disorders, the evidence supports a “diametrical model” where the expressions of autistic and psychotic traits are the result of reciprocal variations to a single common mechanism. Critically, this predicts that when the traits from both disorders are expressed at the same time, they will essentially cancel each other out and result in ‘normal’ trait expression. Therefore, autistic or psychotic traits would only be apparent if they have a higher relative expression of traits from one of those disorders. Abu-Akel et al (2016a; 2016b) assessed the relative expression of autistic and psychotic traits in neurotypical

subjects and its relationship to performance on proactive inhibition tasks. Subjects had to engage in a variation of the global/local task from chapter 2 and in a face-scene perception task. In both tasks, they found that higher relative expression of autistic traits resulted in lower interference from salient distractors and that higher relative expression of psychotic traits resulted in greater interference from salient distractors. As predicted by Chisholm et al (2015), when expression of psychotic and autistic traits were equally expressed, the degree of distractor interference was in between the previous two conditions, as if the effects were cancelled out. The authors suggested that this may reflect preferential use of proactive inhibition in high-autism individuals and preferential use of reactive inhibition in high-psychosis individuals.

Abu-Akel et al (2016b) followed up on the possible relationship between relative expression of autistic and psychotic traits, and proactive and reactive control. They had neurotypical subjects engage in a reactive inhibition task, the t-task from DiQuattro and Geng (2011; Chapter 3 and 4), and a proactive inhibition task, a morphed faces discrimination task. They found that relative expression of autistic and psychotic traits had inverted effects on performance. In the reactive task, a high relative expression of psychotic traits improved performance, whereas a high relative expression of autistic traits impaired performance. This opposite pattern of results was found in the proactive task. This double dissociation suggests that relative expression of autistic and psychotic traits is predictive of which mode of cognitive control will be preferentially engaged during salience inhibition tasks. It also may help to explain some of the conflicting results in the literature, since even young, healthy, neurotypical subjects can show vastly different patterns of results on the same tasks depending on their individual differences.

Moreover, it has been shown that relative expression of autistic and psychotic traits can be associated with distinct brain activation patterns during the same task. In a mentalizing task, Abu-Akel et al (2016c) found that high relative expression of autism was associated with decreased activity in the right ventral posterior temporo-parietal junction (rvpTPJ) and increased activity in the right ventral anterior temporo-parietal junction (ravTPJ). Conversely, high relative expression of psychosis was associated with increased activity in the rvpTPJ and decreased activity in the ravTPJ. This suggests that the right ventral attentional system, which is engaged differentially by proactive and reactive control processes, may be modulated as a function of relative expression of autism and psychosis. As such, the left lateralized ventral attention network (proposed by DiQuattro and Geng, 2011), and therefore the effect of TMS on this network, may also be influenced by the subjects' individual trait expression.

This has potentially significant implications for the studies in this dissertation, particularly the TMS study in Chapter 4. In a pilot study, Ashinoff et al (2016) reported that the effect of TPJ stimulation during the same t-task as in Chapter 4 did indeed change as a function of the relative expression of autism and psychosis. As a quick reminder, subjects had to discriminate between an upright and inverted 't' shape in the presence of a high or low salience distractor. Subjects could engage reactive control to use the salient distractor as an anti-cue, typically showing better performance when the salient distractor was present in the display. In Chapter 4, stimulating left TPJ disrupted the reactive control process and result in a reduced performance benefit. However, Ashinoff et al (2016) found a reduced performance benefit after TPJ stimulation only if the subject had a high relative expression of autism. If the subject had a high relative

expression of psychosis, TPJ stimulation actually improved the performance benefit. This suggests that the left TPJ plays a different role in reactive inhibition for individuals who have high relative expression of autism or psychosis. In chapter 4, it was suggested that the left TPJ may play a different role in spatial attention during salient and similar trials, but these data suggest that this may be taken further: the TPJ may play a different role in spatial attention from person to person. While these results were only from a pilot study, they are certainly interesting and warrant further investigation.

Beyond the TMS study, if psychosis and autism trait expression can have such significant and opposite effects on the engagement of proactive and reactive control, it may be prudent to consider them as a matter of course in this type of research. Because they have opposite effects on performance, it is possible that previous studies did not identify deficits in proactive or reactive inhibition because the two groups of participants effectively cancelled out each other's data. Further, there may be other relevant individual differences besides autistic and psychotic trait expression that would predict engagement of proactive and reactive control. These individual differences should be sought out and studied.

Practical Applications

While the academic research presented here is interesting for many reasons, it carries very little meaning if this research can't be applied to improve people's lives in some way. First, it can be used to inform cognitive rehabilitation research and programs for aging populations. This dissertation suggests that older people may benefit from regular and active stimulation of both proactive and reactive cognitive abilities via training programs or video games. Second, the inhibition deficit theory of cognitive aging

(Lustig et al, 2007) argues that age-related inhibition deficits underlie age-related deficits in other cognitive domains. Therefore, this research may help to explain age-related differences in brain activity beyond just inhibition, though this will require further research. And third, knowledge of the role of the left IPS and left TPJ may help medical doctors predict cognitive impairments after strokes or traumatic brain injury, in both young and aging populations. This will allow them to prepare more effective treatment plans.

Conclusion

In conclusion, this dissertation was successful in its stated purpose. It has extended literature in a few different ways. First, it showed that both proactive and reactive inhibition are impaired in ageing populations (Chapter 2 and 3). Second, it showed that proactive and reactive control can be engaged simultaneously in aging populations (Chapter 2). Third, it established that inhibition impairments in aging populations cannot be accounted for by impairments to attentional allocation prior to inhibition (Chapter 5). And fourth, it demonstrated that the left IPS is involved in proactive suppression and that the left TPJ/left IFG are involved in reactive suppression (Chapter 2 and 4). Future research should focus on understanding if, how, and when proactive and reactive control interact (supporting or supplanting each other) or do not interact (independent engagement) under varying circumstances in young and aging cohorts, the brain mechanisms that mediate these interactions, and the effects of individual differences beyond age on performance and brain function.

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