THE AGING RESEARCH CENTER (ARC), DEPARTMENT OF
NEUROBIOLOGY, CARE SCIENCES AND SOCIETY
Karolinska Institutet, Stockholm, Sweden

INTERFERENCE CONTROL IN WORKING MEMORY: NEUROBEHAVIORAL PROPERTIES AND AGE DIFFERENCES

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Stockholm 2018

Published by Karolinska Institutet.

ISBN 978-91-7831-260-3
Printed by Eprint AB 2018

Cover illustration artist: Marcus Olsen

Interference control in working memory: Neurobehavioral properties and age differences

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the glory of our Lord and savior, Christ Jesus.

For there is one God, and one mediator between God and men, the man Christ Jesus; Who gave himself a ransom for all

(*1st letter to Timothy, chapter 2, verses 5 to 6, The Scriptures*)

I will always be captivated by the fine-tuning and complexity found in God’s creation. It has been an honor to explore and delve deep in to something as intriguing as the human mind.

On the glorious splendor of Your majesty
and on Your wonderful works, I will meditate.

(The book of Psalms, chapter 145, verse 5, The Scriptures)

ABSTRACT

This doctoral thesis aimed to investigate the basic processes of interference control (IC) in working memory (WM). We sought to unravel some of the underlying mechanisms of IC by examining brain correlates, while also trying to understand the differences that arise with advancing adult age. The major findings from these studies are summarized below.

Study I. This study consisted of four separate experiments, with different participants in each. Three different versions of the recent-probes task was used to test the effects of a high- compared to a low-interference context on behavioral and neural measures. A combined analysis of all experiments showed that a high-interference context improved performance, both reaction times and accuracy, on the other trial types within the same task. Neuroimaging results revealed greater engagement of inferior frontal gyrus, striatum, parietal cortex, hippocampus, and midbrain in participants performing the task in the high- than participants in the low-interference context.

Study II. This study compared groups of older and younger adults to examine age effects of interference control. A verbal 2-back task including proximal and distant lures revealed that older adults were more affected by interference overall, for both proximal and distant lures. Whereas younger adults overcame and were no longer affected by interference beyond 5-/6-back lures, older adults were still highly affected at the most distant 9-/10-back lures.

Study III. This study expands on study II by examining brain activity during successful interference control, using a similar task setup. Proactive interference and brain activity in bilateral inferior frontal gyrus and dorsal anterior cingulate cortex declined with increasing lure distance. This decline in relevant brain regions was coupled with an increase in brain activity in left anterior hippocampus. In addition, each successfully resolved lure trial was divided into two groups, those that influenced performance negatively and those that did not. A whole brain analysis showed greater brain activity in bilateral inferior frontal gyrus, bilateral middle frontal gyrus, and dorsal anterior cingulate gyrus for the lure trials that took longer time to respond to accurately.

Study IV. This study used four-year follow-up data from the Betula study to examine whether prefrontal brain volumes can be linked to the ability to control interference. Individuals were separated with respect to their ability to control interference. We observed that participants with superior interference control had larger volume of the ventrolateral area of prefrontal cortex (PFC), regardless of participant demographics. Change in volume over a 4-year period could not be linked to change in interference control.

Conclusions. The data in this doctoral thesis contribute with new insight into IC in WM. Data suggests that positive task-scale adjustments, due to conflict, is beyond trial-to-trial adaptation, affecting both behavioral and biological aspects of cognition. Improved performance on non-conflict trials could be explained by an upregulation of resources to cope with the high interference environment. Moreover, a characteristic of the general age-related IC deficit was uniquely demonstrated in older adult's inability to cope with some of the temporal properties of PI, being negatively affected by the most distant lure trials. Results suggest two distinct means for resolving interference in WM. One involves top-down controlled processes for actively resolving lure items within the focus of attention, and the other involves hippocampus related retrieval of source information from outside the focus of attention. The latter is arguably more difficult for older adults due to the strain on hippocampus, and links well with our own results. Results also suggests two distinct levels of influence by interference in WM, which is either being unaffected by PI or being affected negatively by PI, suggesting an ability that can completely overcome PI. Lastly, these results provide new evidence that a relative IC score can be related to volume of specific and relevant regions within PFC, and that this relationship is not modulated by age. This supports a view that grey matter volume in PFC regions play a specific role in overcoming interference during a WM task.

Keywords: *working memory, proactive interference, interference control, aging, n-back, updating, functional MRI, structural MRI, prefrontal cortex, focus of attention, familiarity, retrieval, unbinding*

SAMMANFATTNING

Denna doktorsavhandling hade som mål att undersöka basala processer för hanteringen av interferens i arbetsminnet. Vi försökte reda ut några av de underliggande mekanismer av denna hantering genom att undersöka korrelat i hjärnan, samt även genom att försöka förstå skillnader som uppstår på grund av ökad ålder. Huvudfynden från samtliga studier i denna avhandling summeras nedan:

Studie I. Denna studie innefattade fyra separata experiment, med olika deltagare i varje. Tre olika versioner av en recent-probe uppgift användes för att testa effekten av en hög- jämfört med en låg interferenskontext på beteende samt hjärnaktivitet. En förenad analys av samtliga fyra experiment visade att en kontext innehållande hög interferens förbättrade prestationen, både inom reaktionstid samt träffsäkerhet, på andra problem inom samma uppgift. Hjärnavbildningsresultat visade en ökad involvering av inferiora frontala gyrus, striatum, parietala cortex, hippocampus, och mitthjärnan bland deltagare som utförde uppgiften innehållande hög interferens jämfört med de deltagare som utförde liknande uppgift med låg interferens.

Studie II. Denna studie jämförde en grupp av äldre mot en grupp unga vuxna med målet att undersöka effekten av ålder för hantering av interferens. Proximala och avlägsna ord associerade med interferens användes i en 2-back uppgift för att visa att äldre deltagare vart generellt mer påverkade än de unga vuxna av interferens. Unga vuxna var inte längre högt påverkade av interferens efter 5-/6-back interferensord, medan äldre var fortfarande högt påverkade av de mest avlägsna 9-/10-back interferensorden.

Studie III. Denna studie är en vidareutveckling av studie II där vi använde en liknande uppgift för att undersöka hjärnaktivitet under lyckad hantering av interferens. Interferens samt hjärnaktivitet i bilaterala inferior frontal gyrus och anteriora cingulate cortex minskade med ökad distans på interferensord. Denna minskning av aktivitet i relevanta hjärnregioner var sammankopplad med en ökad aktivitet i vänstra anteriora hippocampus. Utöver detta delades korrekt besvarade ord med interferens in i två grupper, en grupp som påverkade prestation negativt och en som inte gjorde det. En analys av hjärnaktivitet visade mer aktivering i bilaterala inferiora frontala gyrus, bilaterala mediala frontal gyrus, och dorsala anteriora gyrus cinguli för gruppen med interferensord som påverkade prestation negativt.

Studie IV. Denna studie använde sig av en fyra års uppföljning som gjordes i Betula studien för att undersöka ifall prefrontala hjärnvolymer kan länkas till förmågan att hantera interferens. Individer separerades med avseende på deras förmåga att hantera interferens. Vi observerade att deltagare med en överlägsen förmåga att hantera interferens hade större volym i ventrolaterala prefrontala cortex, oberoende av demografiska variabler. Förändringar i volym över en fyra års period kunde inte länkas med en förändring i hantering av interferens.

Slutsatser. Resultaten i denna doktorsavhandling bidrog med nya insikter kring hantering av interferens i arbetsminnet. Data visar på en förbättrad övergripande förmåga att prestera när en uppgift innehåller mycket interferens, och att detta är en konsekvens av uppreglering av resurser i hjärnan. Denna uppreglering verkar alltså drivas i viss mån av en hög nivå interferens i en arbetsminnesuppgift. Ett unikt karaktärsdrag för äldre var den markant försämrade förmågan att hantera avlägsna interferensord, vilket verkar höra ihop med en försämrad förmåga att hantera interferens i arbetsminnet med ökad ålder. Vidare visar samtliga resultat på två olika sätt att lösa interferens i arbetsminnet, dvs. en kontrollerad minnesprocess för aktiv hantering av interferens som är inom vår uppmärksamhetsfokus, och en minnesprocess för avlägsen information utanför vår uppmärksamhetsfokus. Det sistnämnda är förhållandevis mycket svårare för äldre på grund av involvering av hippocampus, vilket bekräftas av våra resultat. Samtliga resultat visar även på två olika utfall av interferens som introduceras i arbetsminnet. Dessa två utfall kan summeras genom interferens som påverkar prestation negativt, och interferens som inte gör det. Vilket betyder att det är möjligt att vara opåverkad från det negativa inflytandet av interferens, detta via en mekanism som är enligt resultaten olik från aktiv hantering av interferens. Slutligen kunde resultaten även visa att de mått som använts i denna doktorsavhandling för att mäta hantering av interferens kunde relateras till en större hjärnvolym i prefrontala cortex. En större volym i detta område verkar vara knutet till förmågan att bemästra interferens till den grad att man inte längre är negativt påverkad under en arbetsminnesuppgift.

LIST OF SCIENTIFIC PAPERS

I. **Samrani G**, Marklund P, Engström L, Broman D, Persson J. Behavioral facilitation and increased brain responses from a high interference working memory context. *Scientific Reports*, 2018; 8(1), 15308. http://doi.org/10.1038/s41598-018-33616-3

II. **Samrani, G**, Bäckman, L, Persson, J. Age-differences in the temporal properties of proactive interference in working memory. *Psychology and Aging*, 2017; 32(8), 722–731. http://doi.org/10.1037/pag0000204

III. **Samrani G**, Bäckman L, Persson J. A prefrontal – hippocampal shift underlies the temporal dissipation of proactive interference in working memory. *Manuscript*.

IV. **Samrani G**, Bäckman L, Persson J. Interference control in working memory is associated with ventrolateral prefrontal cortex volume. *In review*.

ADDITIONAL PUBLICATIONS NOT INCLUDED IN THE THESIS

1. Ziaei, M, **Samrani, G**, Persson J. Age differences in the neural response to emotional distraction during working memory encoding. *Cognitive, Affective, & Behavioral Neuroscience*, 2018. http://doi.org/10.3758/s13415-018-0610-8

CONTENTS

LIST OF ABBREVIATIONS

AIS	Accuracy Interference Score
EF	Executive Function
fMRI	Functional Magnetic Resonance Imaging
IC	Interference Control
IFG	Inferior Frontal Gyrus
MFG	Middle Frontal Gyrus
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
PFC	Prefrontal Cortex
PI	Proactive Interference
ROI	Region of Interest
RT	Reaction Time
RTIS	Reaction Time Interference Score
WM	Working memory

1 INTRODUCTION

1.1 Cognition

We face many situations in our everyday lives that demand our attention, memory, judgement, reasoning, decision making, and comprehension to be able to deal with our environment and thrive. Cognition can be defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses" (Oxford dictionary) and encompasses every aspect of aware and unaware processes in our minds. Normally, these cognitive processes are in turn related to biological processes in the brain. Cognitive neuroscience attempts to bridge cognition with brain as a tool to understand the underlying mechanisms of our cognition. The current thesis applies the framework of cognitive neuroscience to investigate some of the basic mechanisms of cognition, specifically the ability to inhibit goal-irrelevant information, and how this relates to brain structure and function.

1.2 Executive functions

Executive functions (EFs) are high-level cognitive processes that govern thoughts and actions in goal-directed behavior (Diamond, 2014). EFs may coordinate sensory information and basic cognitive processes in order to support more complex functions such as interference resolution, flexibility, problem solving, planning, impulse regulation, concept formation, abstract thinking, and creativity (Collins & Koechlin, 2012), and are crucial for goal-directed everyday interactions with the environment and people, especially in non-routine situations (Banich, 2009; Diamond, 2014). Originally, the central executive was conceptualized as a unitary entity (Baddeley & Hitch, 1976; Kimberg & Farah, 1993), but later behavioral, neuropsychological, and neuroimaging evidence suggests an executive control system divided into several partly separate functions (A Miyake et al., 2000; Smith & Jonides, 1999). A prominent theory shows evidence for three general categories of executive functions; shifting (shifting between mental sets or tasks), updating (updating and monitoring of working memory contents), and inhibition (inhibition of prepotent responses; Miyake et al., 2000). However, when separating executive functions into these three factors, they seem to share underlying commonalities and are therefore not fully independent, suggesting both unity and diversity of executive functions (A Miyake et al., 2000). For example, it has been demonstrated that while inhibition and shifting was not directly related to measures of intelligence, updating was strongly linked to intelligence (Friedman et al., 2006). In the same study it was also shown, using structural equation models, that even when controlling for inter-EF correlations, updating remained strongly associated with intelligence, while relations of inhibiting and shifting to intelligence were small and not significant (Friedman et al., 2006).

The prefrontal cortex (PFC) have long been identified as a critical hub for executive functions, involved in coordinating information from bottom-up sensory systems (Alvarez & Emory, 2006; Collins & Koechlin, 2012). A relationship between EFs and PFC is further supported by patient data demonstrating that PFC lesions result in impairments in EFs (Jacobs, Harvey,

& Anderson, 2007; Robbins, 1996), and there is much imaging data linking PFC structure and functional estimates to different EFs (Badre, 2008; Duncan & Owen, 2000; Glascher et al., 2012; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Smith & Jonides, 1999). Moreover, EFs generally decline with aging (Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2017), which is understandable due to EF's high dependency on age-sensitive regions in PFC (Raz et al., 2005).

1.3 Processing speed

Cognitive processing speed is the speed in which information is processed, and is essential for higher-order cognitive task performance (Salthouse, 1996, 2000). Processing speed is separate from top-down executive functions, and instead is supposed to reflect the signal transmission between neuronal cells in the brain. The highest quantity of neuronal tracts (or axons), where signals travel can be found in the white-matter segments of the central nervous system. The role of white matter as the biological basis of processing speed has been validated extensively Furthermore, cross-sectional and longitudinal (Schaie, 2005) studies strongly indicate that processing speed peaks at around the mid-30's followed by a generally linear decline onward. Much of the age-related decline in processing speed underlines declines in other higher-order cognitive functions and EFs (Hedden, Lautenschlager, & Park, 2005; Levitt, Fugelsang, & Crossley, 2006; Rabbitt et al., 2007; Salthouse, 1995, 1996, 2005; Salthouse & Coon, 1993; Salthouse & Ferrer-Caja, 2003). Since performance on cognitive tasks seems to be affected with age, especially when investigating reaction time (RT) measures, adjusting raw performance scores for processing speed (see section 3.3.1) has been one of the major novel themes of this doctoral thesis, to minimize inter-individual differences on basic cognitive skills like processing speed.

1.4 Working memory

Working memory (WM) is widely viewed as a unique cognitive system consisting of short-term maintenance and active processing of small amounts of information, thereby permitting its use in reasoning, planning, decision-making, language comprehension, and other higher cognitive abilities (Baddeley & Hitch, 1974). WM is similar to short-term memory, but is commonly viewed as a system also involved in top-down control processes, such as updating and manipulation of information, whereas short-term memory is simply a temporary storage of information. WM is therefore central to cognition, and highly related to variability in performance on different measures of mental aptitude, such as fluid intelligence (Engle, Laughlin, Tuholski, & Conway, 1999). WM can be understood as the part of consciousness that humans are aware of at any given time, and the basis for goal-directed behavior. WM allows humans to comprehend their environment, construct mental representations, retrieve and retain information from the past, gain new knowledge, solve problems, and disentangle, formulate and act upon current goals (Baddeley & Logie, 1999). The WM model proposed by Baddeley and Hitch (1974) is the most extensively used framework to understand the different components of WM. This model assumes a central controlling unit and several storage systems. The central control unit (or central executive) coordinates information from the phonological loop, the visuospatial sketchpad, and the episodic buffer. Each storage system (or slave system) can be understood as follows; the phonological loop temporarily stores and manipulates speech-based information; the visuospatial sketchpad stores and manipulates visuospatial information, i.e. objects, and where they are in space; the episodic buffer holds and integrates episodes or pieces of information, acting partly like a buffer between the phonological loop and visuospatial sketchpad, but also links WM to long-term memory (Baddeley, 2000). Conceptualizing upon the many components of WM and testing these in the environment of cognitive science and neuroscience has so far been proven fruitful. This thesis project is revolved around WM, attempting to disentangle and advance further the understanding of specific components of WM.

WM performance increases during childhood and adolescence (Gathercole, Pickering, Knight, & Stegmann, 2004), while deteriorating in old age (Nyberg, Dahlin, Stigsdotter Neely, & Bäckman, 2009; Rieckmann, Pudas, & Nyberg, 2017), suggesting an inverted U-shaped relationship between age and WM performance. In addition, WM performance is largely determined by differences in attentional control rather than by the absolute amount of storage capacity (Adam, Mance, Fukuda, & Vogel, 2015). Thus, it becomes increasingly difficult for older adults to focus on goal-relevant information and suppress interference, avoid distraction, while maintaining information in WM (Adam et al., 2015). Another motivation for understanding the components of WM has to do with the extensive impairments seen in WM described in various neurological and psychiatric diseases. Almost all forms of dementia exhibit deficits in WM performance (Huntley & Howard, 2010; Maestú et al., 2011; Stopford, Thompson, Neary, Richardson, & Snowden, 2012), also with Huntington disease (Huber & Paulson, 1987; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004), Parkinson's disease (Di Rosa et al., 2017; Gilbert, Belleville, Bherer, & Chouinard, 2005; Possin, Filoteo, Song, & Salmon, 2008), schizophrenia (Goldman-Rakic, 1994; Lett, Voineskos, Kennedy, Levine, & Daskalakis, 2014), and depression (Hubbard et al., 2016; Rose & Ebmeier, 2006).

1.5 Interference control

A crucial function of the WM system is to distinguish between relevant and goal-irrelevant information while maintaining task goals. This is especially true in today's high-information and technological society. With such a heavy flow of information, it is important that the contents of WM are monitored and updated efficiently, especially in the face of competing or distracting information (Engle et al., 1999). One such disruption in WM is proactive interference (PI) that occurs when previously relevant, but currently irrelevant, information interrupt goal-directed cognition (Baddeley, 1990; Keppel & Underwood, 1962). The ability to control this specific disturbance is referred to as interference control (IC). IC is highly related to fluid intelligence (Burgess, Gray, Conway, & Braver, 2011; Shipstead, Harrison, & Engle, 2016; Unsworth, 2010), and essential for good WM functioning (Bunting, 2006; Dempster & Corkill, 1999; Lustig, May, & Hasher, 2001; May, Hasher, & Kane, 1999; McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010), and will be the main focal point of this doctoral thesis. In brief, PI arises in cognitive tasks as a consequence of not being able to successfully suppress or control goal-irrelevant information (Altmann & Gray, 2002; Berman, Jonides, & Lewis, 2009; Keppel & Underwood, 1962; Oberauer & Lewandowsky, 2013; Underwood, 1957). Many of the mechanisms underlying superior IC in WM, and age-related decline therein, is not fully understood and open for investigation.

Note that IC is distinct from other types of inhibition, such as response inhibition or resistance to distracters (e.g. Friedman & Miyake, 2004). For example, cognitive tasks such as Stroop (Macleod, 1991) or the Eriksen flanker task (Eriksen & Eriksen, 1974) present goal-irrelevant information in the immediate attention span (Figure 1). In these tasks, a participant is in one way or the other currently observing a conflict to be resolved in the immediate attention. Suppressing the goal-irrelevant information in such cases is a form of response inhibition, similar to suppressing automatic, impulsive, and habitual responses that stir up in the moment. IC is different in the sense that it denotes when previously relevant, but presently irrelevant, information is retrieved from memory causing interference with a task goal. This doctoral thesis exclusively employ tasks that require IC, the n-back and recent probes task (see section 3.2.1 and 3.2.2).

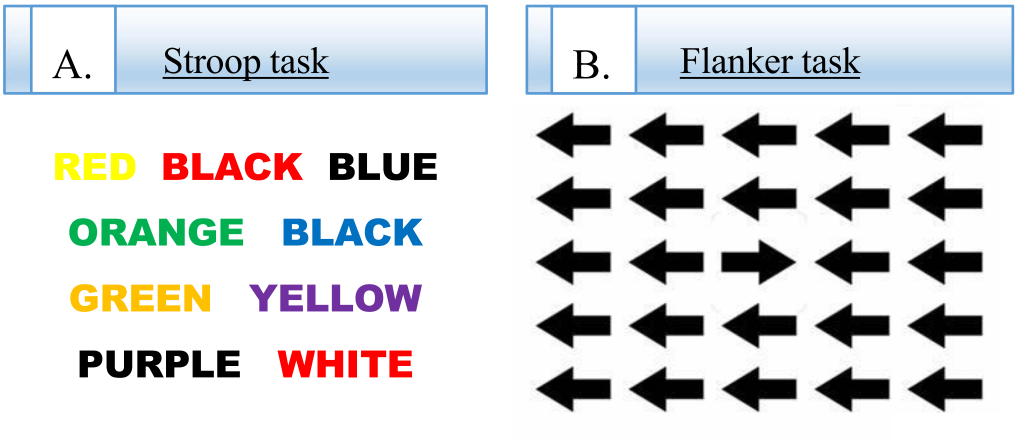

Figure 1. An example of two common tasks for investigating inhibitory control, and not interference control **A:** Stroop task, **B:** The Eriksen flanker task. In **A**. the color does not correspond to the color-name, and in **B**. one arrow is pointing in the opposite direction. Important to note here is that in both tasks the presence of conflict is within the presented stimuli-set. For example, resolving the conflict in **A.** requires to inhibit the reflexive urge to say the color, and instead say the word.

1.5.1 Interference control and age

The ability to control goal-irrelevant information, specifically to suppress PI, is impaired in older age (Hasher & Zacks, 1988). This deficit is discussed within the inhibitory-deficit theory and thought to contribute to impairments in multiple other cognitive domains together with WM (Hasher, Lustig, & Zacks, 2008; Stoltzfus, Hasher, & Zacks, 1996). Age-related deficits in IC might therefore account for some of the age-related decline in WM (Babcock & Salthouse, 1990; Bopp & Verhaeghen, 2007; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Park et al., 2002). Despite much evidence for older adults' susceptibility to PI, age differences are not consistently observed in tasks assessing inhibition (Spieler, Balota, & Faust, 1996; Verhaeghen, 2011; Verhaeghen & De Meersman, 1998; Weeks & Hasher, 2014). A recent review paper argued that interference within the focus of attention, and interference retrieved into focus of attention was a key component in differences between cognitive tasks that showing clear age-differences, and those that do not (Lustig & Jantz, 2014). The concept of 'focus of attention', refers to the limited number of representations (4 +/- 1) that we are aware of at a given moment (Cowan, 2000). These arguments put forward by Lustig and Jantz (2014) suggests that interference during immediate attention is easier for older adults due to being less taxing on executive functions and retrieval processes, which are known impairments in old age. A clearer age difference in IC can therefore be expected when using cognitive tasks that stresses retrieval capabilities. A good example is the difference between a Stroop task (see section 1.1.3) and the n-back task (see section 3.2.1), where the n-back would involve retrieval into the focus of attention and thus to a higher degree depend on IC-related processes. The n-back task was for this reason used in three studies in the current doctoral thesis (**Studies II**, **III** and **IV**).

Older adults tend to rely more on familiarity driven-responses, mainly due to a compromised ability of recollection with advancing age (Koen & Yonelinas, 2016; Yonelinas & Levy, 2002). Familiarity is an implicit sense of recognizing a stimulus, regardless of contextual details, and is relatively well preserved in old age. On the other hand, recollection involves deliberate retrieval of details associated with a past episode, and is negatively affected by age (Koen & Yonelinas, 2016; Yonelinas & Levy, 2002). This discrepancy between familiarity and recollection becomes crucial when conflict in WM needs to be resolved accurately. Hasher and colleagues (1999) proposed an inhibitory function that restrains or suppresses interference from strong familiar cues. Similarly, the conflict-monitoring hypothesis interweaves both familiarity- and recollection-driven responses to be aided by a supervising monitoring unit (Botvinick, Braver, Barch, Carter, & Cohen, 2001). A deficit in this monitoring unit or inhibitory function may explain observed age-related declines in IC, leading to a greater influence of familiarity during conflict. The conflict-monitoring hypothesis has been postulated to protect WM against interference during updating by the monitoring unit, prioritizing recollection over familiarity in the midst of a conflict (Szmalec, Verbruggen, Vandierendonck, & Kemps, 2011).

1.5.2 Interference control and brain

The specific relationship between prefrontal brain engagement and IC in WM is unclear (Aron, Cai, Badre, & Robbins, 2015). EFs likely draw on multiple brain regions with separate, but interconnected, components (Friedman & Miyake, 2017), as highlighted in section (1.2). Despite the interplay between brain regions, this thesis project attempts to understand some of the separate and specific components of EFs mainly in prefrontal brain regions. There is support for such an approach in the literature. Regions central to IC are inferior frontal gyrus (IFG; (Atkins, Berman, Reuter-Lorenz, Lewis, & Jonides, 2011; Badre & Wagner, 2005; D'Esposito, Postle, Jonides, & Smith, 1999; Dulas & Duarte, 2016; Jonides & Nee, 2006; Nee et al., 2013; Nee & Jonides, 2009; Owen, McMillan, Laird, & Bullmore, 2005; Persson, Larsson, & Reuter-Lorenz, 2013; Rottschy et al., 2012), middle frontal gyrus (MFG; Anderson, Bunce, & Barbas, 2016; Benoit & Anderson, 2012; Benoit, Hulbert, Huddleston, & Anderson, 2015; Jonides & Nee, 2006; Ray Li, 2006; Rottschy et al., 2012), insula (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015; Nee, Wager, & Jonides, 2007; Rottschy et al., 2012; Wager et al., 2005; Xu, Xu, & Yang, 2016), and dorsal anterior cingulate cortex (dACC; Botvinick, Cohen, & Carter, 2004; Bush, Luu, & Posner, 2000). Apart from prefrontal regions, this doctoral thesis also covers the medial temporal lobe (MTL) as an additional region of interest in **Study III**. The involvement of MTL is prominent in IC and WM (Öztekin & McElree, 2007; Öztekin, McElree, Staresina, & Davachi, 2009), and is critical to long-term memory retrieval (Badre & Wagner, 2007). Furthermore, MTL is critical for efficient memory encoding that involves associative binding (Addis & McAndrews, 2006), and responsible for strengthening goal-relevant features during long-term memory encoding (Blumenfeld & Ranganath, 2007).

2 AIMS

2.1 General aims

The overall aim of this doctoral thesis is to elucidate basic processes of interference control in WM, and delineate how these processes might be altered in aging.

2.2 Specific aims

The general aim was addressed in four separate studies. The specific aim of each study is described below:

1. To investigate brain and behavioral adjustments to a high-interference context, using functional magnetic resonance imaging (fMRI) and several behavioral experiments. (**Study I**)

2. To examine age differences in the temporal properties of proactive interference in WM in younger and older adults. (**Study II**)

3. To extend the findings of Study II by also investigating the neural mechanisms of these temporal boundaries, using fMRI. (**Study III**)

4. To investigate the link between interference control and prefrontal brain volumes in younger and older adults, both cross-sectionally and longitudinally. (**Study IV**)

3 MATERIALS AND METHODS

3.1 Study samples

This doctoral thesis is based on five independent convenience samples (**Studies I**, **II**, and **III**). This thesis also contains data from the population-based Betula study (**Study IV**). Below is each sample described in detail:

3.1.1 Sample characteristics for studies 1-3

Studies I, **II**, and **III** were based on several different data collections and cognitive experiments. Each data collection is described below:

1. Eighty-nine younger adults (20 men; age range: 18–30 years) were recruited for one behavioral experiment in **Study I**. All participants were recruited from the Stockholm University community, mostly through posted advertisements. All participants were native Swedish speakers and had normal or corrected to normal vision. Participants were assigned to one of two groups: one received the high-interference version of the recent-probes task, and the other group received a low-interference version of the recent-probes task. The groups were matched on age and sex.

2. Thirty-two healthy young adults (16 men; age range 19–28 years) were recruited for one behavioral experiment in **Study I**. All participants were recruited from the Skövde University community. All participants were native Swedish speakers, right-handed, and reported normal or corrected to normal vision. In a randomized counterbalanced within-subjects design, participants performed a high- and a low-interference version of the recent-probes task on a computer. To avoid context effects that might occur in a test session, participants were tested on two separate days.

3. Thirty-two younger adults (24 men; age range: 18-30 years) were recruited for one fMRI experiment in **Study I**. All participants were recruited from the Umeå University community through posted advertisements. They were all right-handed native Swedish speakers, who reported no existing neurological or psychiatric illness. Vision was normal or corrected near normal using MRI compatible glasses or contact lenses. Participants first completed health screening over the telephone to ensure that they were suitable to take part in an fMRI session. Participants were assigned to one of two groups: one received the high-interference version of the recent-probes task, and the other received a low-interference version of the same task.

4. Fifty-four healthy younger adults (17 men; age range: 18-31 years) and fifty-nine healthy older adults (17 men; age range: 65-80) were recruited for two behavioral studies in this thesis (**Studies I** and **II)**. All participants were recruited from the Stockholm area, through flyers, local newspaper ads, and web pages. All participants were native Swedish speakers and had normal or corrected to normal vision. None of the participants were diagnosed with cognitive impairments or had a history of neurological disease. Participants answered several questionnaires before being tested on two tasks, a 2-back task, and a recent-probe task.

Participants were assigned to one of two groups: one received a high-interference version of the recent-probe task, and the other received a low-interference version of the same task. The age groups were balanced across the two interference groups.

5. Twenty-four healthy younger adults (11 men, age range: 18-35) were recruited for one fMRI experiment in **Study III**. All participants were recruited from the Stockholm area, through another large-scale behavioral study, and by word-of-mouth. All participants spoke and understood English fluently (the task included English words as experimental stimuli), had normal or corrected to normal vision, and were right-handed. Individuals with neurological conditions, or with past surgery and therefore unfit for MRI scanning were excluded.

3.1.2 The Betula study

The population-based Betula study started in 1988 and is an ongoing, longitudinal study, undertaken in the area of Umeå, Sweden (Nilsson et al., 1997). The Betula study aims to investigate memory and health factors across the adult life span by mapping cognitive and biological markers of dementia, and successful aging. To date, Betula involves six data collection waves, T1: 1988-90, T2: 1993-95, T3: 1998-00, T4: 2003-05, T5: 2008-10, T6: 2013-2015, and is still ongoing. All individuals undergo extensive cognitive and health assessments. There are in total approximately 4500 individuals partaking in this study. Some of the individuals were not tested at each test wave, and new samples were added in almost each test wave. This is partly done to control for test-retest effects on cognitive tasks, and due to new emerging hypotheses, but also to fill in for the attrition and drop-out over the years.

The ImAGen cohort

A large brain imaging data collection was initiated under the name ImAGen at the fifth collection wave of the Betula study. ImAGen is an acronym for **Im**aging **A**ging and **Gen**etics, and data were used for **Study IV** in this thesis. The ImAGen project started 2008 with 376 individuals, and has been followed up once already in 2013-15. The 376 individuals were contacted and drawn from the sample 1, 3 and 6 in Betula, and had successfully completed the cognitive testing at T5. Selection of individuals to ImAGen was stratified by age and gender, but blind to cognitive performance and other personal characteristics. Each individual was screened before including the individuals in the MR experiment. Individuals who had any of the following were excluded: metal implant(s), pacemaker, were pregnant, have had a stroke, have had heart/brain surgery, low motoric function, and severe visual impairment.

3.2 Cognitive tasks

This doctoral thesis contains two WM tasks: the n-back task (**Studies II**, **III**, and **IV**) and the recent-probe task (**Study I**). Each task was modified from their original versions by including trials in which the need for interference control is high. Details for the cognitive tasks is described below:

3.2.1 n-back task

The n-back is a widespread WM task where IC can be investigated by including lure items as familiar, but goal-irrelevant information (Gray, Chabris, & Braver, 2003; Jonides & Nee, 2006; Kane, Conway, Miura, & Colflesh, 2007; Loosli, Rahm, Unterrainer, Weiller, & Kaller, 2014; Mccabe & Hartman, 2008; McElree, 2001; Marklund & Persson, 2012). In an n-back task, each item is presented in a continuous manner, one at a time. An item could be a letter, a number, a word, or a picture. The idea is that participants have to decide (‘Yes’ or ‘No’) whether or not the current item they see matches the item presented “n” items back. “n” can be any positive whole number, and for this thesis that number was 2 for all experiments that included the n-back task (**Studies II**, **III**, and **IV**). This means that each item that has been presented exactly 2 words ago is a target trial, and should be answered ‘Yes’. Interference arises when re-occurring items are displayed on a position other than n = 2, (e.g. 3-back). These trials are referred to as ‘lure trials’ and requires IC for an accurate response. Increased need for IC associated with lure trials results in less accurate and slower responses compared to non-lures (Jonides & Nee, 2006; Kane et al., 2007).

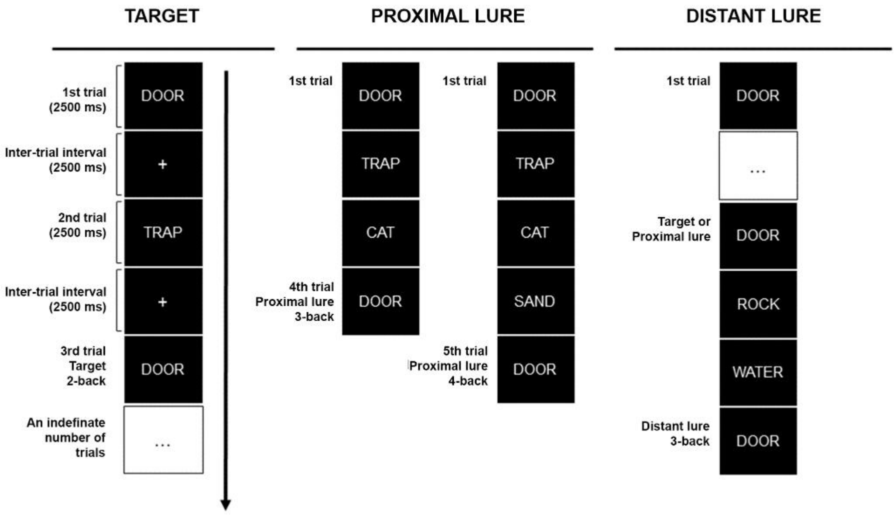

Figure 2. An overview of all trial conditions in a modified 2-back task. Each square represents what is presented on a computer screen. The images are presented one at a time, in order, and the image is either a fixation cross or a word. Each word has to be answered either yes or no if it corresponds to the word presented two words earlier (2-back position; Target). There were four conditions in total: non-familiar trial (new items), target trial, proximal lure, and distant lure.

The n-back task is typically described as an updating task, being rather difficult (especially for older adults) due to the high demand on cognitive control processes. Updating of information in WM is cognitively demanding, and is present in tasks where information in WM is actively manipulated to cope with changing circumstances. For example, a specific context has to be assigned to each new item presented in an n-back (e.g. “This is the most recent item I have seen”), while former items re-assigned their context (e.g. “This *was* the 2nd recent item I had seen, but is *now* the 3rd recent item”). Thus, information in WM has to be continuously updated as the task progresses. Lure trials are therefore usually more difficult since they interfere with the updating process. Much of this doctoral thesis is focused on the difference between target and lure trials, as a proxy for the level of interference (see section 3.3.1). This difference (if positive) can be taken as an indicator of extra effort that was required to resolve interference.

3.2.2 Recent probes task

The recent probes task is based on the item-recognition task devised by Sternberg (1966). Similar to n-back, the recent probes task has been used extensively (Jonides & Nee, 2006; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998) to examine how IC can be related to behavioral and neural outcomes. The task can be divided into three separate stages: First, a number of stimuli (usually 4-6 items) are simultaneously presented as a target set. Every item in the target set needs to be encoded and maintained for a while, until a probe is presented, in the form of a single item. After the probe is presented the participant must decide whether the probe matches one of the items in the target set just presented. Some probes are designed to match the target set, while others are not. The task continues by presenting a new list of items and a corresponding probe. Interference arises when the probe is a letter shown in the previous set of letters, but not in the current set. Recent probes are prone to more errors and take extra time to answer correctly compared to distal probes (Neumann & Deschepper, 1992).

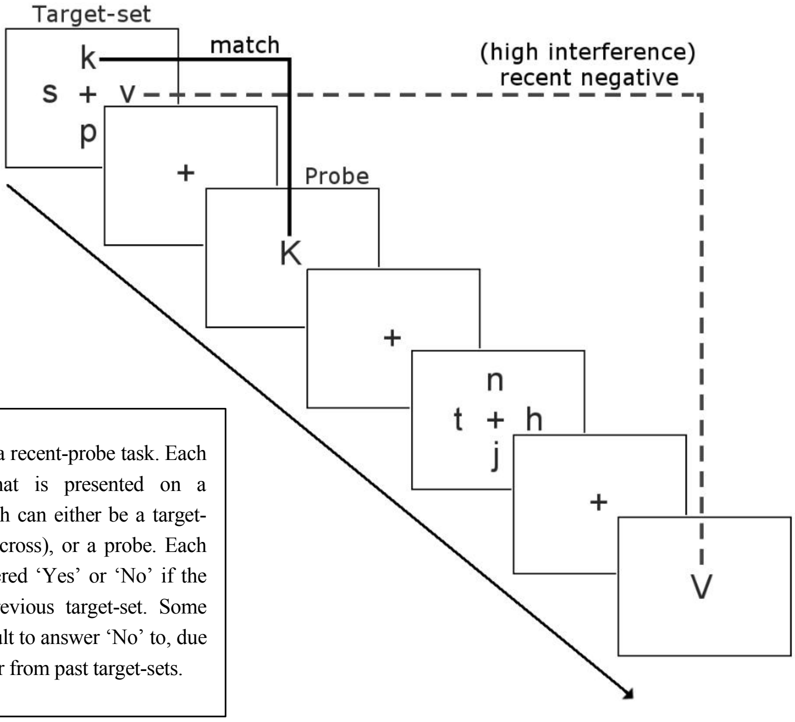

Figure 3. Example of a recent-probe task. Each square represents what is presented on a computer screen, which can either be a target-set, a waiting period (cross), or a probe. Each probe has to be answered 'Yes' or 'No' if the probe matches the previous target-set. Some probes are more difficult to answer 'No' to, due to recognizing the letter from past target-sets.

The Betula test battery

In **Study IV**, tasks from the Betula test battery were also included as off-line tests. These tasks are described in detail elsewhere (Nilsson et al., 1997). A short summary of each task is provided below:

Episodic memory

Episodic memory performance was measured by combining five episodic tasks. The first two tasks involved immediate free recall of action sentences (16 items each) that were either enacted or rehearsed without enactment. The number of sentences recalled (correct verb and noun) in the enacted and non-enacted conditions were used in the present analysis. In the next two conditions, and following a brief retention interval, participants were asked to recall as many nouns as possible from the sentences described earlier. The four categories (e.g., fruits, animals) to which each noun belonged served as retrieval cues. The final task was an immediate free recall test of 12 unrelated nouns. The maximum combined score was 76.

Block Design

The Block Design test was used to estimate fluid IQ. In this test, participants were asked to use colored blocks to produce spatial patterns presented on cards. The raw total number of correctly assembled blocks from a total of 51 trials was used (maximum score = 51). This test was originally extracted from the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981)

Word Fluency

Word fluency was determined by instructing participants to generate as many words as possible, during 60 seconds: (1) words starting with the letter ‘A’; (2) five letter words starting with the letter ‘M’; and (3) names of professions starting with the letter ‘B’.

Processing speed

Processing speed was assessed using three paper and pencil tests. In the first task (letter-digit comparison) participants were required to pair letters with digits according to a letter-digit-transformation key given on the top of the paper form with a time limit of 60 seconds. Participants’ score was based on the number of correct digits (maximum score = 125). The second task was a speeded comparison task where participants had to decide whether pairs of non-word 3-9 letter strings were identical or not. Participants’ responses were scored for each correctly judged pair during 30 seconds (maximum score = 21). The third speed test was similar to the second, but involved judging between pairs of abstract line figures during 30 seconds (maximum score = 30).

3.3 Outcome measures

3.3.1 Interference control

Interference control is commonly measured as the raw difference between new items (or non-familiar trials) and lure trials in n-back (e.g. Schmiedek et al., 2009), or recent probe tasks (e.g. Oberauer, 2001). In this doctoral thesis, we instead implemented a relative difference score by calculating the relative difference between non-familiar trials and lure trials, both for accuracy and RTs separately.

$$\left(\left(\frac{lure}{non\_familiar}\right)-1\right)*100$$

Interference is thus estimated by the relative difference (in %) between lure trials and non-familiar trials. A positive relative score implies that the lure trials were more difficult than the non-familiar trials. For example, an increase in RT or a decrease in accuracy would reflect being affected by PI. On the other hand, a close to zero or negative value hand would determine being unaffected by the lure trials. Using a relative measure aims to utilize a more salient estimate of IC effort than using only the raw difference. The main reason being that a relative measure controls for individual differences (e.g. age) in basic cognitive skills, such as processing speed (Salthouse, 1996), which can differ markedly between subjects. Interference scores based on accuracy data are referred to as accuracy interference score (AIS), and interference scores based on RT data are referred to as RT interference score (RTIS).

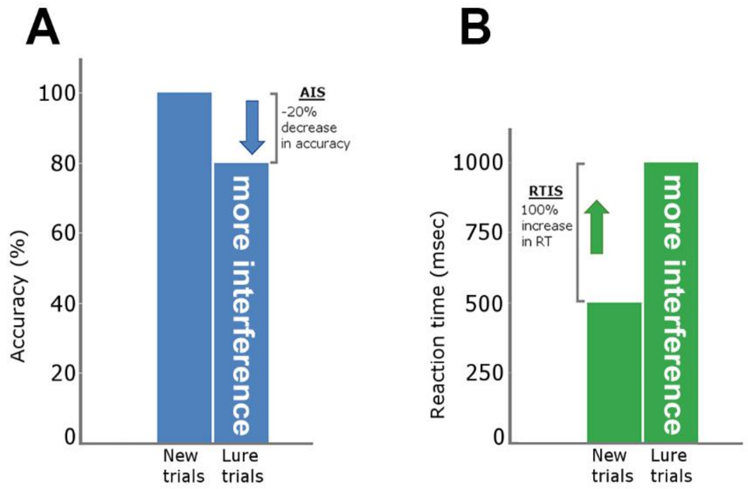

Figure 4. Two hypothetical examples illustrating the interference effect investigated throughout this doctoral thesis. **A**. Accuracy interference score (AIS), portrayed as a relative decrease from the easier new trial to the more difficult lure trial. **B**. Reaction time interference score (RTIS), portrayed as the relative increase from the easy new trials to the more difficult lure trials.

3.3.2 MRI assessment

This thesis includes brain scanning from multiple sites, with different MR scanners. Details for each scanner used, and corresponding sequence parameters for all protocols are described below.

In **Study I**, scanning was performed at the MRI research facility, Umeå University Hospital, Umeå, Sweden, using a Philips 3.0 Tesla high-speed echo-planar imaging device with a quadrature head-coil. Structural high-resolution T1-weighted images were acquired using a

3D turbo field-echo sequence with the following parameters: repetition time: 10.5 ms, echo time: 5 ms, flip angle: 8°, and field of view: 24 x 24 cm, and 170 slices with a slice thickness of 1 mm. Functional scanning parameters were as follows: repetition time: 1512 ms, echo time: 30 ms, flip angle: 70°, field of view: 22 x 22 cm, matrix: 64 x 64, and 31 slices with a slice thickness of 4.65 mm.

In **Study III**, scanning was performed at the MR Research Center, Karolinska Institutet, Solna, Sweden, using a General Electric Discovery MR750 3.0 Tesla scanner and an 8-channel head coil. Structural T1-weighted images were acquired using a 3D spoiled fast gradient echo sequence (SPGR) with the following parameters: repetition time: 8.2 ms, echo time: 5 ms, flip angle: 12°, field of view 25 x 25 cm, and 170 slices with a slice thickness of 1 mm. Functional scanning parameters were as follows: repetition time: 2000 ms (42 slices acquired), echo time: 30 ms, flip angle: 70°, field of view: 25 x 25 cm, and 42 slices with slice thickness of 3 mm.

In **Study IV**, scanning was performed at the Umeå University Hospital, Umeå, Sweden, using a General Electric Discovery MR750 3.0 Tesla scanner and a 32-channel head coil. Structural T1-weighted images were acquired with a 3D spoiled fast gradient echo sequence with the following parameters: repetition time: 8.2 ms, echo time, 3.2 ms, flip angle: 12°, field of view: 25 x 25 cm, and 180 slices with a 1 mm thickness.

3.3.3 Structural MRI

In **Study IV**, we measured grey matter volume. Within the central nervous system, we find the highest density of neuronal cell bodies in the grey matter. These are the brain cells that have been shown to be involved in all cognitive functions. (Miller, Alston, & Corsellis, 1980).

There are several different ways to extract grey matter volumes using MRI data. Manually delineating brain regions, for example, requires expertise and a lot of time. Even though manual segmentation of brain regions is considered the gold standard, there are automatic tools that can estimate deep and difficult-to-assess cortical regions in the brain with high accuracy (Morey et al., 2009). In this doctoral thesis we extracted grey matter volumes from T1-weighted images using FreeSurfer software (version 5.3.4; http://surfer.nmr.mgh.harvard.edu). Automated cortical and subcortical parcellation tools in the FreeSurfer software were used for volumetric segmentation, cortical surface reconstruction, and parcellation to quantify the brain volumes of interest. Cortical reconstructions and volumetric segmentations were performed on all images by executing a semi-automatic processing step (recon-all) within this software (Dale, 1999; Fischl et al., 2002). Segmentations of cortical areas are based on a probabilistic atlas (see below 'Desikan-Killiany'). The automatic processing steps included: removal of non-brain tissue, Talairach transformation, volumetric segmentation, intensity normalization, tessellation of borders between grey- and white-matter boundaries, applying intensity gradients to localize grey matter/white matter and fluid boundaries in the images. Images from the baseline together with the follow-up were processed through the FreeSurfer longitudinal processing stream, creating a within-subject template for each individual participant, thus increasing the reliability of the segmentation and parcelation of brain regions (Reuter, Schmansky, Rosas, & Fischl, 2012). The cortical regions of interests (ROIs) used were based on the "Desikan-Killiany" atlas in FreeSurfer (Desikan et al., 2006). In addition, grey matter volume for every ROI in this thesis was calculated as a sum of corresponding measures in left and right hemispheres.

3.3.4 Functional MRI

Functional brain imaging attempts to discriminate signal from hundreds of thousands of small elements (voxels) every few seconds. A voxel is usually a 1.5 x 1.5 x 1.5 to 3 x 3 x 3 mm volumetric cube, and would normally contain several thousands of neurons. The measured signal in each voxel is a proxy of how much the containing neurons are activated, during a task for instance. How it works is based on the demand for oxygen rising with cell activity, which in turn would change the balance of oxyhemoglobin (hemoglobin with oxygen attached) and deoxyhemoglobin (hemoglobin with no oxygen attached) in surrounding extra-cellular areas. Functional MRI captures this ratio on the basis of their differential magnetic susceptibilities, oxygenated hemoglobin being paramagnetic, and deoxygenated hemoglobin being diamagnetic, also referred to as the Blood-oxygen-level dependent imaging (BOLD). The active delivery of blood to supplement cells that are active is called the hemodynamic response and can be captured with statistical methods to later be related to behavior. However, there are several preprocessing and statistical steps before a functional image can become something of scientific importance.

MR-images are acquired in slices that cover the entire brain, but at different time-points within a specific time interval (usually 1.5 to 2 seconds). Meaning, there will be slices that are not aligned in time. This temporal displacement is corrected through a procedure known as slice timing. Secondly, head movement during the scanning session is corrected for by rigidly aligning each image volume to the first volume to the first volume in the series of images. Thirdly, all images are unwarped to correct for image distortions caused by interactions between head movement and inhomogeneities in the magnetic field. Fourth, the images are spatially normalized to a common space to be able to do group analyses, since every individual vary in shape, size and morphology of their brains. In **Study I**, the normalization step was to the Montreal Neurological Institute (MNI) template. In **Study III**, the normalization was in a two-step fashion by first normalizing to a sample-specific template (DARTEL, see below), based on the study sample, and thereafter normalized to MNI-space. This additional sample-specific template was created with SPM 12 using an algorithm named Diffeomorphic Anatomical Registration by means of Exponentiated Lie algebra, DARTEL for short (Ashburner, 2007). This normalization step is done by segmenting structural T1-images from each and every individual into grey and white matter components. These segmentations are imported to DARTEL space and averaged into one summarized template. Using this template, the deformation of each individual was computed. The inverse of these results were applied to the individual's grey/white-matter image. A new template was created from the mean of the deformed individual-specific images. Furthermore, this procedure was iterated six times to create a final template. T1-weighted images from each participant was then normalized to the final template using individual-specific flow fields. Finally, the normalized data is smoothed by averaging data over adjacent voxels using a Gaussian spatial filter. Both **Study I** and **III** used a size of 8 millimetres for this filter. In general, smoothing improves the signal-to-noise ratio and the validity of statistical tests by averaging the signal, making parameter errors more normally distributed.

The most commonly used method to analyze fMRI data is to consider the BOLD-signal from each voxel as a separate dependent variable. The effects from the experimental manipulations are thereafter modeled using multiple regression, i.e a (Friston, Poline, Holmes, Frith, & Frackowiak, 1996). In short, expected time series for each voxel are modeled with general linear model (GLM). In this approach, the changes in signal intensity during an fMRI session is defined by a set of regressors (i.e., predictors). These regressors are used for each condition in the experimental task, and then convolved with the hemodynamic response function. The vascular system response to brain activity is very sluggish and covers several seconds, whereas brain activity is immediate and within a few milliseconds. All studies in this thesis project used event-related designs which means that each trial was treated as a separate event, and each condition was specified by a regressor in the model independently from the other conditions. Moreover, when the model with all the regressors has been specified (i.e. the design matrix), each regressor is then further estimated to find the combination of parameter weights that minimized residual and unexplained variance, compared to the measured time-course of the voxel. As a result, the effects of the regressors can be tested statistically at the voxel-level. How this is tested is first by setting up a contrast on an individual-level, for example a contrast between two conditions in a task (lure trials vs. non-familiar trials). fMRI does not assess absolute levels of activation, but rather compares and tests between two activity patterns to see if they differ. Simply put, an estimated difference in parameter weights between the contrasting conditions is being tested for each voxel in the brain. A group based analysis is made by combining multiple contrasts from the individual-analysis and then tested using t-test or F-test. Voxels or clusters are normally thresholded at a predetermined alpha-level (e.g., $p < 0.001$) to determine which voxels show statistically significant effects. In other words, how likely it is that the activity is related to the condition manipulation, on a group-level. For instance, in **Study I** groups were tested for significant differences using a family-wise error cluster corrected threshold $P < 0.05$, based on an auxiliary uncorrected voxel-wise threshold of $P < 0.001$.

Region-of-interest (ROI) analysis is a little different from a voxel-based approach, and involves analyses of BOLD signal from a selected set of a priori preselected brain regions. In this way, there are less voxels in the statistical analysis to compare between, reducing the amount of corrections needed and consequently type II errors (false negatives). For example, apart from the whole brain analysis in **Study III**, five a priori brain regions were selected for ROI analyses. The software Marsbar toolbox (http://marsbar.sourceforge.net/) was used to create these ROIs, and to extract each ROI's mean BOLD parameter estimate value for each condition and participant. The parameter estimates were then used for plotting the results in SPSS statistics software (Version 25.0, IBM Corp.), as well as for brain – behavior correlations.

Functional images in this doctoral thesis were pre-processed and analyzed using versions 8 or 12 of Statistical Parametric Mapping (SPM; Wellcome Department of Imaging Science, Functional Imaging Laboratory) implemented in Matlab versions 7.6 or 9.3 (Mathworks Inc., MA, US).

3.4 ETHICAL CONSIDERATIONS

Ethical permissions have been obtained to cover all parts of this doctoral thesis (2007-871-31, 2013-92-31M, 2014-2212-31-1).

There are some aspects of data collection that could be considered demanding for some participants. First, a considerable amount of time is required from some of the participants in order to complete all questionnaires. Second, the entire session in **Study III** was demanding in terms of time spent inside the MRI scanner. The long MR-scanning and other behavioral sessions are taken into account by including a break in the scanning session after half of the data have been acquired, or a break between questionnaires and the cognitive task. During the break, the participant will be served refreshments and evaluated if eligible to continue. Both an oral and a written consent is signed by each participant before all experiments. Participants are informed that they can drop out from the study at any moment without needing to provide any explanation. MRI scanning in general is non-invasive and considered as harmless. Permission from the principal investigator is required before using any of the data collected. Completed questionnaires are kept in locked drawers. All researchers involved in these projects use anonymized data where each participant is identified by a coded number without any reference to the person's name or personal ID.

The personal ID numbers of every participant are replaced during the MRI scanning with a code before any analysis is conducted. The same applies to behavioral testing, where each subject is characterized by a code, and no personal ID information. The information that connects the participants' ID with the code is stored by the principal investigator, separate from any files of brain imaging and behavioral data. The structural and functional MRI data for each participant are only used for scientific purposes and will not be used by us to diagnose any disease. T2-weighted FLAIR images are routinely collected for all projects at the MR-center in both Solna and Umeå, and further evaluated by a clinician for each participant as a precautionary measure. The participant is contacted if abnormalities are found in the clinical images.

4 MAIN RESULTS

The main results from all four studies included in this doctoral thesis are summarized below. Please see the published papers and manuscripts at the end of this thesis for more detailed information.

4.1 Study I

Complementary analysis using behavioral data from experiment 1, 2, 3 and 4.

Study I consisted of 4 separate experiments, in which participants performed either a high or a low-interference recent probes task. Data from the four experiments were combined into a complementary analysis to estimate the overall effects. We found that RTs on non-recent negative trials and positive trials were faster for participants in the high- than in the low-interference group. Similarly, we found that accuracy was higher for both the positive trials and the non-recent negative trials, in the high-interference group. RTs and accuracies were similar across experiments, indicating no big difference between the experiments. Also, there were no interaction effects in the complementary analysis.

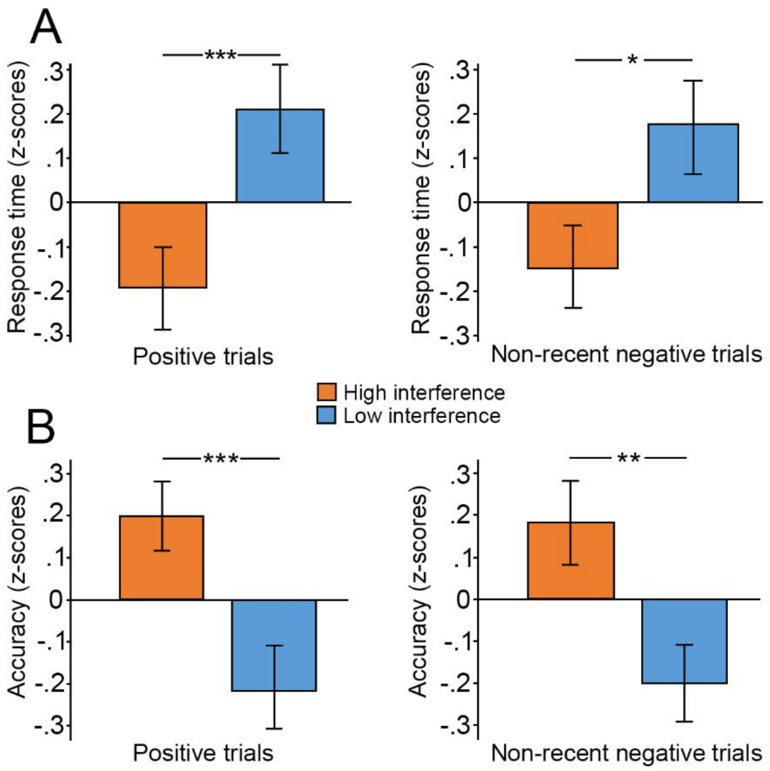

Figure 5. Normalized z-scores showing differences in performance between the group that did the high-interference version of the recent probe task, compared to participants doing the low interference version. **A.** Reaction times, lower reaction times being better, for both positive and non-recent negative trials. **B.** Accuracy, higher accuracy being better, in both positive and non-recent negative trials. Asterisk indicate main effect (*P < 0.05; **P < 0.01; ***P < 0.005)

Unique contributions from each behavioral experiment

In Experiment 1, we additionally looked for known trial-to-trial effects that precedes high interference trials. We found that no-interference trials proceeding high-interference trials took as expected more time to respond to, and had lower accuracy than no-interference trials following other no-interference trials. This trial-to-trial effect was in contrast to the overall effect of having high-interference trials in the task, as seen in the complementary analysis. The context sensitive adjustments due to a high-interference context were therefore above and beyond the trial-to-trial negative effects.

In Experiment 2, context sensitive adjustments could be observed also using a within-group design, in which participants performed the two versions of the task on separate days. The high-interference task still induced improved performance on the no-interference trials within the same task.

In Experiment 3, we found that a higher task-load (from 4-load to 6-load) reduced the context effect and that participants in the high- and low-interference groups performed at the same level. A higher task-load did not show any positive improvement in the high-interference context for the other trial-types.

Greater prefrontal brain activity in the high-interference group

In Experiment 4, we studied differences in brain activation in the high- and low-interference groups for positive probes, which is one of the other trial-types beside high-interference trials (recent negative trials). Brain activity in the high-interference group was greater in striatum (putamen), mesencephalic substantia nigra/ventral tegmental area (SN/VTA) of the midbrain, bilateral IFG, insula, premotor cortex, supplementary motor area/anterior cingulate cortex (SMA/ACC), angular gyrus, and medial temporal lobe (MTL). Additionally, the high-interference group exhibited greater deactivation in two regions of the default-mode network, the caudal posterior cingulate cortex/precuneus and medial ventral PFC. For the non-recent negative trials, the high-interference group showed greater activity in the bilateral putamen, left thalamus, SMA, and insula.

4.2 Study II

Lure trials are more difficult to control for older adults than younger adults

We used a long-range set of distant lure trials (3- to 10-back) to examine the temporal boundary conditions of proactive interference (PI) in younger and older adults. We showed that PI was present for the most proximal lures (3-back & 4-back) and that older adults were more affected than younger adults. Younger adults had overcome almost all influences of interference for distant lures 5-/6-back and onward. Lure trials presented up to 10-back still affected older adults negatively, with slower RTs and lower accuracy. This indicates that overall, older adults are more affected by PI, and especially have problems dealing with distant goal-irrelevant information while performing a current goal-directed task.

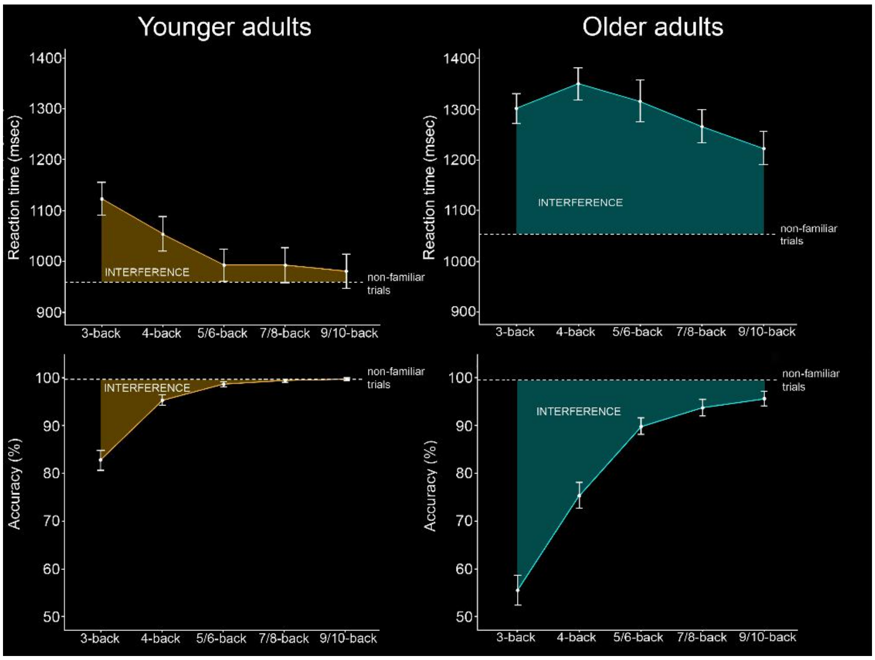

Figure 6. RTs and accuracy values for different lure trial distances (3- to 10-back) in a 2-back task. A comparison of the level of interference between older and younger adults. The highlighted area depicts the level of interference. The dotted line represents performance on new trials (non-familiar).

4.3 Study III

A reduction in proactive interference is linked to reduced activity in prefrontal brain regions

Similar to **Study II**, a long-range set of distant lures (3- to 10-back) were used to examine the brain activity patterns during control of PI. We extracted IC-relevant ROIs to examine signal changes across lure distance. First, we observed that the behavioral effect of PI was reduced with increasing lure distance. Second, brain activity in IC-relevant brain regions also decreased with increasing lure distance in left lateral IFG and dorsal ACC. This decrease was coupled with an increase in left anterior hippocampal activity, showing a shift of brain involvement when resolving PI with increasing lure distance. A MTL-based transition in WM was needed to successfully resolve conflict from more distal lures, indicating a long-term memory involvement.

In an additional analysis we also compared two different lure trials having same lure distance (3-back), to examine whether trial repetition reduced PI in WM. To achieve this, we separated between lure trials that had been presented first as a new item, and then as a lure, compared to lure trials presented an additional time on top of that (recycled). We observed less PI and lower activity in left lateral IFG and dorsal ACC for recycled lure trials. Dealing with the same distance lure trials required less prefrontal activity and were faster to respond accurately to.

Lure trials that cause interference activate prefrontal regions to a greater extent than lure trials that do not cause interference

We separated each lure trial into two groups, high interference and no interference, depending on how much each lure influenced behavioral performance. We found that high interference lure trials were associated with greater activity in bilateral IFG, MFG, and dorsal ACC, along with parietal and temporal areas. In addition, lure trials that evoked no interference showed no extra brain activity compared to new trials, indicating that conflict might not be present in lure trials that have been overcome.

4.4 Study IV

Lure trials become more difficult to resolve with increasing age

To strengthen the results from **Study II** regarding age-related differences in IC, we examined the cross-sectional effect of age using relative measures of IC. We conducted a linear regression at the T5 sample, which showed that AIS decreased (worse performance) with age (from 25 to 85 years of age), whereas RTIS did not. In the T6 sample (4 years later) however, AIS showed the same pattern (worse performance) along with an increase in RTIS (worse performance) across age. We found no 4-year change-change relationship between age and RTIS/AIS. Increasing age was thus linked to a reduced ability to accurately resolve proximal interference, and also to a need for more time to resolve interference.

Individuals with superior ability to control interference had larger brain volumes in IFG and insula

Both at baseline (T1), and at follow-up (T2; 4 years later), we observed that larger volumes of specific prefrontal regions were linked to the ability to overcome PI in a 2-back task. A minority of individuals (T5: n=35, T6: n=29) were unaffected by PI, and had larger IFG and insula regions. None of the findings could be accounted for by differences in age, sex, education, mini-mental state examination (MMSE), cognitive scores, or total intra-cranial volume (TIV). Additional analyses were conducted where individuals were separated according to IFG volume, where the 27 individuals with the largest IFG volume were compared to the 27 individuals with the smallest IFG volume. Confirming the previous results, the group with larger IFG volumes had better IC. However, change in volume over time was not associated with change in IC.

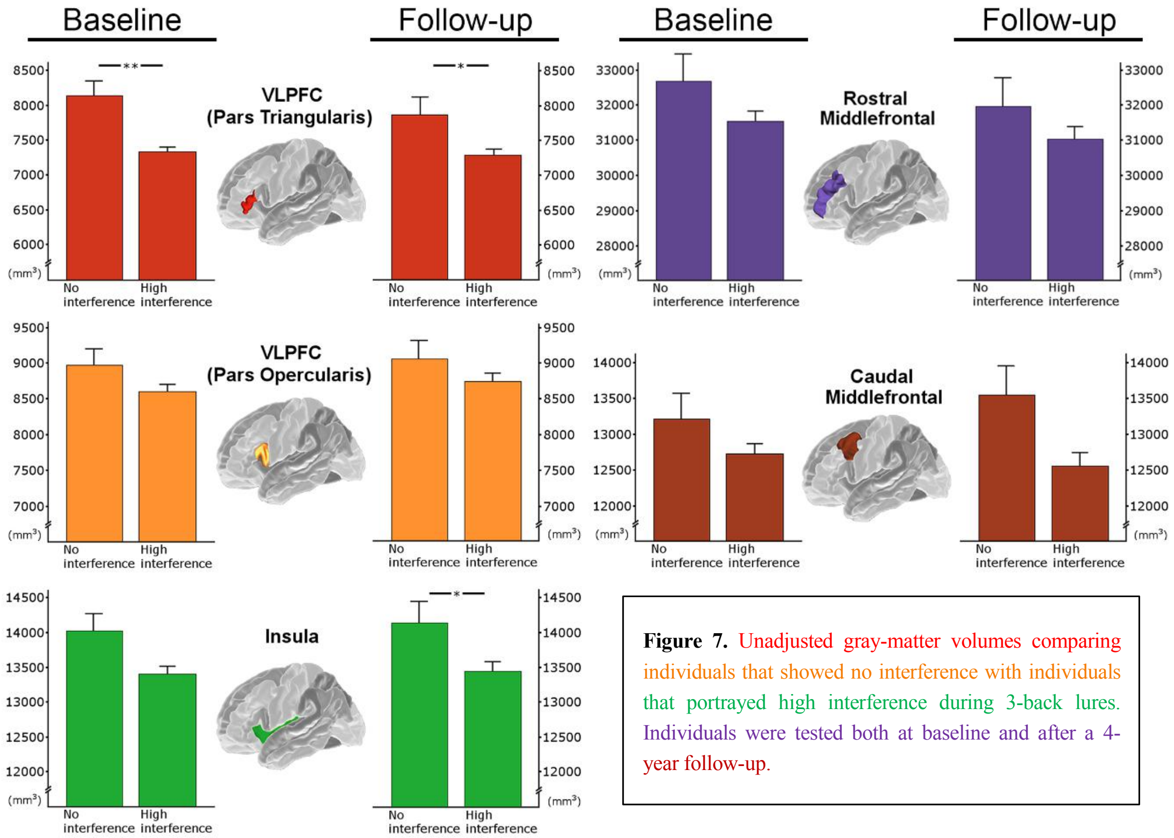

Figure 7. Unadjusted gray-matter volumes comparing individuals that showed no interference with individuals that portrayed high interference during 3-back lures. Individuals were tested both at baseline and after a 4-year follow-up.

Accuracy interference score was related to other cognitive measures

We determined the link between the AIS and RTIS measures and composite scores of episodic memory, processing speed, and word fluency from the Betula test battery. AIS was associated with performance on episodic memory, processing speed and word fluency for both time points tested. RTIS, on the other hand, was unrelated to all composite scores at both time points. Compared to target trial accuracy, the relative accuracy score (AIS) showed a stronger relationship to fluid intelligence.

5 DISCUSSION

The general aim of the current thesis was to explore neurocognitive mechanisms underlying interference control in WM. Four separate studies in this doctoral thesis have addressed this aim. The impact of each contribution is discussed below.

A high interference context improves performance on other trial types while engaging PFC

Well known trial-to-trial conflict adaption, or congruency effects (see Egner, 2007, for review) could be found in **Study I**, with non-interference trials being affected negatively if preceded by a high-interference trial. Results from **Study I** further showed that conflict adaptation effects are not restricted to congruency tasks, like the Stroop task (Szmalec et al., 2011). Intriguingly, in a high-interference context, RTs and accuracy were generally improved in all other trial-types in the same task (Experiment 1 & 2 in **Study I**). This may reflect adaptation to task difficulty more generally, or alternatively engage specific processes in response to a high-interference context, and that these effects generalize beyond trial-to-trial effects. Importantly, the improvements in performance evoked by a high-interference context was observed despite negative trial-to-trial conflict adaptation effects, indicating that this effect was sustained across the task and not just an accumulation of trial-to-trial effects. This pattern is in line with results from other studies using a similar task-manipulation (high recency/interference) showing that participants are largely unaware of the conflict in the recent probes task (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Nee, Jonides, & Berman, 2007). This suggests that observed improvements in performance are triggered implicitly rather than voluntarily, which is also in line with research pointing to cognitive processes being up-regulated from implicit cues (Chelazzi, Perlato, Santandrea, & Della Libera, 2013; Serences, 2008).

Adjustments due to a high-interference context may thus come from sustained engagement of cognitive control processes throughout the task, spilling over to all the other trial conditions. Supporting this claim, results from **Study I** showed a distinct difference in brain involvement for the high-interference group, specifically in bilateral IFG, insula, and ACC. These are brain regions known to be involved in executive control processes, and also play a key role in IC (Bush, Luu, & Posner, 2000; Nee et al., 2013; Rottschy et al., 2012; Wager, & Jonides, 2007). While the exact processes sub-served by these regions in response to a high-interference context remains unclear, results from **Study I** demonstrate that activation in these regions is upregulated in response to increased task demands, and that this upregulation is beneficial also for non-interference trials. Activity in these areas may reflect a conflict-triggered WM system that enhances performance on supposedly low interference conditions within the same task. Many other studies have found that experimentally manipulating variables such as effortful control (Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011; Jansma, Ramsey, De Zwart, Van Gelderen, & Duyn, 2007; Lim, Wu, Wang, Detre, & Dinges, 2010), task difficulty (Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Shigemune, Tsukiura, Nouchi, Kambara, & Kawashima, 2017), task preparation (Wylie, Javitt, & Foxe, 2006), alertness (Wang, Zhao, Xue, & Chen, 2016), and motivation (Jimura, Locke, & Braver, 2010) affects neurocognitive measures as well. Results from **Study I** are the first to extend this phenomenon to the field of IC in WM, linking neurocognitive upregulation to improved overall performance.

Unique characteristics of IC are revealed in brain and behavior by investigating the temporal boundaries of PI

The modified 2-back task used in this thesis covered a more extensive temporal window than related previous studies (Mccabe & Hartman, 2008; Schmiedek et al., 2009), by including distant lures up to 9-/10-back. In the 2-back task, younger adults overcame most of the negative effects from PI after a certain lure distance (5-/6-back), whereas older adults were still greatly affected by most distant lures (9-/10-back). Thus, **Study II** added novel information on age differences in how PI affects performance when the target-lure distance increases. Moreover, the combined results of **Study II,** and **IV** showed that older adults are less efficient in dealing with PI in general, both for proximal and distant lures. Age-related deficits in IC (e.g. Hasher & Zacks, 1988) were demonstrated in how strongly affected older adults were by the more distant lures.

However, there are several demonstrations of no age effects in susceptibility to interference (Spieler et al., 1996; Verhaeghen, 2011; Verhaeghen & De Meersman, 1998; Weeks & Hasher, 2014), indicating perhaps low executive demands. Age-related deficits in cognition may simply not extend to functions needed to suppress or inhibit impulses and habitual responses in inhibitory control tasks. One framework for explaining this common difference between cognitive tasks used to test age differences is discussed in a recent review article (Lustig & Jantz, 2014). They argued that age differences in IC performance are more evident in tasks in which interfering information have to be retrieved into the focus of attention, compared to resolving conflict between information already present in the focus of attention. In addition, there is evidence showing that older adults have a tendency to be affected negatively on later tasks after having unnecessarily encoded distracting items (Biss, Campbell, & Hasher, 2013; Campbell, Hasher, & Thomas, 2010; Thomas & Hasher, 2012). However, lure trials in an n-back task are all encoded with the assumption that they might return in the target 2-back position. Therefore, encoded items that are presented a second time as a lure trial were previously relevant to the task, but are now goal-irrelevant. Distractions, on the other hand, are inherently unimportant and goal-irrelevant pieces of information. The performance difference between younger and older adults were most profound at the most distant lures (9-/10-back), indicating age differences for information that has to be retrieved into the focus of attention (Lustig & Jantz, 2014). This idea also relates to findings showing preserved familiarity and impaired recollection in aging (Koen & Yonelinas, 2016; Prull, Dawes, Martin 3rd, Rosenberg, & Light, 2006). Older adults may thus rely more on familiarity-driven "match" responses rather than a recollection-driven "mismatch" response when resolving a lure trial (Szmalec et al., 2011). Task responses that are based on a familiarity signal can give rise to conflict because of a lack of contextual specificity. Recognizing an item is not sufficient for determining its proper and goal-relevant context.

PI decrements that occur with increased target-lure distance (Schmiedek et al., 2009; Shipstead et al., 2016) is somewhat expected. The reason for this is that if there is no mechanism by which interference is reduced with time, the vast amounts of information in our everyday life would overwhelm us. In **Study III** we demonstrated that IC-relevant regions in the PFC (IFG, MFG, and dorsal ACC) jointly decrease in activity when lure distance increases. Similarly, a proportional increase of activity and PI is seen in an associative memory paradigm (Dulas & Duarte, 2016), demonstrating increased cognitive effort to resolve greater conflict. In addition, an interaction between decreased activity in IFG and dorsal ACC along with increased left anterior hippocampus was observed, which may indicate a transitional shift from prefrontal (controlling interference from immediate representations) to MTL (relying on long-term representations). These results fit nicely with the idea that items outside the focus of attention necessitate long-term memory processes. This shift might also explain our results in **Study II** and **IV** showing a clear IC deficit in aging, and may reflect age differences in retrieval strategies in WM known to involve hippocampus (Anderson et al., 2016). The shift to hippocampus-based control would then be affected by age-related losses in hippocampal volume (Gorbach et al., 2017). Information in WM undergoes relatively superficial encoding, enough for immediate retrieval. There is little to suggest that MTL would be engaged in such short-term retrieval (de Vanssay-Maigne et al., 2011; Montaldi & Mayes, 2010). Instead, and in line with the shift seen in **Study III**, MTL is involved when the to-be-remembered information is retrieved from outside the focus of attention (McCabe, 2008; N. S. Rose, Craik, & Buchsbaum, 2015; Unsworth & Engle, 2007). Within the WM model proposed by Baddeley (2000), the observed shift to MTL-based control corroborates well with a limited-capacity WM system (the episodic buffer), which is capable of binding information from long-term memory, and relies heavily on attentional control. Moreover, **Study IV** only covered prefrontal regions when looking at grey matter volume and IC, and therefore no analyses of MTL volume were performed. Also, the 2-back task in **Study IV** only included proximal lures, and no distant lures. A 2-back task setup similar to that used in **Study II** or **III**, including distant lures, would be more appropriate for a morphological MTL analysis. Future studies that attempt to directly link IC to MTL structure and function, and aging, are therefore, warranted.

Overcoming proactive interference, a result of good interference control and larger PFC volumes

Younger adults were able to successfully overcome PI after a certain temporal distance, as demonstrated in **Study II** and **III**. **Study II** additionally revealed that, for younger adults, RTIS approached 0% at further lure distances. Nonetheless, in **Study II**, **III** and **IV**, there were already numerous trials at the most proximal lures where PI did not affect performance. The traditional way of estimating individual interference scores is to average RTs and accuracy scores for each condition of interest. As a result, the degree of interference would then be demonstrated as an average of all lure trials in that condition, and single lure trials which did not affect performance negatively would likewise be part of that average. However, even within a condition in which the degree of interference in presumably high on average (e.g. proximal 3-back lures), there are evidently single lure trials in which no behavioral effect is observed (i.e. similar performance as for non-interference trials). Is it because some lure trials are forgotten or do these items become unfamiliar? In **Study III,** participants performed an off-line recognition task approximately 45 minutes after the 2-back fMRI experiment, and results from this test showed that participants were highly accurate in recognizing the words used in the 2-back fMRI task. This demonstrates that the reduced interference observed with increased temporal lure distance is not related to forgetting the item per se, indicating that the degree of familiarity might not have as much influence on IC (Szmalec et al., 2011), and can be overcome. The selection of groups in **Study IV**, and trials in **Study III** was based on the assumption that some trials do not result in interference or cause effects on performance. These trials inherently differ from the same type of trials that cause interference, and this difference should have a biological basis in regions important for IC. Toward this end, both **Study III** and **IV** revealed structural and functional brain correlates of IC in WM.

A closer look into volumetric PFC differences between individuals who were not affected by PI, compared to those with low ability to control interference, showed that the unaffected individuals had larger IFG and insula regions than the interference group. All additional PFC regions that were included in the analyses showed an effect in the same direction, although these effects were not statistically reliable. That said, results in **Study IV** are most likely affected by the low number of participants in the no interference group (n=35 for T5 and n=29 for T6), thus reducing statistical power. Interestingly, none of the findings could be accounted for by differences in age, sex, education, MMSE, cognitive scores, or total intra-cranial volume (TIV), indicating that the primary results were relatively specific to the IC measures. These results corroborate past work showing a link between executive functions and PFC volume. For example, in a recent meta-analysis, it was found that larger PFC volume was associated with better executive performance (Yuan & Raz, 2014; see also Zimmerman et al., 2006). Moreover, some IC-relevant brain regions were close to being significantly bigger in individuals that were unaffected by interference, but did not reach the statistical threshold likely due to lack of power.

The findings from **Study III** showed functional IFG and ACC engagement for familiar lure trials compared to non-familiar trials, supporting many previous studies of increased activation in these regions during interference control (Nee, Jonides, et al., 2007). These results were further underscored by showing that bilateral IFG, MFG, and dorsal ACC were more activated in lure trials where the influence of conflict was high than in lure trials where conflict did not affect performance. This suggests that the active cognitive processes for resolving interference were different in lures that caused interference, compared to lures that did not affect performance. Accurately resolving PI in WM can therefore be divided into either overcoming PI or being affected by PI. In the current thesis, we managed for the first time to disentangle cognitive behaviors and neural underpinnings during PI in WM. The involvement of IFG, MFG, and ACC regions suggests that a present conflict is processed in high-interference lure trials, but less so for similar lure trials not affect performance. This likely reflects that no real conflict was present in the lure trials that did not negatively affect performance. Conceivably, IC-relevant brain regions are expected to be engaged during conflict, may it be during post-retrieval selection of competing information (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Badre & Wagner, 2007; Nee & Jonides, 2009), accurate control over the influence of familiarity- over recollection-based information (Feredoes & Postle, 2010), suppression of episodic retrieval in WM (Anderson et al., 2016; Benoit & Anderson, 2012; Benoit et al., 2015), or monitoring conflict in WM (Botvinick et al., 2004). Yet, no greater brain involvement was observed for lure trials that were overcome, strengthening the notion that no actual conflict was being processed in these trials. Activity in IFG is commonly demonstrated even in paradigms where accurate and inaccurate responses are intermixed in the analysis (Dulas & Duarte, 2016). IFG is critical to successfully resolving PI (Badre & Wagner, 2007) when conflicting information is retrieved. Taken together, there is an element of overcoming interference that is uniquely highlighted in this doctoral thesis, where PI has no direct negative influence on performance. **Studies III** and **IV** could demonstrate separate patterns of neuronal activity (low PFC activity), and separate grey matter volumetrics (larger PFC regions) in connection to this point.

One would assume that old age affects the ability to overcome interference in the same manner as old age affects many executive functions negatively, e.g. IC. An interesting observation in the present work is that a substantial number of both younger and older adults were unaffected by interference, indicating that many older adults managed to overcome interference to the same extent as younger adults, despite the repeatedly observed age-related PI deficit. All in all, the ability to overcome PI suggests a separate mechanism, not heavily taxing on executive functions that are active during current conflict. Overcoming PI might be found in preparatory processes not related to resolving the conflict at hand, like efficient encoding or good retrieval. Efficient encoding and/or accurate retrieval might affect the degree of actual conflict, but PI can theoretically still occur even if pieces of information are encoded well and accurately recollected. The lack of proactive interference for a subset of interference trials, together with similar brain engagement as non-interference trials may indicate that these trials could be successfully disconnect from previously encoded item-context episodes. Unbinding the item from its context would lead to that item familiarity can no longer can be associated with a previous, but now goal-irrelevant, context, thus not evoking conflict. This idea stems from evidence showing that WM representations do not decay (Berman et al., 2009; Lewandowsky, Geiger, Morrell, & Oberauer, 2010; Oberauer & Lewandowsky, 2013), but instead undergo an active removal process (De Beni & Palladino, 2004; Ecker, Lewandowsky, & Oberauer, 2013; Ecker, Oberauer, & Lewandowsky, 2014; Hasher et al., 1999). A similar brain activity pattern for lure trials that were overcome and new trials indicate that these two trial types were similarly resolved without conflict.

The validity of relative interference measures and the n-back task

The n-back has been shown through prior research to relate weakly to other WM measures (Kane et al., 2007; Redick & Lindsey, 2013), questioning the validity of n-back. Nonetheless, the n-back and WM-span are highly related to each other at the latent level, implying that higher-order cognitive constructs (e.g. WM) are difficult to capture effectively with specific tasks or paradigms. (Schmiedek, Lövdén, & Lindenberger, 2014). Apart from WM, the n-back is more than apt as a tool to investigate inter-individual differences in higher cognitive functions (Jaeggi, Buschkuehl, Perrig, & Meier, 2010), such as IC. This doctoral thesis has namely focused on IC, and IC-related mechanisms in WM, and not specifically WM at large. Further, this doctoral thesis has repeatedly demonstrated relationships between novel IC measures extracted from n-back to behavior, age, brain volume, and brain activity. By such, highlighting the usefulness of previously untapped measures from n-back to explain inter-individual differences in higher cognitive functions in WM.

In contrast to the majority of related studies, all stimuli in **Studies II**, **III** and **IV** were only shown a maximum of three times, and was thereafter not shown again. This allowed for greater lure-trial specificity, since every non-familiar trial was actually unfamiliar, resulting in a stronger contrast between unique and repeated items. The modest effects of PI seen in related work (e.g. Schmiedek et al., 2009) verifies this notion. In brief, small effects of PI in related work might be due to a limited number of stimuli being repeated multiple times throughout the task, as seen with n-back tasks that use letters or numbers. While being less familiar compared to familiar trials, the supposedly non-familiar trials may therefore induce interference, albeit at a lower level. Indeed, **Studies II**, **III** and **IV** suggest that the effects of interference may be long-lasting, and such effects are most likely observed in previous studies that used recycled items as stimulus material. First, older adults demonstrated long-lasting influence of PI in general, up to 9-/10-back or 35-40 s. To repeat stimuli within this temporal window (3- to 10-back) would evoke unwanted effects of PI on older adults. Second, immediately repeating a stimulus once, at an identical lure position, lowered the influence of PI and consequently IC-relevant brain activity. Careless stimulus repetition might therefore also attenuate desired PI effects.

The measures for IC were extracted from the same lure trials, but were different in their relation to brain volume, aging, and performance in other cognitive domains. The group separation in **Study IV** was based on RTIS cutoffs, as was the trial selection in **Study III**, allowing for more specific analyses of brain-behavior associations provided in this doctoral thesis. The novel use of a relative RT difference, instead of a raw difference, may help to overcome the otherwise problematic inter-individual differences that arise with age associated with processing speed (Salthouse, 1996, 2000). Using a relative approach for measuring interference was also implemented for lure-trial accuracy in **Study IV**, but not deemed necessary in the other studies due to the ceiling effects of non-familiar trials. Overall, accuracy measures were mostly utilized as a means to include accurately resolved lure trials. In summary, accuracy and RT estimates seem to capture separate cognitive processes involved in IC, and are known to be weakly correlated with each other in an n-back task (Redick & Lindsey, 2013). Accuracy and RT measures were not interpreted interchangeably, but were used in a complementary manner throughout this doctoral thesis.

5.1 Limitations and future directions

The findings presented in this doctoral thesis raises some questions and have several limitations worth considering. Some of the most major points are discussed below:

First, many of the associations made between brain and behavior in these studies do not explain causality. Therefore, any direct claims of underlying mechanisms surrounding IC still needs further inquiry. Nevertheless, much of this thesis work resulted in theory development and added new insights in the field of interference control. In particular, I believe that this doctoral thesis has increased the understanding on how the underlying mechanisms might operate. This was especially prominent in **Study III** where several neural underpinnings and temporal properties of IC could be specified. Observing the interplay between brain regions during IC, by using our IC-measures and task manipulations, would be of great interest. A sample of a likely interaction can be found in **Study III** where an independent PFC - MTL shift could be observed during WM operations. This relationship could be further explored by looking at functional connectivity measures between these two regions. In general, a major avenue for future research on IC would be to combine neuroimaging methods, or multi-modal imaging, perhaps in combining MRI with electrophysiological measures such as EEG/MEG. All of which may add to understanding the underlying IC mechanism during PI. None of the studies included in this doctoral thesis had more than one neuroimaging method applied. Future work could consider adding complementary information, like combining structural and functional data, and perhaps also resting state and white matter measurements. This would be more reliable than inferences drawn from cross-study observations.

In **Study IV**, the 2-back task was likely to have been poorly understood by participants, younger as well as older adults. Unfortunately due to this, many individuals in **Study IV** had to be excluded based on rather strict inclusion criteria with regards to performance. Results from **Study II** indicates that younger and older adults had no difficulties understanding a similar 2-back task, where even older adults (65-80 years old) performed really well. A difference from **Study IV** was that **Studies II** and also **III** included a detailed explanation of the task, and a test run to make certain that every participant understood the task. Moreover, individuals recruited for **Study II** are likely to be high-performing older adults and may thus not be representative of the population, compared to the not as biased selection in **Study IV**. Another reason for the generally poor performance in **Study IV** was the short task-run, resulting in a limited number of trials per condition. For example, there were eight lure trials (3-back lures) in total, and many participants had 0, 1 or 2 correctly answered lures. All in all, much of these factors inspired a strict inclusion criteria as a means to maintain a reliable basis for estimating average lure performance, both in accuracy and RT.

A major limitation of this doctoral thesis would be the narrow and perhaps limited approach to investigate IC, using only results from two different tasks to obtain measures of IC. It should be pointed out that a large portion of the variance in the results presented in this thesis was not explained by measures of IC drawn from a single 2-back task. Much of the remaining variance could be noise, but also an indication of the unspecific nature of EFs (Friedman &

Miyake, 2017; Stuss, 2011). The collective results are quite in line with recent evidence pointing to both a domain-general and a domain-specific neural involvement when resolving cognitive conflict (Hsu, Jaeggi, & Novick, 2017).

Another limitation is that a single-sample study design with only two measurement points was used in **Study IV**. Long-term trajectories of change was therefore not adequately determined with two measurement points. The 4-year follow-up period might not have been enough time to capture a change-change relationship between brain volume and performance. The design in **Study IV** did not permit independent estimations of test-retest effects either, which are known to influence longitudinal data (Ghisletta, Rabbitt, Lunn, & Lindenberger, 2012; Salthouse, 2013, 2014). Future work with three or more time points could reveal long-term trajectories of change that we are unable to show in the current study designs, and may also help in estimating test-retest effects.

6 ACKNOWLEDGEMENTS

I thank Christ Jesus our Lord, who has given me strength to do His work.
He considered me trustworthy and appointed me to serve him
(1st letter to Timothy, chapter 1, verse 12, The Scriptures)

First and foremost, I would like to give thanks and love to our Lord and redeemer, **Christ Jesus**. This doctoral thesis would never have been possible if it were not by humbling myself before God, and by picking up my cross daily, just like **Jesus** did.

I would like to express my deepest gratitude for my loving **family** (**Romel, Josephine,** and **Charbel**). Thank you for always praying for me and supporting me through trials and tribulation. I have truly been blessed with a loving and caring family, always eager to be there for me. This off course includes my **family in Christ** as well. I am truly undeserving such loving brothers and sisters, that regard me above themselves. Not to forget the many **friends** that have given their support throughout the years, I am very thankful for you all.

I want to highlight the pivotal roles of my main supervisor **Jonas Persson** and co-supervisor **Lars Bäckman** in leading me to complete this thesis work. The genuine eagerness to help me in every issue I bring forward is a privilege I know many students do not have. This despite the fact that I have raised many questionable matters over the years. Nonetheless, just like your office doors, your hearts were wide open to me, and I pray many more will experience the same reception and care I received from you, thank you.

Lastly, I would like to extend my gratitude to all my **colleagues**, past and present, Umeå and Stockholm, staff and researchers, Italian and non-Italian. To me, it is all just one big family. May the Lord bless your days to come, as you have been a blessing to me during my time at the Aging Research Center.

7 REFERENCES

Adam, K. C. S., Mance, I., Fukuda, K., & Vogel, E. K. (2015). The contribution of attentional lapses to individual differences in visual working memory capacity. *Journal of Cognitive Neuroscience*, *27*(8), 1601–16. http://doi.org/10.1162/jocn_a_00811

Addis, D. R., & McAndrews, M. P. (2006). Prefrontal and hippocampal contributions to the generation and binding of semantic associations during successful encoding. *NeuroImage*, *33*(4), 1194–1206. http://doi.org/10.1016/j.neuroimage.2006.07.039

Altmann, E. M., & Gray, W. D. (2002). Forgetting to remember: the functional relationship of decay and interference. *Psychological Science : A Journal of the American Psychological Society / APS*, *13*(1), 27–33. http://doi.org/10.1111/1467-9280.00405

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, *16*(1), 17–42. http://doi.org/10.1007/s11065-006-9002-x

Anderson, M. C., Bunce, J. G., & Barbas, H. (2016). Prefrontal–hippocampal pathways underlying inhibitory control over memory. *Neurobiology of Learning and Memory*, *134*, 145–161. http://doi.org/10.1016/j.nlm.2015.11.008

Aron, A. R., Cai, W., Badre, D., & Robbins, T. W. (2015). Evidence Supports Specific Braking Function for Inferior PFC. *Trends in Cognitive Sciences*, *19*(12), 711–712. http://doi.org/10.1016/j.tics.2015.09.001

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. http://doi.org/10.1016/j.neuroimage.2007.07.007

Atkins, A. S., Berman, M. G., Reuter-Lorenz, P. A., Lewis, R. L., & Jonides, J. (2011). Resolving semantic and proactive interference in memory over the short-term. *Memory & Cognition*, *39*(5), 806–17. http://doi.org/10.3758/s13421-011-0072-5

Babcock, R. L., & Salthouse, T. A. (1990). Effects of Increased Processing Demands on Age Differences in Working Memory, *5*(3), 421–428.

Baddeley, A. D. (2000). The episodic buffer: A new component of working memory? *Trends in Cognitive Sciences*, *4*(11), 417–423. http://doi.org/10.1016/S1364-6613(00)01538-2

Baddeley, A. D., & Hitch, G. J. (1974). Working memory. In G. A Bower (Ed.), *recent advances in learning and motivation* (pp. 47–90). New York: Academic Press.

Baddeley, A. D., & Hitch, G. J. (1976). Verbal reasoning and working memory. *Quarterly Journal of Experimental Psychology*, *28*, 603–621.

Baddeley, A. D., & Logie, R. H. (1999). Working Memory: The Multiple-Component Model. In A. Miyake & P. Shah (Eds.), *Models of Working Memory* (pp. 28–61). Cambridge: Cambridge University Press. http://doi.org/10.1017/CBO9781139174909.005

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends in Cognitive Sciences*, *12*(5), 193–200. http://doi.org/10.1016/j.tics.2008.02.004

Badre, D., Poldrack, R. A., Paré-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable Controlled Retrieval and Generalized Selection Mechanisms in Ventrolateral Prefrontal Cortex. *Neuron*, *47*(6), 907–918. http://doi.org/10.1016/j.neuron.2005.07.023

Badre, D., & Wagner, A. D. (2005). Frontal lobe mechanisms that resolve proactive interference. *Cerebral Cortex*, *15*(12), 2003–2012. http://doi.org/10.1093/cercor/bhi075

Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia*, *45*(13), 2883–2901. http://doi.org/10.1016/j.neuropsychologia.2007.06.015

Banich, M. T. (2009). Executive Function: The Search for an Integrated Account. *Current Directions in Psychological Science*, *18*(2), 89–94. http://doi.org/https://doi.org/10.1111/j.1467-8721.2009.01615

Benoit, R. G., & Anderson, M. C. (2012). Opposing Mechanisms Support the Voluntary Forgetting of Unwanted Memories. *Neuron*, *76*(2), 450–460. http://doi.org/10.1016/j.neuron.2012.07.025

Benoit, R. G., Hulbert, J. C., Huddleston, E., & Anderson, M. C. (2015). Adaptive top-down suppression of hippocampal activity and the purging of intrusive memories from consciousness. *Journal of Cognitive Neuroscience*, *27*(1), 96–111. http://doi.org/10.1162/jocn_a_00696

Berman, M. G., Jonides, J., & Lewis, R. L. (2009). In search of decay in verbal short-term memory. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *35*(2), 317–33. http://doi.org/10.1037/a0014873

Biss, R. K., Campbell, K. L., & Hasher, L. (2013). Interference from previous distraction disrupts older adults' memory. *Journals of Gerontology - Series B Psychological Sciences and Social Sciences*, *68*(4), 558–561. http://doi.org/10.1093/geronb/gbs074

Blumenfeld, R. S., & Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: An integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist*, *13*(3), 280–291. http://doi.org/10.1177/1073858407299290

Bopp, K. L., & Verhaeghen, P. (2007). Age-related differences in control processes in verbal and visuospatial working memory: storage, transformation, supervision, and coordination. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *62*(5), P239–P246. http://doi.org/62/5/P239 [pii]

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, *108*(3), 624–52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11488380

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences*, *8*(12), 539–546. http://doi.org/10.1016/j.tics.2004.10.003

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. E. (2002). Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. *Neuron*, *33*(2), 301–11. http://doi.org/10.1093/brain/124.10.2074

Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain : A Journal of Neurology*, *124*(Pt 10), 2074–86. http://doi.org/10.1093/brain/124.10.2074

Bunting, M. (2006). Proactive interference and item similarity in working memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *32*(2), 183–196. http://doi.org/10.1037/0278-7393.32.2.183

Burgess, G. C., Gray, J. R., Conway, A. R. A., & Braver, T. S. (2011). Neural mechanisms of interference control underlie the relationships between Fluid intelligence and working memory span. *Journal of Experimental Psychology. General*, *140*(4), 674–92. http://doi.org/10.1037/a0024695.Neural

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends.Cogn Sci.*, *4*(6), 215–222. http://doi.org/10.1016/S1364-6613(00)01483-2

Campbell, K. L., Hasher, L., & Thomas, R. C. (2010). Hypoer-binding: A unique age effect. *Psychological Science*, *21*(3), 399–405. http://doi.org/10.1177/0956797609359910

Chelazzi, L., Perlato, A., Santandrea, E., & Della Libera, C. (2013). Rewards teach visual selective attention. *Vision Research*, *85*, 58–62. http://doi.org/10.1016/j.visres.2012.12.005

Cieslik, E. C., Mueller, V. I., Eickhoff, C. R., Langner, R., & Eickhoff, S. B. (2015). Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. *Neuroscience and Biobehavioral Reviews*, *48*(4), 22–34. http://doi.org/10.1016/j.neubiorev.2014.11.003

Collins, A., & Koechlin, E. (2012). Reasoning, learning, and creativity: Frontal lobe function and human decision-making. *PLoS Biology*, *10*(3). http://doi.org/10.1371/journal.pbio.1001293

Cowan, N. (2000). The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and Brain Sciences*, *24*(1), 87–185. http://doi.org/10.1017/S0140525X01003922

D'Esposito, M., Postle, B. R., Jonides, J., & Smith, E. E. (1999). The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(June), 7514–7519. http://doi.org/10.1073/pnas.96.13.7514

Dale, a M. (1999). Optimal experimental design for event-related fMRI. *Human Brain Mapping*, *8*(2–3), 109–114. http://doi.org/10.1002/(SICI)1097-0193(1999)8:2/3<109::AID-HBM7>3.0.CO;2-W

De Beni, R., & Palladino, P. (2004). Decline in working memory updating through ageing: intrusion error analyses. *Memory (Hove, England)*, *12*(1), 75–89. http://doi.org/10.1080/09658210244000568

de Vanssay-Maigne, A., Noulhiane, M., Devauchelle, A. D., Rodrigo, S., Baudoin-Chial, S., Meder, J. F., … Chassoux, F. (2011). Modulation of encoding and retrieval by recollection and familiarity: mapping the medial temporal lobe networks. *NeuroImage*, *58*(4), 1131–8. http://doi.org/10.1016/j.neuroimage.2011.06.086

Demeter, E., Hernandez-Garcia, L., Sarter, M., & Lustig, C. (2011). Challenges to attention: a continuous arterial spin labeling (ASL) study of the effects of distraction on sustained attention. *NeuroImage*, *54*(2), 1518–29. http://doi.org/10.1016/j.neuroimage.2010.09.026

Dempster, F. N., & Corkill, A. J. (1999). Individual differences in susceptibility to interference and general cognitive ability. *Acta Psychologica*, *101*, 395–416. http://doi.org/10.1016/S0001-6918(99)00013-X

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. http://doi.org/10.1016/j.neuroimage.2006.01.021

Di Rosa, E., Pischedda, D., Cherubini, P., Mapelli, D., Tamburin, S., & Burigo, M. (2017). Working memory in healthy aging and in Parkinson's disease: evidence of interference effects. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *24*(3), 281–298. http://doi.org/10.1080/13825585.2016.1202188

Diamond, A. (2014). Executive Functions. *Annual Review of Clinical PsychologyPsychol.*, *64*, 135–168. http://doi.org/10.1146/annurev-psych-113011-143750.Executive

Dulas, M. R., & Duarte, A. (2016). Age-related changes in overcoming proactive interference in associative memory: The role of PFC-mediated executive control processes at retrieval. *NeuroImage*, *132*, 116–128. http://doi.org/10.1016/j.neuroimage.2016.02.017

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences*, *23*(10), 475–483. http://doi.org/10.1016/S0166-2236(00)01633-7

Ecker, U. K. H., Lewandowsky, S., & Oberauer, K. (2013). Removal of information from working memory: A specific updating process. *Journal of Memory and Language*, *74*, 77–90.

http://doi.org/10.1016/j.jml.2013.09.003

Ecker, U. K. H., Oberauer, K., & Lewandowsky, S. (2014). Working memory updating involves item-specific removal. *Journal of Memory and Language*, *74*, 1–15. http://doi.org/10.1016/j.jml.2014.03.006

Egner, T. (2007). Congruency sequence effects and cognitive control. *Cognitive, Affective & Behavioral Neuroscience*, *7*(4), 380–90. http://doi.org/10.3758/CABN.7.4.380

Engle, R. W., Laughlin, J. E., Tuholski, S. W., & Conway, A. R. A. (1999). Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *Journal of Experimental Psychology: General*, *128*(3), 309–331. http://doi.org/10.1037/0096-3445.128.3.309

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143–149. http://doi.org/10.3758/BF03203267

Feredoes, E., & Postle, B. R. (2010). Prefrontal control of familiarity and recollection in working memory. *Journal of Cognitive Neuroscience*, *22*(2), 323–330. http://doi.org/10.1162/jocn.2009.21252

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. http://doi.org/10.1016/S0896-6273(02)00569-X

Fjell, A. M., Sneve, M. H., Grydeland, H., Storsve, A. B., & Walhovd, K. B. (2017). The Disconnected Brain and Executive Function Decline in Aging. *Cerebral Cortex (New York, N.Y. : 1991)*, *27*(3), 2303–2317. http://doi.org/10.1093/cercor/bhw082

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *Journal of Experimental Psychology: General*, *133*(1), 101–135. http://doi.org/10.1037/0096-3445.133.1.101

Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*, *86*, 186–204. http://doi.org/10.1016/j.cortex.2016.04.023

Friedman, N. P., Miyake, A., Corley, R. P., Young, S. E., Defries, J. C., & Hewitt, J. K. (2006). Not all executive functions are related to intelligence. *Psychological Science*, *17*(2), 172–9. http://doi.org/10.1111/j.1467-9280.2006.01681.x

Friston, K. J., Poline, J. B., Holmes, A. P., Frith, C. D., & Frackowiak, R. S. (1996). A multivariate analysis of PET activation studies. *Human Brain Mapping*, *4*(2), 140–51. http://doi.org/10.1002/(SICI)1097-0193(1996)4:2<140::AID-HBM5>3.0.CO;2-3

Gathercole, S. E., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: Evidence from national curriculum assessments at 7 and 14 years of age. *Applied Cognitive Psychology*, *18*(1), 1–16. http://doi.org/10.1002/acp.934

Ghisletta, P., Rabbitt, P., Lunn, M., & Lindenberger, U. (2012). Two thirds of the age-based changes in fluid and crystallized intelligence, perceptual speed, and memory in adulthood are shared. *Intelligence*, *40*(3), 260–268. http://doi.org/10.1016/j.intell.2012.02.008

Gilbert, B., Belleville, S., Bherer, L., & Chouinard, S. (2005). Study of verbal working memory in patients with Parkinson's disease. *Neuropsychology*, *19*(1), 106–14. http://doi.org/10.1037/0894-4105.19.1.106

Glascher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., … Tranel, D. (2012). Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. *Proceedings of the National Academy of Sciences*, *109*(36), 14681–14686. http://doi.org/10.1073/pnas.1206608109

Goldman-Rakic, P. S. (1994). Working memory dysfunction in schizophrenia. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *6*(4), 348–57. http://doi.org/10.1176/jnp.6.4.348

Gorbach, T., Pudas, S., Lundquist, A., Orädd, G., Josefsson, M., Salami, A., … Nyberg, L. (2017). Longitudinal association between hippocampus atrophy and episodic-memory decline. *Neurobiology of Aging*, *51*, 167–176. http://doi.org/10.1016/j.neurobiolaging.2016.12.002

Gray, J. R., Chabris, C. F., & Braver, T. S. (2003). Neural mechanisms of general fluid intelligence. *Nature Neuroscience*, *6*(3), 316–22. http://doi.org/10.1038/nn1014

Hasher, L., Lustig, C., & Zacks, R. (2008). Inhibitory Mechanisms and the Control of Attention. In A. Conway, C. Jarrold, M. Kane, A. Miyake, & J. Towse (Eds.), *Variation in Working Memory* (pp. 227–249). New York: Oxford University Press. http://doi.org/10.1093/acprof:oso/9780195168648.003.0009

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view BT - The psychology of learning and motivation. *The Psychology of Learning and Motivation*. http://doi.org/10.1016/s0079-7421(08)60041-9

Hasher, L., Zacks, R. T., & May, C. P. (1999). Inhibitory control, circadian arousal, and age. In D. Gopher & A. Koriat (Eds.), *Attention and Performance XVII* (pp. 653–675). Cambridge, MA: MIT Press. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=1999-02468-022&lang=fr&site=ehost-live

Hedden, T., Lautenschlager, G., & Park, D. C. (2005). Contributions of processing ability and knowledge to verbal memory tasks across the adult life-span. *The Quarterly Journal of Experimental Psychology. A, Human Experimental Psychology*, *58*(1), 169–90. http://doi.org/10.1080/02724980443000179

Hsu, N. S., Jaeggi, S. M., & Novick, J. M. (2017). A common neural hub resolves syntactic and non-syntactic conflict through cooperation with task-specific networks. *Brain and Language*, *166*, 63–77. http://doi.org/10.1016/j.bandl.2016.12.006

Hubbard, N. A., Hutchison, J. L., Turner, M., Montroy, J., Bowles, R. P., & Rypma, B. (2016). Depressive thoughts limit working memory capacity in dysphoria. *Cognition & Emotion*, *30*(2), 193–209. http://doi.org/10.1080/02699931.2014.991694

Huber, S. J., & Paulson, G. W. (1987). Memory impairment associated with progression of Huntington's disease. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *23*(2), 275–83. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2956061

Huntley, J. D., & Howard, R. J. (2010). Working memory in early Alzheimer's disease: a neuropsychological review. *International Journal of Geriatric Psychiatry*, *25*(2), 121–32. http://doi.org/10.1002/gps.2314

Jacobs, R., Harvey, A. S., & Anderson, V. (2007). Executive function following focal frontal lobe lesions: Impact of timing of lesion on outcome. *Cortex*, *43*(6), 792–805. http://doi.org/10.1016/S0010-9452(08)70507-0

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent validity of the N -back task as a working memory measure. *Memory*, *18*(4), 394–412. http://doi.org/10.1080/09658211003702171

Jansma, J. M., Ramsey, N. F., De Zwart, J. A., Van Gelderen, P., & Duyn, J. H. (2007). fMRI study of effort and information processing in a working memory task. *Human Brain Mapping*, *28*(5), 431–440. http://doi.org/10.1002/hbm.20297

Jimura, K., Locke, H. S., & Braver, T. S. (2010). Prefrontal cortex mediation of cognitive enhancement in rewarding motivational contexts. *Proceedings of the National Academy of Sciences*, *107*(19), 8871–8876. http://doi.org/10.1073/pnas.1002007107

Jonides, J., & Nee, D. E. (2006). Brain mechanisms of proactive interference in working memory. *Neuroscience*, *139*(1), 181–193. http://doi.org/10.1016/j.neuroscience.2005.06.042

Jonides, J., Smith, E. E., Marshuetz, C., Koeppe, R. A., & Reuter-Lorenz, P. A. (1998). Inhibition in verbal working memory revealed by brain activation. *Psychology*, *95*(July), 8410–8413. http://doi.org/10.1073/pnas.95.14.8410

Kane, M. J., Conway, A. R., Miura, T. K., & Colflesh, G. J. (2007). Working memory, attention control, and the N-back task: a question of construct validity. *J Exp Psychol Learn Mem Cogn*, *33*(3), 615–622. http://doi.org/2007-06096-010 [pii]\r10.1037/0278-7393.33.3.615

Keppel, G., & Underwood, B. J. (1962). Proactive inhibition in short-term retention of single items. *Journal of Verbal Learning and Verbal Behavior*, *1*, 153–161. http://doi.org/10.1016/S0022-5371(62)80023-1

Kimberg, D. Y., & Farah, M. J. (1993). A unified account of cognitive impairments following frontal lobe damage: the role of working memory in complex, organized behavior. *Journal of Experimental Psychology. General*, *122*(4), 411–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8263463

Koen, J. D., & Yonelinas, A. P. (2016). Recollection, not familiarity, decreases in healthy ageing: Converging evidence from four estimation methods. *Memory (Hove, England)*, *8211*(January 2015), 1–14. http://doi.org/10.1080/09658211.2014.985590

Krebs, R. M., Boehler, C. N., Roberts, K. C., Song, A. W., & Woldorff, M. G. (2012). The involvement of the dopaminergic midbrain and cortico-striatal-thalamic circuits in the integration of reward prospect and attentional task demands. *Cerebral Cortex*, *22*(3), 607–615. http://doi.org/10.1093/cercor/bhr134

Lemiere, J., Decruyenaere, M., Evers-Kiebooms, G., Vandenbussche, E., & Dom, R. (2004). Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation--a longitudinal follow-up study. *Journal of Neurology*, *251*(8), 935–42. http://doi.org/10.1007/s00415-004-0461-9

Lett, T. A., Voineskos, A. N., Kennedy, J. L., Levine, B., & Daskalakis, Z. J. (2014). Treating working memory deficits in schizophrenia: a review of the neurobiology. *Biological Psychiatry*, *75*(5), 361–70. http://doi.org/10.1016/j.biopsych.2013.07.026

Levitt, T., Fugelsang, J., & Crossley, M. (2006). Processing speed, attentional capacity, and age-related memory change. *Experimental Aging Research*, *32*(3), 263–95. http://doi.org/10.1080/03610730600699118

Lewandowsky, S., Geiger, S. M., Morrell, D. B., & Oberauer, K. (2010). Turning simple span into complex span: Time for decay or interference from distractors? *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *36*(4), 958–978. http://doi.org/10.1037/a0019764

Lim, J., Wu, W., Wang, J., Detre, J. A., & Dinges, D. F. (2010). Perfusion Study of the Time-On-Task Effect. *Neuroimage*, *49*(4), 3426–3435. http://doi.org/10.1016/j.neuroimage.2009.11.020.Imaging

Loosli, S. V, Rahm, B., Unterrainer, J. M., Weiller, C., & Kaller, C. P. (2014). Developmental change in proactive interference across the life span: evidence from two working memory tasks. *Developmental Psychology*, *50*(4), 1060–72. http://doi.org/10.1037/a0035231

Lustig, C. A., & Jantz, T. (2014). Questions of age differences in interference control: When and how, not if? *Brain Research*, *1612*, 59–69. http://doi.org/10.1016/j.brainres.2014.10.024

Lustig, C. A., May, C. P., & Hasher, L. (2001). Working Memory Span and the Role of Proactive Interference. *Journal of Experimental Psychology. Applied.*

Macleod, C. M. (1991). Haifa Century of Research on the Stroop Effect: An Integrative Review. *Psychological Bulletin*, *109*(2), 163–203. http://doi.org/10.1037/0033-2909.109.2.163

Maestú, F., Yubero, R., Moratti, S., Campo, P., Gil-Gregorio, P., Paul, N., … Nevado, A. (2011). Brain activity patterns in stable and progressive mild cognitive impairment during working memory as evidenced by magnetoencephalography. *Journal of Clinical Neurophysiology : Official Publication of the American*

Electroencephalographic Society, *28*(2), 202–9. http://doi.org/10.1097/WNP.0b013e3182121743

May, C. P., Hasher, L., & Kane, M. J. (1999). The role of interference in memory span. *Memory & Cognition*, *27*(5), 759–767. http://doi.org/10.3758/BF03198529

McCabe, D. P. (2008). The role of covert retrieval in working memory span tasks: Evidence from delayed recall tests. *Journal of Memory and Language*, *58*(2), 480–494. http://doi.org/10.1016/j.jml.2007.04.004

McCabe, D. P., Roediger, H. L., McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The Relationship Between Working Memory Capacity and Executive Functioning: Evidence for a Common Executive Attention Construct. *Neuropsychology*, *24*(2), 222–243. http://doi.org/10.1037/a0017619.The

Mccabe, J., & Hartman, M. (2008). Working Memory for Item and Temporal Information in Younger and Older Adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, *5585*(May), 574–600. http://doi.org/10.1080/13825580801956217

McElree, B. (2001). Working memory and focal attention.pdf. *Journal of Experimental Psychology: Learning, Memory, and Cognition*.

Miller, A. K., Alston, R. L., & Corsellis, J. A. (1980). Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. *Neuropathology and Applied Neurobiology*, *6*(2), 119–32. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7374914

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, a H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cognitive Psychology*, *41*(1), 49–100. http://doi.org/10.1006/cogp.1999.0734

Montaldi, D., & Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus*, *20*(11), 1291–314. http://doi.org/10.1002/hipo.20853

Morey, R. A., Petty, C. M., Xu, Y., Hayes, J. P., Wagner, H. R., Lewis, D. V, … McCarthy, G. (2009). A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. *NeuroImage*, *45*(3), 855–66. http://doi.org/10.1016/j.neuroimage.2008.12.033

Nee, D. E., Brown, J. W., Askren, M. K., Berman, M. G., Demiralp, E., Krawitz, A., & Jonides, J. (2013). A meta-Analysis of executive components of working memory. *Cerebral Cortex*, *23*(2), 264–282. http://doi.org/10.1093/cercor/bhs007

Nee, D. E., & Jonides, J. (2009). Common and distinct neural correlates of perceptual and memorial selection. *NeuroImage*, *45*(3), 963–75. http://doi.org/10.1016/j.neuroimage.2009.01.005.Common

Nee, D. E., Jonides, J., & Berman, M. G. (2007). Neural mechanisms of proactive interference-resolution. *NeuroImage*, *38*(4), 740–51. http://doi.org/10.1016/j.neuroimage.2007.07.066

Nee, D. E., Wager, T. D., & Jonides, J. (2007). Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cognitive, Affective, & Behavioral Neuroscience*, *7*(1), 1–17. http://doi.org/10.3758/CABN.7.1.1

Neumann, E., & Deschepper, B. G. (1992). An inhibition-based fan effect: Evidence for an active suppression mechanism in selective attention. *Canadian Journal of Psychology/Revue Canadienne de Psychologie*, *46*(1), 1–40. http://doi.org/10.1037/h0084309

Nilsson, L.-G., Bäckman, L., Erngrund, K., Nyberg, L., Adolfsson, R., Bucht, Gös., … Winblad, B. (1997). The betula prospective cohort study: Memory, health, and aging. *Aging, Neuropsychology, and Cognition*, *4*(1), 1–32. http://doi.org/10.1080/13825589708256633

Nyberg, L., Dahlin, E., Stigsdotter Neely, A., & Bäckman, L. (2009). Neural correlates of variable working memory load across adult age and skill: dissociative patterns within the fronto-parietal network. *Scandinavian Journal of Psychology*, *50*(1), 41–6. http://doi.org/10.1111/j.1467-9450.2008.00678.x

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences*, *16*(5), 292–305. http://doi.org/10.1016/j.tics.2012.04.005

Oberauer, K. (2001). Removing irrelevant information from working memory: a cognitive aging study with the modified Sternberg task. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *27*(4), 948–957. http://doi.org/10.1037/0278-7393.27.4.948

Oberauer, K., & Lewandowsky, S. (2013). Evidence against decay in working memory. *Journal of Experimental Psychology. General*, *142*(2), 380–411. http://doi.org/10.1016/j.jml.2014.02.003

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 46–59. http://doi.org/10.1002/hbm.20131

Öztekin, I., & McElree, B. (2007). Proactive interference slows recognition by eliminating fast assessments of familiarity. *Journal of Memory and Language*, *57*(1), 126–149. http://doi.org/10.1016/j.jml.2006.08.011

Öztekin, I., McElree, B., Staresina, B. P., & Davachi, L. (2009). Working memory retrieval: contributions of the left prefrontal cortex, the left posterior parietal cortex, and the hippocampus. *Journal of Cognitive Neuroscience*, *21*(3), 581–93. http://doi.org/10.1162/jocn.2008.21016

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging*, *17*(2), 299–320. http://doi.org/10.1037//0882-7974.17.2.299

Persson, J., Larsson, A., & Reuter-Lorenz, P. a. (2013). Imaging fatigue of interference control reveals the neural basis of executive resource depletion. *Journal of Cognitive Neuroscience*, *25*(3), 338–51.

http://doi.org/10.1162/jocn_a_00321

Possin, K. L., Filoteo, J. V., Song, D. D., & Salmon, D. P. (2008). Spatial and object working memory deficits in Parkinson's disease are due to impairment in different underlying processes. *Neuropsychology*, *22*(5), 585–95. http://doi.org/10.1037/a0012613

Prull, M. W., Dawes, L. L., Martin 3rd, A. M., Rosenberg, H. F., & Light, L. L. (2006). Recollection and familiarity in recognition memory: adult age differences and neuropsychological test correlates. *Psychol Aging*, *21*(1), 107–118. http://doi.org/10.1037/0882-7974.21.1.107

Rabbitt, P., Scott, M., Lunn, M., Thacker, N., Lowe, C., Pendleton, N., … Jackson, A. (2007). White matter lesions account for all age-related declines in speed but not in intelligence. *Neuropsychology*, *21*(3), 363–70. http://doi.org/10.1037/0894-4105.21.3.363

Ray Li, C. -s. (2006). Imaging Response Inhibition in a Stop-Signal Task: Neural Correlates Independent of Signal Monitoring and Post-Response Processing. *Journal of Neuroscience*, *26*(1), 186–192. http://doi.org/10.1523/JNEUROSCI.3741-05.2006

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, *15*(11), 1676–1689. http://doi.org/10.1093/cercor/bhi044

Redick, T. S., & Lindsey, D. R. B. (2013). Complex span and n -back measures of working memory : A meta-analysis. *Psychonomic Bulletin & Review*, *20*(6), 1102–1113. http://doi.org/10.3758/s13423-013-0453-9

Reuter, M., Schmansky, N. J., Rosas, H. D., & Fischl, B. (2012). Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage*, *61*(4), 1402–18. http://doi.org/10.1016/j.neuroimage.2012.02.084

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The {Role} of the {Medial} {Frontal} {Cortex} in {Cognitive} {Control}. *Science*, *306*(5695), 443–447. http://doi.org/10.1126/science.1100301

Rieckmann, A., Pudas, S., & Nyberg, L. (2017). Longitudinal Changes in Component Processes of Working Memory. *Eneuro*, *4*(2), ENEURO.0052-17.2017. http://doi.org/10.1523/ENEURO.0052-17.2017

Robbins, T. W. (1996). Dissociating executive functions of the prefrontal cortex. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *351*(1346), 1463–1471. http://doi.org/10.1098/rstb.1996.0131

Rose, E. J., & Ebmeier, K. P. (2006). Pattern of impaired working memory during major depression. *Journal of Affective Disorders*, *90*(2–3), 149–61. http://doi.org/10.1016/j.jad.2005.11.003

Rose, N. S., Craik, F. I. M., & Buchsbaum, B. R. (2015). Levels of processing in working memory: differential involvement of frontotemporal networks. *Journal of Cognitive Neuroscience*, *27*(3), 522–32. http://doi.org/10.1162/jocn_a_00738

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., … Eickhoff, S. B. (2012). Modelling neural correlates of working memory: A coordinate-based meta-analysis. *NeuroImage*, *60*(1), 830–846. http://doi.org/10.1016/j.neuroimage.2011.11.050

Salthouse, T. A. (1995). Selective influences of age and speed on associative memory. *The American Journal of Psychology*, *108*(3), 381–96. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7573609

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403–428. http://doi.org/10.1037/0033-295X.103.3.403

Salthouse, T. A. (2000). Aging and measures of processing speed. *Biological Psychology*, *54*(1–3), 35–54. Retrieved from papers2://publication/uuid/22F2E012-046D-4599-B3F7-123CF2E5EB21

Salthouse, T. A. (2005). Relations between cognitive abilities and measures of executive functioning. *Neuropsychology*, *19*(4), 532–45. http://doi.org/10.1037/0894-4105.19.4.532

Salthouse, T. A. (2013). Effects of first occasion test experience on longitudinal cognitive change. *Developmental Psychology*, *49*(11), 2172–2178. http://doi.org/10.1037/a0032019

Salthouse, T. A. (2014). Frequent assessments may obscure cognitive decline. *Psychological Assessment*, *26*(4), 1063–9. http://doi.org/10.1037/pas0000007

Salthouse, T. A., & Coon, V. E. (1993). Influence of task-specific processing speed on age differences in memory. *Journal of Gerontology*, *48*(5), P245-55. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8366270

Salthouse, T. A., & Ferrer-Caja, E. (2003). What needs to be explained to account for age-related effects on multiple cognitive variables? *Psychology and Aging*, *18*(1), 91–110. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12641315

Schaie, K. W. (2005). What Can We Learn From Longitudinal Studies of Adult Development? *Research in Human Development*, *2*(3), 133–158. http://doi.org/10.1207/s15427617rhd0203_4

Schmiedek, F., Li, S.-C., & Lindenberger, U. (2009). Interference and facilitation in spatial working memory: age-associated differences in lure effects in the n-back paradigm. *Psychology and Aging*, *24*(1), 203–210. http://doi.org/10.1037/a0014685

Schmiedek, F., Lövdén, M., & Lindenberger, U. (2014). A task is a task is a task : putting complex span , n - back , and other working memory indicators in psychometric context. *Frontiers in Psychology*, *5*(December), 1–8. http://doi.org/10.3389/fpsyg.2014.01475

Serences, J. T. (2008). Value-based modulations in human visual cortex. *Neuron*, *60*(6), 1169–81.

http://doi.org/10.1016/j.neuron.2008.10.051

Shigemune, Y., Tsukiura, T., Nouchi, R., Kambara, T., & Kawashima, R. (2017). Neural mechanisms underlying the reward-related enhancement of motivation when remembering episodic memories with high difficulty. *Human Brain Mapping*, *3443*(June 2016), 3428–3443. http://doi.org/10.1002/hbm.23599

Shipstead, Z., Harrison, T. L., & Engle, R. W. (2016). Working memory capacity and fluid intelligence: Maintenance and disengagement. *Perspectives on Psychological Science*, *11*(6), 771–799. http://doi.org/10.1177/1745691616650647

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science (New York, N.Y.)*, *283*(5408), 1657–61. http://doi.org/10.1126/science.283.5408.1657

Spieler, D. H., Balota, D. a, & Faust, M. E. (1996). Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. *J Exp Psychol Hum Percept Perform*, *22*(2), 461–479. http://doi.org/10.1037/0096-1523.22.2.461

Sternberg, S. (1966). High-Speed Scanning in Human Memory. *Science*, *153*(3736), 652–654. http://doi.org/10.1126/science.153.3736.652

Stoltzfus, E. R., Hasher, L., & Zacks, R. T. (1996). Working Memory and Aging: Current Status of the Inhibitory View. *Working Memory and Human Cognition*. http://doi.org/10.1093/acprof:oso/9780195100990.003.0003

Stopford, C. L., Thompson, J. C., Neary, D., Richardson, A. M. T., & Snowden, J. S. (2012). Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *48*(4), 429–46. http://doi.org/10.1016/j.cortex.2010.12.002

Stuss, D. T. (2011). Functions of the frontal lobes: Relation to executive functions. *Journal of the International Neuropsychological Society*, *17*(5), 759–765. http://doi.org/10.1017/S1355617711000695

Szmalec, A., Verbruggen, F., Vandierendonck, A., & Kemps, E. (2011). Control of interference during working memory updating. *Journal of Experimental Psychology. Human Perception and Performance*, *37*(1), 137–151. http://doi.org/10.1037/a0020365

Thomas, R. C., & Hasher, L. (2012). Reflections of distraction in memory: Transfer of previous distraction improves recall in younger and older adults. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *38*(1), 30–39. http://doi.org/10.1037/a0024882

Underwood, B. J. (1957). Interference and forgetting. *Psychological Review*, *64*(1), 49–60. http://doi.org/10.1037/h0044616

Unsworth, N. (2010). Interference control, working memory capacity, and cognitive abilities: A latent variable analysis. *Intelligence*, *38*(2), 255–267. http://doi.org/10.1016/j.intell.2009.12.003

Unsworth, N., & Engle, R. W. (2007). The nature of individual differences in working memory capacity: Active maintenance in primary memory and controlled search from secondary memory. *Psychological Review*, *114*(1), 104–132. http://doi.org/10.1037/0033-295X.114.1.104

Verhaeghen, P. (2011). Aging and Executive Control: Reports of a Demise Greatly Exaggerated. *Current Directions in Psychological Science*, *20*(3), 174–180. http://doi.org/10.1177/0963721411408772.Aging

Verhaeghen, P., & De Meersman, L. (1998). Aging and the Stroop effect: A meta-analysis. *Psychology and Aging*, *31*(1), 120–126. http://doi.org/10.1037/0882-7974.13.1.120

Wager, T. D., Sylvester, C. Y. C., Lacey, S. C., Nee, D. E., Franklin, M., & Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. *NeuroImage*, *27*(2), 323–340. http://doi.org/10.1016/j.neuroimage.2005.01.054

Wang, X., Zhao, X., Xue, G., & Chen, A. (2016). Alertness function of thalamus in conflict adaptation. *NeuroImage*, *132*, 274–282. http://doi.org/10.1016/j.neuroimage.2016.02.048

Wechsler, D. (1981). *WAIS-R manual*. New York: Psychological Corporation.

Weeks, J. C., & Hasher, L. (2014). The disruptive - and beneficial - effects of distraction on older adults' cognitive performance. *Frontiers in Psychology*, *5*(FEB), 1–6. http://doi.org/10.3389/fpsyg.2014.00133

Wylie, G. R., Javitt, D. C., & Foxe, J. J. (2006). Jumping the gun: Is effective preparation contingent upon anticipatory activation in task-relevant neural circuitry? *Cerebral Cortex*, *16*(3), 394–404. http://doi.org/10.1093/cercor/bhi118

Xu, M., Xu, G., & Yang, Y. (2016). Neural Systems Underlying Emotional and Non-emotional Interference Processing: An ALE Meta-Analysis of Functional Neuroimaging Studies. *Frontiers in Behavioral Neuroscience*, *10*(November), 1–15. http://doi.org/10.3389/fnbeh.2016.00220

Yonelinas, A. P., & Levy, B. J. (2002). Dissociating familiarity from recollection in human recognition memory: different rates of forgetting over short retention intervals. *Psychonomic Bulletin & Review*, *9*(3), 575–582. http://doi.org/10.3758/BF03196315

Yuan, P., & Raz, N. (2014). Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *42*, 180–192. http://doi.org/10.1016/j.neubiorev.2014.02.005

Zimmerman, M., Brickman, A., Paul, R., Grieve, S., Tate, D., Gunstad, J., … Gordon, E. (2006). The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. *Am J Geriatric Psychiatry*, *14*(1), 823–833.

8 APPENDIX

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991-2018

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer´s disease. Issues of etiology and validity.
Almkvist Ove. Alzheimer´s disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.
Basun Hans. Biological markers in Alzheimer´s disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)
Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.
Josephsson Staffan. Everyday activities as meeting-places in dementia.
Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.
Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.
Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.
Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)
Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.
Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.
Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.
Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.
Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.
Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)
von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.
Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.
Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.
Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer´s disease.
Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.
Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.
Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.
Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.
De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.
Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.
Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.
Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.
Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.
Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.
Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.
Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007
Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)
Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.
Rehnman Jenny. The role of gender in face recognition. (Stockholm University)
Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?
Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008
Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)
Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.
Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer’s disease and structural brain changes.
Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.
Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)
Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.
Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009
Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.
Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.
Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.
Livner Åsa. Prospective and retrospective memory in normal and pathological aging.
Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010
Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.
Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011
Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.
Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.
Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012
Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.

Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.

Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.

Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.