How the brains of young and old human adults cope with increased working memory demands

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Declaration:

I hereby declare that I have produced the work entitled "How the brains of young and old human adults cope with increased working memory demands", submitted for the award of a doctorate, on my own (without external help), have used only the sources and aids indicated and have marked passages included from other works, whether verbatim or in content, as such. I swear upon oath that these statements are true and that I have not concealed anything. I am aware that making a false declaration under oath is punishable by a term of imprisonment of up to three years or by a fine.

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Please note that parts of this dissertation, like e.g., material and methods, results, and sections of the discussion, were published in the following article:

Höller-Wallscheid, M. S., Thier, P., Pomper, J. K., & Lindner, A. (2017). Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age. *Proc Natl Acad Sci USA*, 114(5), E830-E839.

The journal *Proceedings of the National Academy of Sciences of the United States of America* gave me the permission to use the article including all tables and figures for my doctoral dissertation.

During my PhD studies, I designed and performed the experiments that are presented in this research article. Furthermore, I programmed the respective stimuli and analytical scripts, analyzed all data that I described in the research article, and wrote this article. PD Dr. Axel Lindner, Prof. Dr. Hans-Peter Thier, and Dr. Jörn K. Pomper supervised and supported me during this workflow. Thus, writing "we" in the research article – and also in this dissertation – expresses our collaboration.

Abstract

Working memory tasks are generally more difficult for older adults due to decreasing working memory capacity that is evoked by changes in the ageing brain. To successfully cope with this increased challenge in cognitive demand, elderly adults additionally activate the contralateral counterparts of specific prefrontal brain regions, whereas young adults do engage them unilaterally. At first glance, this strategy seems at odds with the idea of lateralized cognitive functions in cerebral cortex. In this dissertation, I investigated whether bilateral recruitment is a general strategy of the human brain to respond to increased working memory demands that is independent of age, task content and cerebral region. To answer these questions, we conducted our main experiment in which a group of young and a group of old adult participants worked on verbal, spatial, and object-based working memory tasks that had been individually tailored to push each subject to her or his capacity limit in each working memory domain. Simultaneously, we used functional magnetic resonance imaging to measure brain activity associated with working memory maintenance and to compare this activity between cross-hemispheric counterparts of the respective brain regions. Our results clearly indicate that language-related regions such as Broca's area in the left ventrolateral prefrontal cortex, the left supplementary motor area, right lobule VI and crus1 of lobule VII of the cerebellum, and the left ventral premotor cortex maintained their lateralized activation patterns across the two age groups despite our highly challenging working memory tasks. In contrast, dorsolateral prefrontal cortex and anterior prefrontal cortex showed bilateral activation in difficult conditions across all working memory domains and this was true for both age groups. To further confirm that also young adults shift from a unilateral to a bilateral recruitment of these prefrontal brain regions in easy vs. highly demanding working memory tasks, respectively, we conducted an additional control experiment that engaged both the verbal and the spatial working memory domain. The results of this control experiment demonstrated that dorsolateral prefrontal cortex and anterior prefrontal cortex are unilaterally recruited during the easy task variants and – together with the results of the main experiment – they showed that this unilaterality transforms into bilaterality in difficult tasks. The additional activation of contralateral cerebral counterparts seems to be a strategy of the brain to cope with increased cognitive challenges independent of age and working memory task content. This phenomenon mainly emerges in prefrontal cortex – a brain structure that is less specialized and more flexible than other parts of the brain.

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Abbreviations

ANOVA	analysis of variance
aPFC	anterior prefrontal cortex
BA	Brodmann's area
BOLD	blood oxygen level-dependent
c	central load level
cm	centimeter
CRT	cathode ray tube
CRUNCH	compensation-related utilization of neural circuits hypothesis
DLPFC	dorsolateral prefrontal cortex
e.g.	for example
EOI	effects of interest
EPI	echo planar imaging
ERTs	event-related time courses
et al.	and others
etc.	and so on
FEF	frontal eye fields
Fig.	figure
fMRI	functional magnetic resonance imaging
FoA	focus of attention
FOV	field of view
FWE	familywise error
GLM	general linear model
HAROLD	hemispheric asymmetry reduction in older adults
Hz	Hertz
i.e.	that is
IPS	intraparietal sulcus
ISI	interstimulus interval
ITG	inferior temporal gyrus
kHz	Kilohertz
LI	lateralization index
LTM	long-term memory
mm	millimeter
MNI	Montreal Neurological Institute
MR	Magnetic resonance

MRI	magnetic resonance imaging
ms	milliseconds
n	number
p.	page
PASA	posterior-anterior shift in aging
PET	positron emission tomography
PFC	prefrontal cortex
PMd	dorsal premotor cortex
PMv	ventral premotor cortex
ROIs	regions of interest
rTMS	repetitive transcranial magnetic stimulation
s	seconds
SD	standard deviation
SE	standard error
SMA	supplementary motor area
SPL	superior parietal lobule
SPM	Statistical Parametric Mapping
STAC	scaffolding theory of aging and cognition
STM	short-term memory
t	time
TE	echo time
TMS	transcranial magnetic stimulation
TR	repetition time
VLPFC	ventrolateral prefrontal cortex
vs.	versus
WM	working memory
y	years

1 Introduction

Keeping a telephone number in mind until we can dial it, planning a hiking trip in the Alps, creating a marble sculpture – what do these very different activities have in common? To successfully implement these activities, we have to subdivide the overall goal (for instance, carving a marble head) into various subgoals (for instance, making the eyes, nose, and mouth of the head). Then, we have to keep track of the progress of the various subgoals while we pursue our overall goal. This dissertation focuses on a fundamental brain mechanism that is necessary for achieving this and that is, consequently, essential for many activities in our daily lives (Miller, Galanter, & Pribram, 1960). This mechanism, called *working memory* (WM), allows us to maintain and manipulate a limited amount of information for a brief period of time in the absence of sensory input in order to execute a goal-directed behavior (Atkinson & Shiffrin, 1968; Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015).

In many daily activities, WM operates unconsciously so that we pursue our goals without great effort and without continuously thinking about them. However, what will happen when the telephone number we need to remember gets longer and longer or when there are zillions of options to consider when planning the next hiking trip to the Alps? These and other situations that pose increased demand for WM become very challenging because the capacity of WM is highly restricted (Baddeley, 2003; Cowan, 2000, 2008; Eriksson et al., 2015; Miller, 1956). A well-known factor that decreases WM capacity and thus also increases the WM demand for specific tasks is aging (Nyberg et al., 2014; Park, 2012; Park et al., 2002; Park & Reuter-Lorenz, 2009; Schneider-Garces et al., 2010). How will the brain react in demanding WM situations when we grow older and our WM capacity decreases? Do previously suggested changes in brain activation in the face of increased task demand in older adults generalize to younger adults when they experience similarly increased WM demand (e.g., when remembering even longer telephone numbers)? The aim of this dissertation is to answer these questions by investigating how both young and older adult human brains cope with increased WM demands.

In the following chapters, I will present a more detailed characterization of the concept of WM, while also reporting on how WM capacity changes across a lifetime. Then, I will introduce brain regions that are typically associated with WM processes, before providing ideas about how the human brain may respond to demanding WM situations. Such ideas mainly come from the field of the cognitive neuroscience of aging. Afterwards, I will present my specific research hypotheses and describe and discuss the experiments and their respective results which I conducted in the framework of this dissertation.

2 Working memory

In this chapter, I will provide an overview of the concept of WM by defining it and by introducing well-known cognitive WM models and typical characteristics of WM including its various domains, its limited capacity that varies across persons, and the development of such a capacity limit across a lifetime. I will end this chapter by presenting psychophysical paradigms with which one can measure WM performance and reveal WM processes. Please note that WM is a widely investigated topic in the field of cognitive neuroscience (D'Esposito & Postle, 2015; Wager & Smith, 2003), which makes it impossible to highlight all aspects of its investigational scope. Here, I will focus on those aspects that are necessary to understand the experimental research of this dissertation.

2.1 Definition of working memory

Hermann Ebbinghaus, a German psychologist, established memory as an experimental research field when he investigated the acquisition and loss of meaningless syllables (Ebbinghaus, 1885). Later in 1890, William James differentiated between primary and secondary memory. *Primary memory* refers to memory contents that are currently and consciously in memory, whereas *secondary memory* corresponds to memory contents that are unconscious, have been accumulated over an individual's lifetime, and belong to his or her psychological past (James, 1890). The distinction between these two memory types is typical for the early theories of memory because they were *dual-store memory models*. This type of model distinguished between *short-term memory* (STM) and *long-term memory* (LTM), which are comparable to primary vs. secondary memory, respectively (Schermer, 2014; see section 2.2 of this dissertation for further details).

The concept of WM originally arose out of STM (Baddeley, 2010). Consequently, these two ideas are closely linked to each other and are overlapping in various aspects. However, it is not trivial to clearly differentiate between them because different researchers have applied different definitions for the concept of WM (Baddeley, 2003; Cowan, 2008; Eriksson et al., 2015). For instance, Miller and colleagues (Miller et al., 1960) created the term "working memory" in 1960 to highlight STM that one uses in order to plan and execute behavior (Baddeley, 2010; Cowan, 2008). Under their definition, WM is what allows us to successfully build a model airplane by storing which steps of the construction manual we have already finished and which ones we have to plan next. Comparable to Miller et al. (1960), Atkinson and Shiffrin treated STM and WM alike (Atkinson & Shiffrin, 1968). They defined both concepts as the temporary maintenance and manipulation of small amounts of information over brief

periods of time. Here, a typical example is that of repeating a telephone number in memory until one can dial the number or write it down (Grady, 2012). In contrast, Alan Baddeley – an investigator who developed one of the most persistent and influential WM models (D'Esposito & Postle, 2015; Eriksson et al., 2015) – clearly differentiated between WM and STM (Baddeley & Hitch, 1974; see below on page 7 for further details of his WM model): Baddeley and Hitch's (1974) model emphasizes that WM comprises not only STM – a system that keeps things in mind for a short period of time – but also the executive processes which connect perception and LTM to cognition and action (Baddeley, 2000, 2003, 2010). They highlight attention in particular as one of these important executive processes, which support us to effectively apply STM (Baddeley, 2000, 2003; Baddeley & Hitch, 1974; Cowan, 2008). After Baddeley and Hitch (1974) proposed their model of WM, the term "working memory" generally became more popular in the field of memory research stressing the interplay between various memory components and other cognitive processes (Cowan, 2008). Although attention plays a dominant role in almost all WM theories (Eriksson et al., 2015; Wager & Smith, 2003), some investigators define attention as the driving factor in their WM models in the sense that attention activates inner LTM or sensory representations and thereby returns them into WM content (Cowan, 1995, 1999, 2008; D'Esposito & Postle, 2015; Engle & Kane, 2004; Eriksson et al., 2015).

In summary, although the various definitions of WM differ slightly, most of them emphasize that a) WM maintains information for a brief period of time in the range of several seconds to minutes while there is no sensory input (Eriksson et al., 2015), b) WM is characterized by an interplay between various cognitive processes (Cowan, 2008; Eriksson et al., 2015), and c) WM is required for the successful execution of goal-directed behavior (D'Esposito & Postle, 2015; Eriksson et al., 2015; Wager & Smith, 2003). Consequently, one can consider WM as a system that is responsible for the temporary maintenance and manipulation of information, which makes it essential for many daily activities (Smith & Jonides, 1999; Wager & Smith, 2003). In this dissertation, I will use the term "working memory" according to the definition that is given in this paragraph.

2.2 Cognitive models of working memory

As mentioned above, the original models of memory were multi-store models, more specifically dual-store models differentiating between STM on the one hand and LTM on the other hand (James, 1890; Schermer, 2014). Later, Atkinson and Shiffrin (1968) added a further storage – the *sensory register* (see below for further details) – and hence offered a *triple-store model* of memory. In these models, the short-term store was typically considered as a unitary

system (Baddeley, 2003). In contrast, Baddeley and Hitch (1974) further subdivided this STM system into various crucial processes that are necessary for the successful temporary maintenance and manipulation of information and named it WM (Baddeley, 2000, 2003; Baddeley & Hitch, 1974). This *multi-component model of WM* as well as former multi-store models of memory stress the idea that memory is subdivided into independent short-term and long-term stores that can interact with each other, while a specific memory content cannot be in STM/ WM and LTM simultaneously. More specifically, memory content that is stored in LTM has to be transferred to a separate WM system when a person is currently thinking about it (Baddeley, 2003; Eriksson et al., 2015). The basic ideas of Baddeley and Hitch's model (1974) are still influential in today's WM research (Cowan, 2008; Schermer, 2014), though there is an increasing shift to the so-called *state-based models of WM*. These models emphasize the idea that WM and LTM are not independent from one another in the sense that LTM content is said to transform into WM content when this part of LTM is activated by means of attention (Cowan, 1995, 1999, 2008; D'Esposito & Postle, 2015; Eriksson et al., 2015). In this section, I will present the famous models of Atkinson and Shiffrin (1968) and Baddeley and Hitch (1974) as representatives of the multi-store approach to memory and Cowan's WM model (Cowan, 1995, 1999, 2008) to explain the essential characteristics of state-based WM models. However, beforehand, I will introduce the concepts of STM and LTM in more detail because they are crucial to understanding all memory models.

2.2.1 Short-term memory vs. long-term memory

As described previously, James (1890) introduced the idea of distinguishing between STM and LTM (Cowan, 2008; Schermer, 2014). Also, Hebb (1949) suggested such a distinction between STM and LTM that – according to him – was based on temporary electrical activation versus neuronal growth, respectively (Baddeley, 2003; Hebb, 1949). Empirical evidence for the general idea that STM and LTM are two different memory systems comes from clinical studies showing that specific amnestic patients have problems with one memory system but not the other. For instance, a special type of amnesia that is caused by bilateral damage to the temporal lobes, the hippocampi and the mammillary bodies and that is characteristic for Korsakoff's syndrome (Victor & Yakovlev, 1955) leads to an impairment of LTM while STM is unaffected (Atkinson & Shiffrin, 1968; Baddeley, 1983; Schermer, 2014). Also, a famous patient named H.M. developed comparable symptoms after he had surgery on bilateral hippocampi due to severe epileptic seizures (Atkinson & Shiffrin, 1968; Milner, 1966). Conversely, another class of patients who had lesions in the temporoparietal cortical parts of the left hemisphere showed intact LTM and perturbed STM (Baddeley, 2010).

Atkinson and Shiffrin (1968) proposed that STM maintains a limited amount of information for a brief period of time. This definition contains two typical characteristics that distinguish STM from LTM: *temporal decay* and *capacity limitation* (Cowan, 2008; Schermer, 2014). More specifically, content of STM decays as a function of time within a few seconds unless subjects preserve it through active *maintenance rehearsal* (Brown, 1958; Cowan, 2008; Peterson & Peterson, 1959), a strategy of repeating information aloud or in their thoughts by means of inner speech (Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974; Cowan, 2008). Consequently, humans have to use rehearsal to keep information in STM, which is not the case for LTM (Schermer, 2014). Furthermore, researchers often measure STM capacity by means of the *memory span*, which is a measure of how many elements of a memory set can be remembered after a single presentation (Schermer, 2014). Although there is no consensus on how many items humans can hold in STM (Eriksson et al., 2015), investigators agree on the fact that we are highly restricted in the number of items that we are able to simultaneously maintain in STM (Baddeley, 2003; Cowan, 2000, 2008; Eriksson et al., 2015; Miller, 1956). For example, Miller (1956) proposed that human adults can maintain on average between five and nine elements. On the contrary, Cowan (2000) estimated the capacity limit of STM to be three to four elements and compelling empirical evidence supports such a capacity limit (Eriksson et al., 2015). However, these two proposals may not be as different as they first appear: Cowan (2000) agreed with Miller (1956) that a person's memory span can encompass approximately seven items; however, he argued that each of these seven elements might not represent a separate entity. This is because humans can expand the number of elements that they are able to hold in STM through a strategy called "chunking" (Cowan, 2000, 2008). *Chunks* are the smallest information unit in STM and *chunking* refers to a strategy of using LTM knowledge to decrease the WM load by combining various elements to a meaningful group, which results in a smaller number of units one has to remember (Miller, 1956). For instance, if a subject sees the letter series "V W W H O," he or she might use previous knowledge to connect various letters of the series to the meaningful acronyms "VW" and "WHO." In this way, the person can decrease the original memory load of five single elements to two chunks.

Contrary to STM, LTM is said to be almost unlimited in the capacity of adding new information to its tremendous buffer (Cowan, 2008; Eriksson et al., 2015; Schermer, 2014). More specifically, LTM is the part of our memory which represents all the information and learning that we have accumulated during our lifetime (Atkinson & Shiffrin, 1968; Schermer, 2014). Consequently, such memory contents are very broad and range from personal experiences (e.g., memories from our last vacation in Madrid), to acquired factual knowledge about the world (e.g., that Madrid is Spain's capital) to motoric skills like riding a bike. Accordingly, researchers have subdivided LTM in various classes: on the one hand, there is *explicit LTM* which is also often called *declarative LTM* because a person can easily verbally

describe its contents. *Explicit* LTM stores information that can become consciously accessible when it is recalled and is further subdivided into *episodic* and *semantic LTM*, which represent memory for specific personal episodes in time and space and factual knowledge about the world, respectively (Schermer, 2014; Tulving, 1972). On the other hand, there is *implicit LTM* (also named *procedural* or *non-declarative LTM*) whose contents refer to highly automatized motor skills like, for example, executing a well-trained dance move. Implicit memories stay unconscious through acquisition and use (Schermer, 2014; Tulving, 1985).

2.2.2 Atkinson and Shiffrin's triple-store memory model

The original multi-store models of memory assumed that memory contains various storage systems that build on one another with information first entering STM before it is forwarded to LTM (Baddeley, 2010; Schermer, 2014). The most famous and enduring of these ideas came from Atkinson and Shiffrin (1968) who added the concept of the "sensory register" to former dual-store theories and thus divided memory into three storage systems: sensory register, short-term store and long-term store (see also figure 1).

According to this model, the processing of information from our environment starts with the sensory organs sending their sensory inputs to the first memory store of the model – the *sensory register* (Atkinson & Shiffrin, 1968). Characteristically, the sensory register stores a relatively high amount of information in its original physical appearance and its contents decay within several hundred milliseconds (Atkinson & Shiffrin, 1968; Sperling, 1960). Although Atkinson and Shiffrin (1968) assumed that there is a sensory register for each sensory modality, clear empirical evidence for this assumption only exists for visual and acoustic stimuli (Schermer, 2014). In the sensory register, specific information is selected by attentional processes, which then is passed forward to the capacity-limited *short-term store* that can transfer it even further to the *long-term store* by means of rehearsal processes repeating the information again and again. Without such a rehearsal mechanism, the information would decay in the short-term store within several seconds. Furthermore, when information is retrieved from the long-term store, it is transferred back to the short-term store by copying it (Atkinson & Shiffrin, 1968). In their model, Atkinson and Shiffrin (1968) called the short-term store WM because this memory subsystem not only maintains information for a brief period of time but also actively manipulates its flow into and out of the long-term store, a process which is integral for complex cognition (Baddeley, 2003, 2010).

This memory model suffered from two shortcomings (Baddeley, 1983, 2003, 2010): First, it claims that the mere repetition of information of the short-term store leads to a transfer to the long-term store. This assumption turned out to be wrong because it is not the quantity

of repetitions that drives this transfer but the way in which it is repeated. More specifically, more profound processing strategies – like, for instance, connecting STM content semantically to previous knowledge stored in LTM or to emotions – are usually necessary for successful long-term learning (Craik & Lockhart, 1972). Second, the model assumes that the short-term store operates as WM and that information that enters the long-term store has to be first processed in the short-term store. Consequently, persons with deficits in STM should be affected in a wide range of cognitive processes for which WM is necessary and they should not be able to pass information to LTM (Baddeley, 2010; Baddeley & Hitch, 1974). However, there were patients with impaired STM (Shallice & Warrington, 1970) who were not very cognitively impaired and who were capable to create new LTM contents (Baddeley, 1983, 2010; Baddeley & Hitch, 1974).
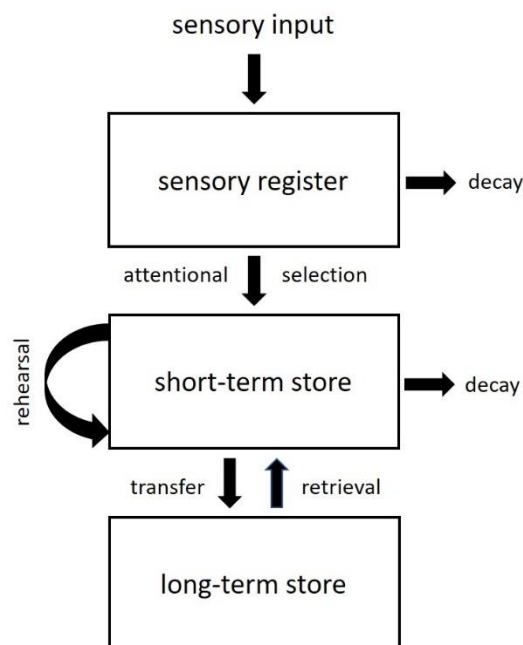
Figure 1. **Atkinson and Shiffrin's triple-store model of memory.**

This model suggests three independent memory stores through which incoming sensory information travels in a sequential order: the sensory register, the short-term store, and the long-term store. This illustration was modified from Atkinson, R. C. & Shiffrin, R. M., Human memory: a proposed system and its control processes, in K. W. Spence & J. T. Spence (Eds.), *Psychology of learning and motivation*, 1968, Vol. 2, p. 93 (Fig. 1) and p. 113 (Fig. 2). Copyright © 1968 by the Academic Press Inc. (published by Elsevier). Modified with permission from Elsevier (license number: 4159520593814).

2.2.3 Baddeley and Hitch's multi-component model of working memory

Inspired by the limitations of Atkinson and Shiffrin's memory model (1968), Baddeley and Hitch (1974) examined the question if intact STM is truly necessary for more complex

cognitive tasks which are thought to be essentially influenced by WM. Therefore, they restricted the capacity of short-term maintenance in information-processing tasks (like reasoning, comprehension, and learning) by using a further independent task which was a STM task requiring pure serial repetition of digits. Surprisingly, performance on the tasks that strongly depend on WM was not much worse when their healthy subjects worked on both tasks concurrently than when they separately worked on these tasks (Baddeley, 1983, 2003, 2010; Baddeley & Hitch, 1974). Baddeley and Hitch (1974) concluded from these results that STM/ WM cannot be a unitary system as it had been described in former STM theories (Atkinson & Shiffrin, 1968). On the contrary, they assumed that there are various subsystems which can function independently of each other as well as interact with each other. They used the term "working memory" to describe that entire system (Baddeley, 1983, 2000; Baddeley & Hitch, 1974).

More specifically, the original multi-component model of WM created by Baddeley and Hitch (1974) and Baddeley (1983) distinguished between three WM components (see also figure 2): two domain-specific STM systems which are called "phonological loop" and "visuo-spatial sketch pad," respectively, and an attentional control system, named "central executive."
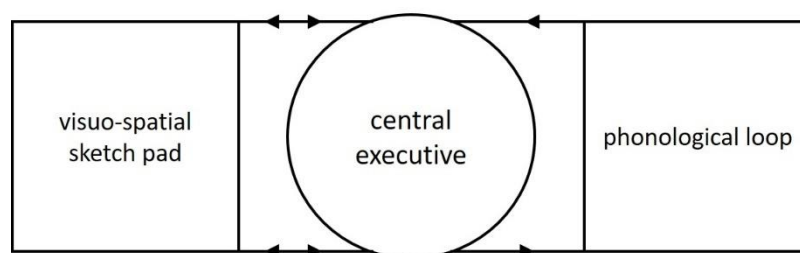
Figure 2. **Baddeley and Hitch's original three-component model of WM.**

This model assumes that WM comprises two domain-specific STM buffers (the visuo-spatial sketch pad and the phonological loop) and an attentional control system (the central executive). This illustration was adapted from Baddeley, A., Functional aspects of human memory - Working memory, *Phil Trans R Soc Lond B*, 1983, 302(1110), p. 315, Fig. 2. Copyright © 1983 by The Royal Society and from Baddeley, A., Working memory: looking back and looking forward, *Nat Rev Neurosci*, 2003, 4(10), p. 830, Fig. 1. Copyright © 2003 by Nature Publishing Group. Adapted by permissions from The Royal Society (license number: 4219561303326) and Macmillan Publishers Ltd (license number: 4219571415691).

The *phonological loop* consists of both a "phonological STM store" and an "articulatory control process." The *phonological STM store* encodes language- and sound-based information and maintains them for a few seconds. The *articulatory control process* helps to maintain information for a longer time period within the buffer by means of its subvocal

rehearsal. Comparable to the phonological loop, the *visuo-spatial sketch pad* is a STM system storing and rehearsing spatial and object-based information. Both STM subsystems are said to be limited in capacity and to act independently of each other and of LTM. Moreover, the *central executive* is a control system that uses attentional processes to manage and manipulate information within the two domain-specific buffers and their flow in and out of them (Baddeley, 1983; Baddeley & Hitch, 1974). To summarize, the original version of the three-component WM model posits that WM encompasses short-term storage plus further cognitive processing, making it essential for a broad scope of complex cognitive processes (Baddeley, 1983, 2000, 2003, 2010; Baddeley & Hitch, 1974; Cowan, 2008).

The original version of the three-component WM model (Baddeley, 1983; Baddeley & Hitch, 1974) lacked various important aspects, e.g., the maintenance of items that are not verbal or spatial/ visual in nature or the interaction between a) WM and conscious awareness, b) WM and LTM, and c) the two STM storage components (Baddeley, 2000, 2003). To address these issues, Baddeley (2000) revised his former model by including a forth component (see also figure 3): the "episodic buffer."
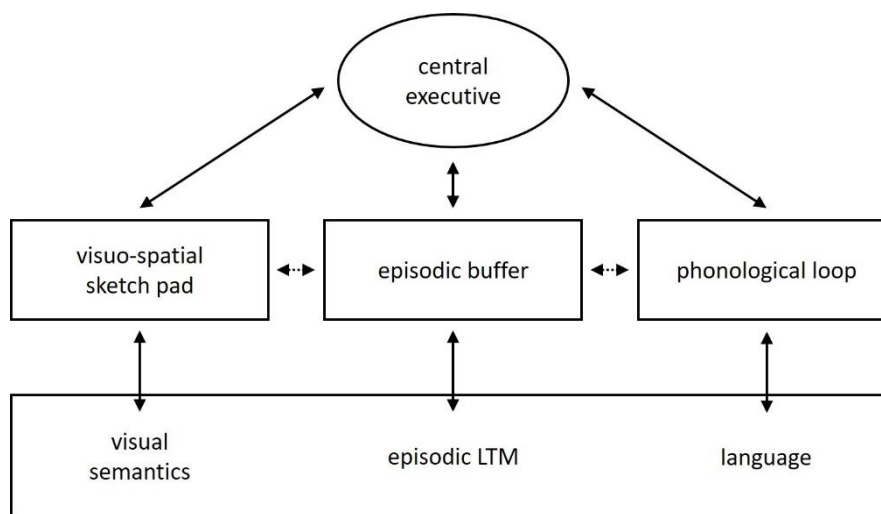
Figure 3. **Baddeley's revised version of the multi-component model of WM.**

Compared to the original model, the revised version adds connections to acquired long-term knowledge (visual semantics, episodic LTM, and language) and a further component – the episodic buffer – that offers a platform in which the various WM components can interact with each other. This illustration was modified from Baddeley, A., The episodic buffer: a new component of working memory?, *Trends Cogn Sci*, 2000, 4(11), p. 421, Fig. 1. Copyright © 2000 by Elsevier and from Baddeley, A., Working memory, *Curr Biol*, 2010, 20(4), p. R138, Fig. 2. Copyright © 2010 by Elsevier. Modified with permission from Elsevier (license numbers: 4159521157909 and 4159530317983).

The *episodic buffer* is a further STM store that – like the phonological loop and the visuo-spatial sketch pad – is limited in capacity and controlled by the central executive through attentional processes. Moreover, the episodic buffer is in charge of the short-term maintenance of items that have neither verbal nor visuo-spatial features. It is accessible through conscious awareness by the central executive, and it provides a platform for the interaction between the phonological loop and the visuo-spatial sketch pad as well as the interaction between the various WM components and information from perception and LTM (Baddeley, 2000). Thus, for instance, it is the episodic buffer that enables us to remember a person's name when we see their face (Cowan, 2008). Baddeley also emphasized that the episodic buffer provides a temporary stage for information from LTM when it is being actively processed in WM (Baddeley, 2000, 2003). In this final point, Baddeley's notion of WM differs from the one of the more recent "state-based WM models" (Baddeley, 2003; Cowan, 2008; D'Esposito & Postle, 2015; Eriksson et al., 2015), whose general ideas I will present in the next section.

2.2.4 State-based models of working memory

The multi-component WM model (Baddeley, 1983, 2000; Baddeley & Hitch, 1974) dominated the field of WM research until *state-based models of WM* became more prevalent in the last years (D'Esposito & Postle, 2015). This group of WM models generally claims that there are no WM-specific storage systems or processes. Instead, the same systems that contribute to the perception and long-term storage of information are also responsible for the WM maintenance of that information. More specifically, the central notion of these models is that LTM content or perceptual representations transform into WM content when they are temporarily activated through attentional processes and, thus, are made more accessible (Baddeley, 2003; Cowan, 2008; D'Esposito & Postle, 2015; Eriksson et al., 2015). Consequently, contrary to former WM models, information stored in WM is defined as a temporary state of heightened accessibility of information that is in LTM and perceptual representations (Cowan, 2008; D'Esposito & Postle, 2015; Eriksson et al., 2015).

Nelson Cowan created the most famous state-based model of WM (D'Esposito & Postle, 2015), namely *the embedded-processes model of working memory*[1] (Cowan, 1988,

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[1] State-based models of WM can be divided into two subgroups: "activated LTM models" and "sensorimotor recruitment models" (D'Esposito & Postle, 2015). Both subgroups of models suggest that focusing attention on mental representations transforms these representations into WM content. The main difference between these two subgroups is the kind of internal representation they describe: while *activated LTM models* focus on internal LTM representations, *sensorimotor recruitment models* refer to internal perceptual representations. Cowan's model (1988, 1995, 1999, 2008) belongs to the activated LTM models. Importantly, these models neglect to explain how sensory stimuli are maintained in WM, which have no LTM representations because they have never been experienced before. However, this aspect is considered by the sensorimotor recruitment models (D'Esposito & Postle, 2015).

1995, 1999, 2008). This model (see also figure 4) assumes that short-term maintenance of information happens in the following way: the perception of specific stimuli in our environment activates their LTM representations, which increases their state of accessibility. Accessibility can be further increased by focusing attention on these activated inner representations. Thus, Cowan defined STM content as activated LTM information existing in an elevated accessible state and distinguished between two different states in WM: "activated LTM" and "focus of attention" (FoA). The *activated LTM* is the part of LTM that is generally activated and whose contents fade when they are not transferred to the FoA by attentional control processes or verbal rehearsal. The *FoA* represents the part of activated LTM that is in its most accessible state because attention is allocated to it. Since the capacity of attention is limited to approximately four chunks, the FoA is therefore similarly limited (Cowan, 1988, 1995, 1999, 2008). To summarize, activated LTM and the FoA both form STM, while activated LTM is less accessible than the FoA but more accessible than inactivated LTM. According to Cowan (2008), WM consists of STM and further central executive processes that help to effectively use STM content.
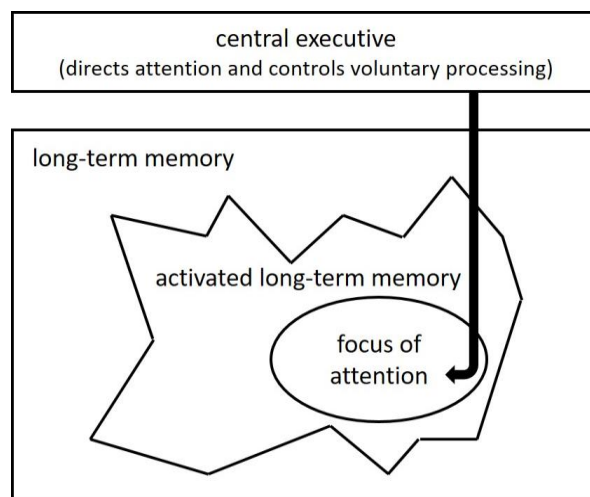
Figure 4. **Cowan's embedded-processes model of WM.**

Cowan's model (1988, 1995, 1999, 2008) represents a multi-component view because according to it, WM encompasses central executive processes plus STM, which is the part of LTM that is temporarily activated. STM information can be brought to a highly accessible state – the focus of attention – by means of central executive processes. This illustration was adapted from Cowan, N., Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system, *Psychol Bull*, 1988, 104(2), p. 180, Fig. 1. Copyright © 1988 by the American Psychological Association and from Cowan, N., What are the differences between long-term, short-term, and working memory?, *Prog Brain Res*, 2008, 169, Fig. 1. Copyright © 2008 by Elsevier. Adapted with permissions from the American Psychological Association and Elsevier (license number: 4159441172720).

Other state-based models of WM are very similar to Cowan's approach but have a varying number of states of accessibility in which WM content can exist (Eriksson et al., 2015). Importantly, state-based WM models do not contradict the basic assumptions of Baddeley's multi-component WM model (2000) (Baddeley, 2010; Cowan, 2008; Eriksson et al., 2015). For instance, both Cowan (1999, 2008) and Baddeley (2000) claimed that STM and executive attentional processes which manipulate maintained STM content are two independent processing types that are both crucial for WM performance. Contrary to Baddeley (2000) however, Cowan (1999, 2008) did not assume that there are independent domain-specific WM storage systems that are restricted to WM. Instead, he suggested that STM is a specific part of LTM that is temporarily brought into a highly accessible state by activating it. Thus, Cowan would interpret Baddeley's phonological loop and visuo-spatial sketch pad (Baddeley, 1983; Baddeley & Hitch, 1974) as activated LTM (Cowan, 2008).

2.3 Working memory domains

The characteristics of the material that is maintained in WM define its WM domain. One of the central ideas in Baddeley's multi-component WM model (Baddeley, 1983; Baddeley & Hitch, 1974) is the subdivision of STM stores according to different WM domains. While the phonological loop stores language- and sound-based material, the visuo-spatial sketch pad is responsible for maintaining spatial and object-based information (Baddeley, 1983; Baddeley & Hitch, 1974). In agreement with this division, researchers usually focus on visual and auditory modalities when examining WM processes by using visual and auditory stimuli (Dade, Zatorre, Evans, & Jones-Gotman, 2001) and differentiate between three main WM domains: "verbal WM," "spatial WM," and "object WM" (Cabeza & Nyberg, 2000; Smith & Jonides, 1999; Wager & Smith, 2003). The *verbal domain* refers to WM material that is mainly linguistically coded and that is stored in WM by means of a rehearsal process, which subvocally repeats the to-be-remembered items. Thus, examples of the verbal WM domain are letters, words and numbers (Wager & Smith, 2003) which can be presented in both visual and auditory modalities (Baddeley, 2003). Contrary, the *spatial domain* refers to the position of items in space and the *object domain* includes maintenance of the appearance of an object independent of its spatial location like, e.g., its shape, size, and color. The latter two domains are mainly investigated in the visual modality (Wager & Smith, 2003). In the scope of this dissertation, I also examined WM processes in the verbal, spatial, and object WM domains and in the visual modality.

2.4 Individual differences in working memory capacity and its development across the lifetime

As STM is a crucial element of all domains of WM (Baddeley, 1983, 2000; Baddeley & Hitch, 1974; Cowan, 2008), the characteristics of STM that I already described on page 5 in more detail are also valid for verbal, spatial, and object WM. Namely – like STM – WM is limited in time in the sense that WM content decays within a few seconds unless it is actively maintained by rehearsal processes (Baddeley, 2000; Cowan, 1999, 2008; Schermer, 2014). WM is also limited in capacity in the sense that humans are highly constrained in the number of items they can concurrently store in WM short-term buffers (Baddeley, 2000; Baddeley & Hitch, 1974; Cowan, 1999, 2008; Miller, 1956; Schermer, 2014). A further important feature of WM – independent of its domain – is its variability of capacity across individuals (Eriksson et al., 2015). Different people are capable of maintaining a different number of elements simultaneously in WM, which usually ranges in healthy adults between two and six items (Cowan, 2008). Although, capacity estimates of WM strongly correlate between WM domains (Kane et al., 2004), a person's capacity limits can differ between various domains (Kane et al., 2004; Thomason et al., 2009).

Moreover, investigations using correlational approaches also have demonstrated that an individual's WM capacity estimate highly correlates with more general measures of his or her cognitive capability like, for instance, intelligence measures, reading comprehension, or academic achievement (Cowan, 2008; Daneman & Carpenter, 1980; Gathercole, Lamont, & Alloway, 2006; Kane et al., 2004). Interestingly, WM measures that include both storage and executive processing correlate more strongly with other measures of cognition than do WM measures coming from simple storage tasks (Cowan, 2008; Daneman & Carpenter, 1980; Engle & Kane, 2004; Kane et al., 2004; Turner & Engle, 1989). Although, it is not clear which exact executive functions determine the correlation of a WM task with other high-cognitive measurements (Baddeley, 2010), there are hints that deploying attentional control under demanding circumstances is the key executive process responsible for these correlations (Engle & Kane, 2004; Eriksson et al., 2015; Kane et al., 2004). Also, it is assumed that interindividual differences in WM capacity result from capacity differences of such an attentional system and not from the capacity of the storage systems per se (Cowan, 2008; Engle, 2002; Kane et al., 2004).

There is not only variance of WM capacity between individuals but also within an individual across their lifetime. Namely, WM capacity increases during childhood until the age of approximately 15 years (Gathercole, Pickering, Ambridge, & Wearing, 2004; Nagel, Herting, Maxwell, Bruno, & Fair, 2013; Ullman, Almeida, & Klingberg, 2014); it then stays relatively stable until it starts to linearly decrease with increasing age. Some researchers propose that

this decline in WM performance starts at the age of approximately 50 (Nyberg et al., 2014), while others found that it begins already in a person's twenties (Park et al., 2002). Age-related WM decline similarly concerns verbal, spatial, and object WM domains (Park et al., 2002). It is more pronounced in tasks that require simultaneous storage and executive processing like manipulation tasks than in tasks requiring mainly simple storage processes, which favors the idea that it is the executive control component of WM that deteriorates with increasing age (Nyberg et al., 2014; Reuter-Lorenz & Sylvester, 2005). Indeed, the WM decline with increasing age is comparable to age-related decline in other cognitive domains like perceptual speed, episodic long-term learning, inhibition, and executive control, all of which encompass an essential contribution of mental efforts, or in other words of executive functions (Baltes & Lindenberger, 1997; Hultsch, Hertzog, Dixon, & Small, 1999; Moscovitch & Winocur, 1992; Park, 2012; Park et al., 2002; Park & Reuter-Lorenz, 2009). In contrast, the cognitive domains of implicit and semantic LTM requiring less mental effort do not show an age-related decline (Hultsch et al., 1999; Park, 2012; Park et al., 2002; Park & Reuter-Lorenz, 2009).

2.5 Psychophysical paradigms to assess working memory capacity and to reveal working memory processes

Traditionally, researchers have measured capacity limits of WM by means of memory span tasks which reveal how much information a person can maintain in WM (Engle & Kane, 2004; Reuter-Lorenz & Sylvester, 2005). As mentioned earlier, multi-component models of WM propose that WM consists of various components working together to ensure successful WM performance. Again, crucial components are short-term storage mechanisms and higher cognitive control processes that help to effectively store information in STM (Baddeley, 1983, 2000; Baddeley & Hitch, 1974; Cowan, 1999, 2008). The specific components researchers are interested in decide what kind of span task they use. For instance, simple *letter*, *word*, and *digit span tasks* (Cowan, 2000; Miller, 1956) measure WM capacity of the short-term storage component (STM span) and require relatively little engagement of executive processes. In these tasks, a series of letters, words, or digits are presented visually or auditorily to the subjects who have to immediately reproduce this series. The *memory load* – which is the number of items that has to be memorized – is varied in these series and the *memory span* is usually defined as the highest memory load at which subjects reproduce all items correctly (Engle & Kane, 2004; Reuter-Lorenz & Sylvester, 2005; Tewes, 1991). In contrast, complex WM span tasks like the *reading span task* (Daneman & Carpenter, 1980) and the *operation span task* (Turner & Engle, 1989) measure WM capacity of short-term maintenance plus executive control processes (WM span). More specifically, subjects work on simple span tasks

while WM is strained through a secondary cognitive task like, for instance, text comprehension in the case of the reading span task and solving arithmetic problems in the case of the operation span task (Engle & Kane, 2004; Reuter-Lorenz & Sylvester, 2005).

Contrary to the span tasks that assess WM capacity, two different WM tasks have occurred frequently in neuroimaging studies to reveal the representation of the various WM components in the human brain. These tasks are the "delayed match-to-sample task" (Sternberg, 1966), also known as "item-recognition task" and the "n-back task" (Reuter-Lorenz & Sylvester, 2005; Smith & Jonides, 1999; Wager & Smith, 2003).

The *delayed match-to-sample task* allows to separately investigate the important WM stages of encoding, maintenance, and recall. In particular, subjects see a series of items either sequentially or simultaneously during the encoding period of a trial. In the subsequent delay or maintenance period, participants are asked to maintain the previously seen items in memory. Finally in the response period, they are presented with a probe item and asked whether it was part of the original series (Sternberg, 1966). Like the simple span tasks, the delayed match-to-sample task was typically used to examine STM processes per se, such as the storage components of WM like phonological rehearsal (Smith & Jonides, 1999). This is usually achieved by choosing memory loads that are relatively low and that lie within an individual's WM capacity (Cowan, 2000; Miller, 1956). However, please note, that it is also possible to evoke executive control processes with the delayed match-to-sample task when using high load levels which bring a person to his or her personal capacity limit (Reuter-Lorenz & Sylvester, 2005; Schneider-Garces et al., 2010; Smith & Jonides, 1999).

In contrast, the *n-back task* requires continuous updating of information in WM and thus evokes executive processes in addition to storage processes (Smith & Jonides, 1999). This makes it a popular choice for measuring executive functions of WM (Baddeley, 2003). In this task, subjects see a long sequence of items, and the subject's task is to indicate for every item if it was presented *n* positions previously in the stimuli series. Commonly, *n* varies between 1 and 3, which determines if a WM task is characterized as a 1-, 2-, or 3-back task (Baddeley, 2003; Smith & Jonides, 1999; Wager & Smith, 2003).

In the next chapter, I will introduce brain regions and lateralization patterns that are associated with the storage and executive control processes of WM. Among other methodological approaches, these brain regions have been detected by using variants of the delayed match-to-sample and n-back tasks, respectively, in neuroimaging studies (Baddeley, 2003; Smith & Jonides, 1999; Wager & Smith, 2003).

3 Brain regions and lateralization patterns associated with working memory processes

In accordance with the assumption that WM is the result of various processes that simultaneously work together (Baddeley, 1983, 2000; Baddeley & Hitch, 1974; Cowan, 1999, 2008; Eriksson et al., 2015), former studies have demonstrated that a variety of different brain regions are concurrently activated to support WM (Baddeley, 2003; Cabeza & Nyberg, 2000; Eriksson et al., 2015; Smith & Jonides, 1999; Wager & Smith, 2003). The exact brain regions that are used for maintaining the items of a task in WM are determined by the WM domain and by the processing requirements of the WM task, e.g., whether it mainly requires storage processes or also additional executive processes (Cabeza & Nyberg, 2000; Eriksson et al., 2015; Smith & Jonides, 1999; Wager & Smith, 2003). For instance, consistently with the model developed by Baddeley and Hitch (1974) and Baddeley (1983), lesion studies and neuroimaging studies with healthy adults demonstrated that the three main components of this WM model are represented by different parts of the brain (Baddeley, 2003; Cabeza & Nyberg, 2000; Eriksson et al., 2015; Smith & Jonides, 1999). While rehearsal processes of the storage components and the executive control component were shown to be mainly situated in prefrontal and premotor brain regions, the actual storage of information is said to be localized more posteriorly in sensory parietal, temporal and occipital regions, which are also known for their contribution to perceptual and LTM processing of the same kind of information (Awh et al., 1996; D'Esposito & Postle, 1999, 2015; Eriksson et al., 2015; Paulesu, Frith, & Frackowlak, 1993; Petrides, 1995). The later point is in line with the main idea of the state-based models of WM assuming that short-term storage of WM shares the same neuronal sources with LTM and perceptual processing (D'Esposito & Postle, 2015; Eriksson et al., 2015; Lewis-Peacock & Postle, 2008).

The aforementioned cerebro-cortical areas are certainly the major constituent of the network of brain regions supporting WM. Nevertheless, it is crucial to stress that various subcortical areas do contribute as well to WM processes (Eriksson et al., 2015; Smith & Jonides, 1999; Stoodley & Schmahmann, 2009; Wager & Smith, 2003). In this dissertation, I will, however, only focus on the earlier cerebro-cortical areas. I will introduce the respective frontal and posterior cerebral regions in the following sections.

3.1 Prefrontal and premotor brain regions

Numerous studies applying a broad range of methods ranging from single-cell recordings in non-human primates (Fuster & Alexander, 1971) to lesion studies (D'Esposito &

Postle, 1999) and neuroimaging approaches with healthy human adults (Cabeza & Nyberg, 2000; Curtis & D'Esposito, 2003; D'Esposito et al., 1998; Fiez et al., 1996; Reuter-Lorenz et al., 2000; Smith & Jonides, 1999; Wager & Smith, 2003) have identified the *prefrontal cortex (PFC)* as one of the key brain regions that is responsible for the successful maintenance of information in WM. Although there is not yet an explicit consensus on how PFC is functionally organized with respect to WM (Eriksson et al., 2015), the WM research community shares the notion that the prefrontal brain areas supporting WM processes are organized according to a) WM domain and b) processing demands of a task (simple storage vs. simple storage plus executive functioning) (Curtis & D'Esposito, 2003; Eriksson et al., 2015; Smith & Jonides, 1999; Wager & Smith, 2003).

With respect to the organization according to WM domain, there is left-lateralization of verbal WM and right-lateralization of spatial WM in PFC (D'Esposito et al., 1998; D'Esposito & Postle, 1999; Owen, McMillan, Laird, & Bullmore, 2005; Reuter-Lorenz et al., 2000; Smith, Jonides, & Koeppe, 1996; Wager & Smith, 2003). This domain-specific lateralization was also found in premotor and insular cortices. For instance, in addition to *Broca's area* that corresponds to Brodmann's area (BA) 44 and BA 45 in the left *ventrolateral prefrontal cortex (VLPFC)* (Berker, Berker, & Smith, 1986), also the *insula*, the *supplementary motor area* (*SMA*), and *ventral premotor cortex* (*PMv*, BA 6) show left-lateralization for verbal WM material in WM tasks mainly requiring simple-storage processes (Awh et al., 1996; Baddeley, 2003; Smith & Jonides, 1999; Smith et al., 1996; Wager & Smith, 2003). Activations in Broca's area, left SMA and left PMv were associated with the phonological loop of Baddeley's model. More specifically, these brain regions – which are known to be crucial for spoken language – also support subvocal repetition of the WM material, which is a basic mechanism of the rehearsal process of the phonological loop (Awh et al., 1996; Baddeley, 2003; Paulesu et al., 1993; Smith & Jonides, 1999). In contrast, several cross-hemispheric counterparts of ventral prefrontal cortex and premotor cortex in the right hemisphere have been related to visuospatial short-term maintenance, namely right BA 47 and right BA 6 (Baddeley, 2003; Fiez et al., 1996; Smith & Jonides, 1999; Smith et al., 1996). Inspired by imaging studies showing that spatial attention and spatial WM both activate the same spots in right premotor cortex (Awh & Jonides, 1998), Smith and Jonides (1999) concluded that activation of right premotor areas during spatial storage-tasks may represent a spatial rehearsal process that covertly moves attention across the locations of the items held in spatial WM.

A further idea of domain-specific organization of PFC is the organization of spatial vs. object items. It is known that for visual processing in posterior parts of the brain there is a dorsal-ventral organization of object location vs. object identity, respectively (Cabeza & Nyberg, 2000; Ungerleider & Haxby, 1994). A similar organization is thought to be preserved

in PFC during WM maintenance, in the sense that spatial items are processed more dorsally than object items (D'Esposito et al., 1998; Smith & Jonides, 1999; Wager & Smith, 2003). Yet, while electrophysiological studies in monkeys (Wilson, Scalaidhe, & Goldman-Rakic, 1993) and neuroimaging studies (Smith & Jonides, 1999) have provided some support for this notion, meta-analyses of relevant studies did not show such a dorsal-ventral distinction between spatial and object material (Cabeza & Nyberg, 2000; Wager & Smith, 2003).

A possible explanation for the studies supporting a dorsal-ventral organization of PFC between WM domains may be that the spatial and object-oriented tasks used in those studies required different executive processes (Eriksson et al., 2015; Wager & Smith, 2003). This interpretation supports the idea that PFC is organized in a dorsal-ventral direction according to processing type in the sense that storage-only tasks rely on ventral PFC, while WM tasks that also evoke executive processes additionally recruit dorsal PFC (Owen et al., 1999; Petrides, 1995). Empirical evidence for this notion comes from neuroimaging studies demonstrating that WM paradigms which engage storage-related and executive processes lead to activations in ventral prefrontal and premotor cortices comparable to those found in storage-only WM tasks (see above). However, the following dorsal parts of frontal cortex are additionally activated (D'Esposito et al., 1998; Owen et al., 1999; Smith & Jonides, 1999; Wager & Smith, 2003), and their activity scales with increasing executive task demand (Braver et al., 1997; Cabeza & Nyberg, 2000; Eriksson et al., 2015; Smith & Jonides, 1999; Wager & Smith, 2003): *dorsolateral prefrontal cortex (DLPFC)* that is situated in BA 46 and BA 9, *anterior prefrontal cortex* (*aPFC*, BA 10), and the *frontal eye fields* (*FEF*) of the *dorsal premotor cortex* (*PMd*), which are located in BA 6 and BA 8. In accordance with these findings and the notion that executive processes are generally associated with DLPFC (Baddeley, 2003; Smith & Jonides, 1999; Wager & Smith, 2003), Baddeley (2003) proposed the central executive of his WM model to be localized in DLPFC.

It is important to note that executive functions related to WM encompass a broad scope of various processes like, for instance, attention, inhibition, planning, updating, refreshing, and manipulation (D'Esposito & Postle, 1999; Smith & Jonides, 1999; Wager & Smith, 2003). Contrary to the domain-specific storage processes, it is thus not trivial to specify a general lateralization pattern of such executive WM processes in PFC. It may possible that various executive functions show different lateralization patterns. Left-lateralization of the executive WM function "refreshing" (Johnson et al., 2005) and right-lateralization of the executive functions "manipulation" (Wager & Smith, 2003) and "updating" (D'Esposito et al., 1998) in DLPFC support this notion.

3.2 Parietal, temporal, and occipital brain regions

Like prefrontal and premotor areas, the parietal cortex is also strongly associated with WM processes (Baddeley, 2003; Cabeza & Nyberg, 2000; Eriksson et al., 2015; Fiez et al., 1996). For instance, left and right *superior parietal lobules* (*SPL*, BA 7) are especially activated in humans when they work on WM tasks that require executive processes independent of the WM domain (Baddeley, 2003; Cabeza & Nyberg, 2000; Wager & Smith, 2003). They are also active during non-mnemonic tasks requiring attention (Cabeza & Nyberg, 2000). Thus, BA 7 is assumed to play an executive processing role in WM (Koenigs, Barbey, Postle, & Grafman, 2009; Wager & Smith, 2003) like, for example, focusing attention (Awh, Vogel, & Oh, 2006; Eriksson et al., 2015).

Furthermore, the *inferior parietal lobule* (BA 40) has been related to short-term maintenance in addition to the frontal areas such as VLPFC, SMA, and PMv, with left and right BA 40 involved in the maintenance of verbal vs. spatial material, respectively (Baddeley, 2003; D'Esposito & Postle, 1999; Smith & Jonides, 1999; Smith et al., 1996; Vallar, Di Betta, & Silveri, 1997). While the three frontal maintenance regions most probably reflect rehearsal mechanisms of the storage WM component (Awh et al., 1996; Baddeley, 2003; Paulesu et al., 1993; Smith & Jonides, 1999), BA40 is assumed to play a role in the actual short-term storage of WM items (Awh et al., 1996; Baddeley, 2003; D'Esposito & Postle, 1999; Smith & Jonides, 1999; Vallar et al., 1997).

Further brain regions located in temporal and occipital cortices have been associated with the storage component of WM (D'Esposito & Postle, 2015; Eriksson et al., 2015; Wager & Smith, 2003). For instance, *inferior temporal gyrus* (*ITG*) is more likely to be activated in storage-only WM tasks than in tasks that additionally require executive processes (Wager & Smith, 2003). This region preferentially maintains object WM material in both hemispheres (Cabeza & Nyberg, 2000; Wager & Smith, 2003). Also, the visual cortex located in *the occipital lobe* (BAs 17, 18, and 19) is recruited in storage-only tasks, particularly visuospatial ones (Cabeza & Nyberg, 2000), rather than in WM tasks requiring executive processes (Wager & Smith, 2003).

The previously reported findings of posterior cortex suggest that there is an overlap between the storage component of WM and perceptual processes in parietal, temporal, and occipital cortices. For instance, as mentioned above, left and right BA 40 play an important role in the WM storage of verbal and spatial items, which aligns with their specializations in verbal (Benson et al., 2001) and spatial (Andersen, 2011; Zimmer, Lewald, Erb, & Karnath, 2006) perceptual processing, respectively. Moreover, the known dissociation between spatial and object items in dorsal parietal vs. ventral temporal perceptual processing streams (Cabeza & Nyberg, 2000; Ungerleider & Haxby, 1994), respectively, is preserved in WM in the sense that

spatial WM storage-only tasks mainly rely on parietal cortex, whereas comparable object WM tasks recruit ITG even when the perceptual and motor requirements of the WM tasks were controlled (Baddeley, 2003; Cabeza & Nyberg, 2000; Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Pisella, Berberovic, & Mattingley, 2004; Smith & Jonides, 1999; Wager & Smith, 2003). As already mentioned, such findings match the main assumption of state-based WM models that the posterior brain regions in parietal, temporal, and occipital cortices, which are involved in perceptual processing and LTM of specific information, are also responsible for the short-term storage of such information (D'Esposito & Postle, 2015; Eriksson et al., 2015). There are further findings in the literature supporting this notion: firstly, although the *medial temporal lobe* – including the hippocampus and the adjacent entorhinal, perirhinal, and parahippocampal cortices – has commonly been linked to LTM processes, more recent studies have shown that it is also important for storing information in WM (Jeneson & Squire, 2011). According to the state-based models, the underlying mechanism might be that information maintained in WM is related to information stored in LTM (Jeneson & Squire, 2011). Secondly, multivariate pattern analyses on human functional neuroimaging data successfully decoded items that were maintained in WM on the basis of activity patterns of LTM and perceptual processing in temporal and occipital cortices, respectively (for an overview, please refer to D'Esposito & Postle, 2015). Such results can only occur when WM shares neural representations with LTM and perceptual processing (D'Esposito & Postle, 2015).

4 How the brain may tackle highly demanding working memory situations

In our everyday life, we quiet often track our goals without great endeavor, while WM operates unconsciously and is not strained very much. However, we also frequently encounter situations in which the pursuit of our goals becomes extremely challenging. For instance, a task that requires WM processes can be highly demanding for a person when this task exceeds the person's WM capacity. As mentioned in chapter 2 of this dissertation, WM capacity is not constant. In contrast, it can vary within a person across various situations. This intrapersonal variation can be either transient, e.g., due to temporary sleep deprivation or illness, or permanent, namely due to changes in the brain elicited by, e.g., brain injury, neurological disease or aging (Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006). In the example of aging, WM capacity decreases with increasing age (compare section 2.4), so that a WM task that is easy for a 20-year old can become highly demanding for this person in his/ her seventies. In the previous chapter, I introduced brain regions and their lateralization patterns that are known for their engagement in relatively simple storage-only WM situations and WM tasks also requiring executive processing. In the following sections, I will focus on ideas that explain how some of these brain regions might manage to successfully deal with highly demanding WM challenges at the limits of human WM capacity. These ideas and the underlying empirical evidence mainly come from the research field of the cognitive neuroscience of aging – which deals with the question how aging affects cognition, brain functions, brain structures, and their interplay and hence focuses on examining older adults (Cabeza, Nyberg, & Park, 2005; Grady, 2012). For this reason, I will begin this chapter with the introduction of typical findings from functional neuroimaging studies investigating age-related differences in brain activation during cognitive tasks. As aging is one of the factors decreasing WM capacity and, thus, increasing the demand of a specific WM task, such studies provide a crucial contribution to answering the question how the human brain might generally cope with increased WM demand.

4.1 Age-related differences in functional neuroimaging studies of cognitive functions: underactivation vs. overactivation

Within the field of the cognitive neuroscience of aging, researchers have conducted functional neuroimaging studies using mainly *positron emission tomography* (PET) or *functional magnetic resonance imaging* (fMRI) with humans of varying age groups while they worked on cognitive tasks to investigate potential age-related differences in brain activation

that is associated with cognitive processes (Grady, 2012; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2010; Reuter-Lorenz & Sylvester, 2005). In accordance with general detrimental developments with increasing age like, for instance, declines in cognitive performance (compare section 2.4), brain volume (Raz, 2000), white matter integrity (Head et al., 2004), and dopamine receptors (Wong, Young, Wilson, Meltzer, & Gjedde, 1997), researchers also found *underactivation*, or in other words reduced neural activation, in several brain areas in elderly subjects compared to younger participants (Cabeza et al., 1997; Grady et al., 1994; Grady et al., 1995; Logan, Sanders, Snyder, Morris, & Buckner, 2002; Park & Reuter-Lorenz, 2009). However, surprisingly, there is quite often also *overactivation* in certain brain areas – frequently in prefrontal areas – in elderly adults relative to their younger counterparts while they cope with the same cognitive tasks (Cabeza et al., 1997; Grady et al., 1994; Gutchess et al., 2005; Madden et al., 1999; Reuter-Lorenz et al., 2000). For instance, Grady et al. (1994) were one of the first to report such overactivation in various brain regions of elderly adults during face- and spatial- visual processing. More specifically, they found that, besides underactivation in occipital and temporal cortices, there was overactivation in prefrontal and parietal areas. This turned out to be a common pattern in aging studies using functional neuroimaging methods (Cabeza et al., 2004; Gutchess et al., 2005), which has been named *posterior-anterior shift in aging (PASA)* (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008).

Please note that underactivation and overactivation are meant in a purely relative manner to compare older adults' activation to that of younger adults (Reuter-Lorenz & Cappell, 2008). More specifically, these terms are used to express a) the activation strength within a specific brain region, b) the number of task-related brain areas that are activated above a statistical threshold criterion, or c) the spatial extent (number of voxels that are activated above a statistical threshold criterion) within a specific brain region in elderly participants relative to the respective activation strength, number of brain areas, or spatial extent within a region in younger adults (Reuter-Lorenz & Park, 2010) (see figure 5 for an illustration).

Underactivation is commonly perceived as evidence for an age-specific deficit that is caused by sub-optimal usage of cognitive strategies or by detrimental structural changes of the aged brain (Grady, 2012; Logan et al., 2002; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005). Overactivation has also been interpreted in a negative way by some researchers. For instance, the *dedifferentiation hypothesis* claimed that additional brain activation in the elderly represents an age-specific neural deficit in the selective recruitment of task-relevant brain regions. In other words, this notion emphasizes that specific functions are supported by specific brain regions in young adults, and that there is a reduction of such specialization (which is dedifferentiation) with increasing age (Baltes & Lindenberger, 1997;

Grady, 2012; Logan et al., 2002; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2010). Support for this hypothesis comes from a neuroimaging study demonstrating that ventral visual cortex, which consists of subregions that selectively respond to visual categories like faces (Kanwisher, McDermott, & Chun, 1997), places (Epstein & Kanwisher, 1998) and written words (Polk et al., 2002) in young adults, loses its specificity to visual categories in older adults, such that visual stimuli from all categories activate all subregions indiscriminately (Park et al., 2004). This finding matches behavioral results showing that cognitive processes become more and more dedifferentiated with increasing age (Park et al., 2004), namely that correlations between various cognitive measures (Li et al., 2004) and between cognitive and sensory measures (Baltes & Lindenberger, 1997) are stronger in elderly than in young adults (see also page 91 in section 8.4.1 for further details).
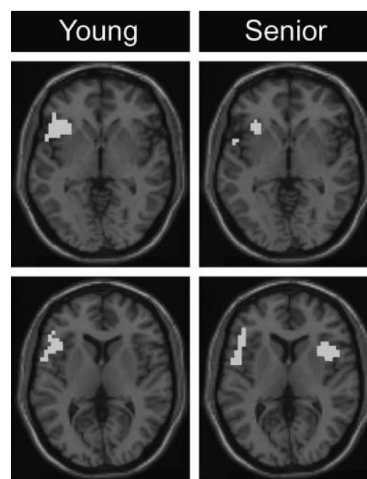
Figure 5. **Illustration of underactivation vs. overactivation.**

This figure illustrates underactivation (first row) vs. overactivation (second row). In this example, older adults (second column) activate a smaller area within a specific brain region than young adults (first column) in the example of underactivation, while they recruit an additional brain area relative to younger adults in the example of overactivation. This figure is reprinted from Reuter-Lorenz, P. A. & Cappell, K. A., Neurocognitive aging and the compensation hypothesis, *Curr Dir Psychol Sci*, 2008, 17(3), p. 178, Fig. 1. Copyright © 2008 by SAGE Publications. Reprinted with permission from SAGE Publications.

In contrast to a detrimental interpretation of overactivation, Grady et al. (1994) interpreted the overactivation of older adults in prefrontal areas as a compensatory mechanism in the sense that elderly adults are able to recruit additional brain areas to compensate for the deficits of other brain areas. This idea was also emphasized by Davis et al. (2008) who proposed that elderly adults have processing deficits in occipitotemporal visual regions that must be compensated by frontal overactivation in order to maintain performance in cognitive

tasks. Indeed, there is converging empirical evidence that the age-related overactivation of prefrontal brain regions is compensatory for reduced neural efficiency of sensory and perceptual brain regions (Park & Reuter-Lorenz, 2009). This evidence comes from studies showing that prefrontal overactivation is linked to improved cognitive performance (Cabeza, Anderson, Locantore, & McIntosh, 2002; Davis et al., 2008; Gutchess et al., 2005; Reuter-Lorenz et al., 2000) and to occipitotemporal decreases in activation in elderly but not younger subjects (Davis et al., 2008; Gutchess et al., 2005).

A particular case of overactivation that is commonly described in the literature is the "hemispheric asymmetry reduction in older adults" (Cabeza, 2002), which I will present in more detail in the next section.

4.2 Hemispheric asymmetry reduction in older adults (HAROLD)

Functional neuroimaging studies have shown that older subjects recruit a less lateralized activation pattern compared to young participants when they complete various cognitive tasks that are based on LTM, WM, perception, and inhibitory control processes (Cabeza, 2002): while young subjects unilaterally activate specific task-relevant brain regions, older adults additionally activate corresponding regions in the other hemisphere (Cabeza, 2002; Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000). This phenomenon was termed *hemispheric asymmetry reduction in older adults* (*HAROLD*) by Cabeza (see also figure 6 for an illustration) and mainly occurs in prefrontal areas like aPFC and DLPFC of high-performing older subjects (Cabeza, 2002).
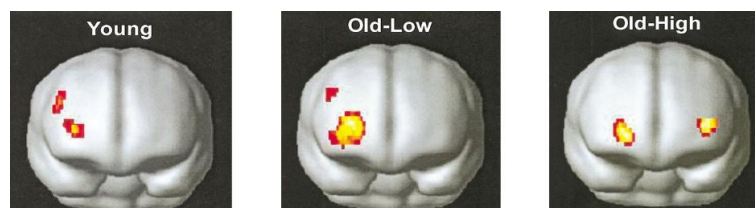
Figure 6. **Illustration of the HAROLD phenomenon.**

This figure illustrates the HAROLD phenomenon by demonstrating unilateral activation of PFC in young and old low-performing subjects during the execution of a cognitive task and bilateral activation of the same brain region in old high-performing subjects. This figure was modified from Cabeza et al. (2002), Aging gracefully: compensatory brain activity in high-performing older adults, *NeuroImage*, 2002, 17(3), p. 1399, Fig. 2. Copyright © 2002 by Elsevier. Modified with permission from Elsevier (license number: 4159420238296).

In the domain of WM, the HAROLD phenomenon was first demonstrated in a neuroimaging study, in which subjects worked on a verbal and a spatial delayed match-to-sample task while they were in a fMRI scanner. While young subjects showed left-lateralized activity for verbal and right-lateralized activity for spatial WM in frontal brain regions, older participants significantly activated both hemispheric counterparts in these regions during both WM tasks (Reuter-Lorenz et al., 2000).

The HAROLD phenomenon was not only demonstrated by means of functional neuroimaging studies but also in studies using *repetitive transcranial magnetic stimulation (rTMS)*. rTMS is a method that manipulates neural activity by using magnetic pulses to induce electric currents in small, circumscribed brain volumes. Depending on the stimulation parameters, rTMS can either facilitate or inhibit neural processing. For instance, rTMS can be used to elicit temporary, reversible disruptions. In young adults, applying rTMS in such "deactivating mode" to the right DLPFC as opposed to the left one during memory retrieval elicited a stronger perturbation in memory performance in LTM tasks (Rossi et al., 2001; Rossi et al., 2004). In contrast, older participants were equally impaired during LTM retrieval no matter whether rTMS was applied to the right or left DLPFC. This result speaks in favor of the ideas that, unlike young adults, old participants use bilateral activation to successfully solve the task and that overactivation in the form of bilateral prefrontal activation patterns represents a compensatory and not a dedifferentiating function (Rossi et al., 2004).

The interpretation that bilateral activation patterns in elderly adults have a beneficial role was also proposed by Cabeza, who suggested that the HAROLD phenomenon may be a mechanism specific to older adults that is deployed to compensate age-related neurocognitive decline (Cabeza et al., 2002; Cabeza et al., 1997). Further empirical evidence for this idea comes from studies showing that bilateral prefrontal activation patterns are associated with better behavioral performance in older adults: for instance, Cabeza et al. (2002) divided their elderly participants into a high-performing and a low-performing old subgroup on the basis of the performance in memory tests during a screening session. During a subsequent verbal memory task, young subjects and low-performing older participants recruited the right aPFC, while high-performing older adults additionally activated the respective counterpart in the contralateral left hemisphere (compare figure 6). Moreover, Reuter-Lorenz et al. (2000) demonstrated that elderly subjects showing bilateral DLPFC activation were faster in a verbal WM task than elderly participants who had a more unilateral activation pattern.

4.3 Banich's model of how cerebral cortex copes with demanding cognitive tasks

The lateralization of specific functions is one of the basic organizational principles of human cerebral cortex. For instance, it is well established that language and speech are predominantly supported by the left hemisphere in right-handed humans and that precise motor control of the hands is controlled by the contralateral hemisphere (Gazzaniga, 1995, 2000; Hervé, Zago, Petit, Mazoyer, & Tzourio-Mazoyer, 2013). Moreover, memory functions in general (Gazzaniga, 2000) and, as was reported earlier in chapter 3, specific WM processes in particular seem to be lateralized such that verbal and spatial WM tasks are supported by the left and right hemisphere, respectively. Considering this lateralized organization of the human brain, the HAROLD phenomenon (Cabeza, 2002) showing that elderly adults recruit apparently dormant nonspecialized cross-hemispheric counterparts of specific brain regions might be astonishing.

A real contradiction would only emerge if there were absolute lateralization in the sense that first, each member of a specific cross-hemispheric pair was restricted to different functions and second, each specific task could be processed by only one of the two members (Höller-Wallscheid, Thier, Pomper, & Lindner, 2017). However, Marie Banich's group (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998) proposed that both hemispheres of the human brain are in principal able to process the same kind of information coming from most cognitive tasks. However, the left and right hemispheres have different degrees of competence to process this information because they are highly specialized with respect to their processing modes. For instance, the left hemisphere predominantly performs verbal processing, while the right hemisphere specializes in visuospatial processing. The cognitive demands of a task and the costs of recombining information following interhemispheric processing by means of the corpus callosum determine if the dominant hemisphere for the task-related processing mode processes the information alone or if the second hemisphere is also recruited. Usually the hemisphere with the specialized mode can process subjectively easy tasks on its own, while in more difficult tasks, the brain increases its capacity by distributing task load among the two hemispheres. In this way, different features of a task can be processed simultaneously and independently in various processing modes (Banich, 1998; Belger & Banich, 1992, 1998).

Empirical evidence for this theory comes from behavioral studies using letter-matching tasks in which subjects indicated whether a target letter matches one of various simultaneously presented probe letters (Banich & Belger, 1990; Belger & Banich, 1992, 1998; Reuter-Lorenz, Stanczak, & Miller, 1999). Cognitive demand of tasks was manipulated in these studies by varying their processing complexity. More specifically, subjects matched letters on the basis of their "physical-identity" (*less-demanding tasks*) or "name-identity" (*more-demanding tasks*).

In the *physical-identity tasks*, all letters were upper-case letters so that participants simply compared target and probe letters on the basis of their physical appearance (e.g., A vs. A). However, in the *name-identity tasks*, the target letter was a lower-case letter, and the probe letters were upper-case letters (e.g., a vs. A). Thus, subjects did not contrast the forms of letters but their names in the latter tasks, which requires processing that is computationally more complex than simply matching the visual appearance of letters (Banich & Belger, 1990; Belger & Banich, 1992, 1998; Reuter-Lorenz et al., 1999). Moreover, some researchers additionally varied task demand within the physical-identity conditions by presenting two (less-demanding tasks) vs. four (more-demanding tasks) probe letters (Belger & Banich, 1992, 1998; Reuter-Lorenz et al., 1999). All these studies compared performance between a) conditions in which all the information that is necessary for a decision (that are the target and matching probe letters) is presented within one visual hemifield and thus initially sent solely to the contralateral hemisphere (*within-hemisphere processing*) and b) conditions in which this information is divided between the left and right visual hemifields and thus requires cross-hemispheric processing in any case (*across-hemisphere processing*). Such studies discovered a within-hemisphere advantage of less demanding tasks and an across-hemisphere advantage of more demanding tasks (Banich & Belger, 1990; Belger & Banich, 1992, 1998; Reuter-Lorenz et al., 1999). Consequently, dividing processing of information between the hemispheres seems to be detrimental vs. beneficial for performance in easier and more difficult tasks, respectively (Banich & Belger, 1990).

Belger and Banich proposed that interhemispheric processing can boost processing capacity in almost all demanding cognitive tasks except for tasks in which only one hemisphere can handle a considerable percentage of the processing. Examples of such a task are linguistic tasks requiring phonetic processing, which is predominantly done by the left hemisphere in right-handed people (Belger & Banich, 1992, 1998). Support for the idea that specific language-based processes like phonology are restricted to the left hemisphere comes from studies on split-brain patients whose cerebral commissures were sectioned in an attempt to treat severe epileptic seizures (Gazzaniga, 1995, 2000). To empirically support their assumption, Banich's group demonstrated that – contrary to other demanding cognitive tasks – cross-hemispheric processing does not have a behavioral advantage over within-hemispheric processing in difficult phonetic tasks (Belger & Banich, 1998).

Based on Banich's ideas and empirical findings (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998), the HAROLD phenomenon does not necessarily need to be interpreted as an age-specific mechanism of the brain that compensates for neurocognitive decline in elderly adults (Cabeza et al., 2002; Cabeza et al., 1997). One could likewise assume that it merely reflects the fact that cognitive tasks used in previous aging studies demonstrating

the HAROLD phenomenon (Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000; Rossi et al., 2004) were subjectively more demanding for older than younger participants. Indeed, subjects of both the young and old age groups were presented with the same memory tasks in these studies despite the fact that cognitive performance in general and WM performance in particular decrease with age (Hultsch et al., 1999; Moscovitch & Winocur, 1992; Nyberg et al., 2014; Park et al., 2002). As already mentioned at the beginning of this chapter, the decreasing WM capacity with increasing age may cause elderly participants to experience the same cognitive tasks as subjectively more demanding than younger subjects. This may have led older subjects to recruit contralateral counterparts in PFC in order to produce behavioral performance comparable with that of their younger counterparts (Höller-Wallscheid et al., 2017; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2010; Schneider-Garces et al., 2010). This latter notion is at odds with the age-specific compensatory interpretation of the HAROLD phenomenon (Cabeza et al., 2002; Cabeza et al., 1997) but, instead, a principle element of the "compensation-related utilization of neural circuits hypothesis" (Reuter-Lorenz & Cappell, 2008), which I will introduce in the next section.

4.4 The compensation-related utilization of neural circuits hypothesis

As mentioned in the previous section, the finding of the HAROLD phenomenon (Cabeza, 2002) does not necessarily mean that the recruitment of bilateral activation patterns represents an age-specific compensation mechanism for neurocognitive decline. For example, the *compensation-related utilization of neural circuits hypothesis* (*CRUNCH*) offers an alternative interpretation suggesting that the recruitment of additional brain areas – including the cross-hemispheric counterparts of specific brain regions – represents an age-independent support mechanism that generally becomes effective as soon as a cognitive task becomes subjectively challenging. More specifically, CRUNCH was proposed to explain overactivations as well as underactivations in the elderly brain and assumes that such overactivations are not a phenomenon that is specific to advanced age but instead are a normal adaptation of the human brain to increased task demand (Reuter-Lorenz & Cappell, 2008).

Please, refer to figure 7 for an illustration of the specific predictions of CRUNCH with respect to brain activation and behavioral performance that I will describe in more detail in this paragraph: according to CRUNCH, neurocognitive decline leads to inefficient processing of information in older adults, which results in increased subjective difficulty of cognitive tasks. Consequently, older adults have to recruit additional neural resources for objectively easy task loads in order to maintain good task performance that is comparable to that of young adults

(compare levels 1 and 2 in figure 7). This overactivation is frequently found in prefrontal brain regions and often looks like bilateral activation patterns. In contrast, younger adults do not experience these objectively easy tasks as demanding and, thus, do not need to recruit additional neural resources. Instead, they show more specialized activation patterns at these lower load levels. However, with increasing task load (compare level 3 in figure 7), tasks should also become subjectively difficult for young adults so that they should also show additional recruitment of neural resources. This additional recruitment in young adults observed at higher objective load levels (compare level 3 in figure 7) should be comparable to that of older adults observed at lower objective task loads (compare level 2 in figure 7), when the respective load levels are subjectively equally difficult for young and old adults. A further idea of CRUNCH predicts that elderly adults cannot further deploy neural resources at high objective task loads since they have already exhausted their compensation resources at lower load levels (their activation plateaus at load level 2 in figure 7). Consequently, as objective task loads increase (compare level 3 in figure 7) older adults should show a decline of performance along with similar activation patterns or even underactivation of brain regions, as compared to young adults (Reuter-Lorenz & Cappell, 2008).
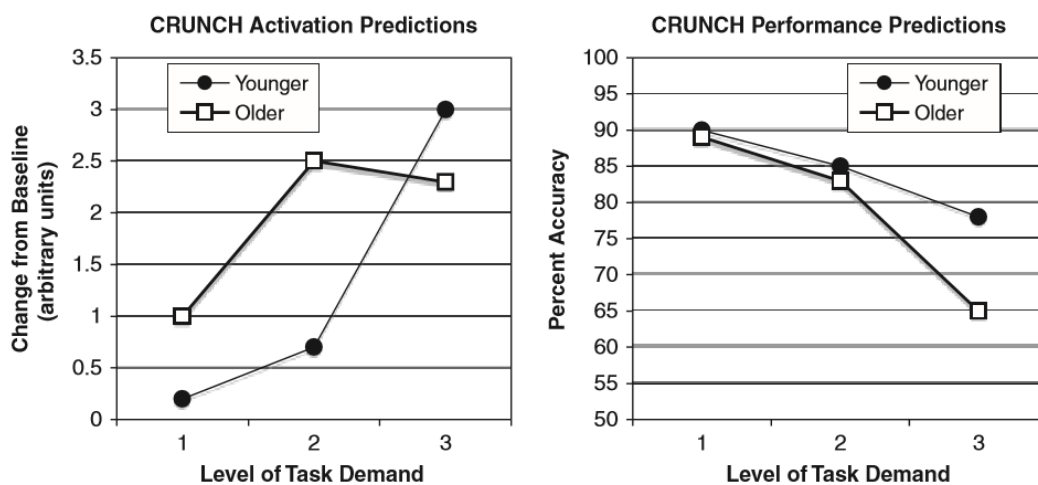
Figure 7. **Predictions of CRUNCH concerning activation strength and performance level.**

This illustration demonstrates the specific predictions of CRUNCH concerning activation strength (arbitrary units, left figure) and performance level (right figure). The left figure illustrates how – compared to young adults – older adults overactivate a specific brain region at lower objective task loads (levels 1 and 2) and underactivate this region at a higher objective task load (level 3). The right figure shows that overactivation in older adults at these lower task levels leads to good task performance that is comparable to that of younger adults. However, since older adults have exhausted their neural compensation resources at lower load levels (left figure), their performance breaks down at the highest task load (right figure). This illustration is reprinted from Reuter-Lorenz, P. A. & Cappell, K. A., Neurocognitive aging and the compensation hypothesis, *Curr Dir Psychol Sci*, 2008, 17(3), p. 180, Fig. 2. Copyright © 2008 by SAGE Publications. Reprinted with permission from SAGE Publications.

In summary, CRUNCH proposes that the basic neural mechanisms to cope with subjectively high task demands are the same in younger and older adults and that older adults use them at lower objective task loads because, unlike for young adults, these task loads are already subjectively challenging for them (Reuter-Lorenz & Cappell, 2008; Schneider-Garces et al., 2010).

5 Aims and hypotheses of this dissertation

What might be the underlying neural mechanism in the human brain that enables us to meet increased WM demands? A potential answer to this question is the additional recruitment of contralateral counterparts of specific task-related brain regions in PFC that is assumed to compensate for growing task demand in a domain-general manner (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998; Park & Reuter-Lorenz, 2009). As described in the previous chapter, empirical evidence for such compensatory prefrontal bilateral recruitment mainly comes from the research field of the cognitive neuroscience of aging. Here, it is well-established that older adults without any neurodegenerative diseases bilaterally activate PFC to compensate for increased WM task demand due to decreased WM capacity that is caused by age-related neurocognitive changes of the brain (Cabeza, 2002; Cabeza et al., 2002; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz et al., 2000). Thus, one can consider the factor "aging" as one possible approach to operationalize increased WM demand. It was unknown whether this bilateral recruitment of PFC is a general age-independent mechanism of the human brain in the face of increased task demands, which might also occur in young adults. Moreover, it was not known whether the recruitment of the contralateral hemisphere in demanding WM situations is specific to PFC or represents a general strategy of WM-related brain regions, and whether such recruitment is limited to specific WM domains or whether it occurs in a domain-general manner.

Hence, the aim of this dissertation was to investigate if the recruitment of contralateral counterparts of brain regions is a general support mechanism of the brain in response to very challenging WM tasks. More specifically, we wanted to find out if such bilateral activation patterns exist in humans independent of a) age, b) brain region and c) WM domain when they work on WM tasks that force them to their capacity limits.

Empirical evidence for the predictions of CRUNCH (Reuter-Lorenz & Cappell, 2008) comes from studies which applied verbal delayed match-to-sample (Cappell, Gmeindl, & Reuter-Lorenz, 2010) and n-back (Mattay et al., 2006) WM tasks. In these studies, elderly subjects showed stronger activation at objectively easier load levels compared to younger subjects in specific prefrontal brain regions, while WM performance was not significantly different between age groups. In contrast, activation strength and performance level were lower for the old than for the young group at more difficult load levels. These studies focused on the increase of activation strength with load levels within specific prefrontal brain regions in young and old subjects. However, they did not analyze if additional brain regions are recruited with increasing WM load and, thus, these studies did not contribute to the question of whether bilateral activation patterns emerge as a response to demanding WM situations. Consequently,

it has not been clear until now if the bilateral recruitment of PFC during WM tasks, which was demonstrated in studies supporting the HAROLD phenomenon (Cabeza, 2002), represents an age-specific compensation mechanism or, alternatively, if this phenomenon is also seen in young adults when they deal with subjectively difficult tasks. To distinguish between these two hypotheses, we asked whether the activation strengths in cross-hemispheric pairs of prefrontal areas differ between hemispheres of both young and old adults when we match the subjective difficulty of WM tasks and keep task demands high. We specifically focused on DLPFC (more posterior parts of BA 46 and BA 9) and aPFC (most anterior parts of BA 46 and BA 10) because they play a domain-general role in WM processes (D'Esposito et al., 1998; Fiez et al., 1996; Smith & Jonides, 1999; Wager & Smith, 2003) and, more importantly, they showed age-related lateralization differences in previous work (Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000; Rossi et al., 2004). We hypothesized that young and old adults would show similar bilateral activation patterns in these prefrontal brain regions when they complete subjectively highly demanding WM tasks, as would be compatible with CRUNCH (Reuter-Lorenz & Cappell, 2008) and also with Banich's model (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998). More specifically, we hypothesized that unilateral activation of these brain regions at easier task loads transforms into bilateral activation during a more difficult task.

As mentioned earlier in section 4.3, Banich's group showed that, in contrast to other difficult non-phonetic cognitive tasks, cross-hemispheric processing is not advantageous compared to within-hemispheric processing in phonetic tasks probably because specific language-based processes can only be processed by the specialized left hemisphere (Belger & Banich, 1998). To find out whether the recruitment of contralateral cortical areas is a general strategy of the human brain irrespective of the area, we also focused on VLPFC (BA 44 and BA 45), an area whose left counterpart is well-known for the processing of language-based information in PFC (Berker et al., 1986). Inspired by Banich's ideas (Belger & Banich, 1992, 1998), we hypothesized that VLPFC maintains its left-lateralized activation pattern even during demanding WM tasks (at least in the verbal domain) because it might process (phonetic) information that cannot be processed by the right hemisphere and therefore does not benefit from parallel bihemispheric processing in difficult situations.

Finally, we wanted to find out if the potential recruitment of cross-hemispheric counterparts of DLPFC and aPFC is restricted to specific WM domains or whether it operates in a domain-general fashion. Banich proposed that the two hemispheres are capable of processing most cognitive tasks in their specialized processing modes (e.g., left hemisphere: verbal processing mode; right hemisphere: spatial processing mode) at demanding load levels and that such a division of processes across the hemispheres is a general support mechanism

of the brain to deal with high cognitive task demands (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998). Accordingly, we expected that it should not matter if, for example, the right or the left hemisphere is recruited in difficult WM tasks as an auxiliary processor in a verbal vs. spatial WM task, respectively. We hypothesized that bilateral recruitment should be seen in DLPFC and aPFC similarly for verbal, spatial, and object WM tasks.

6 Main experiment

To examine our hypotheses, we used fMRI and compared blood oxygen level-dependent (BOLD) responses reflecting WM maintenance between several cross-hemispheric pairs of task-relevant regions of interest (ROIs) in groups of young and old adults. To quantify brain activity related to WM maintenance, we used three versions of a delayed match-to-sample task (Sternberg, 1966), in which young and older subjects memorized either verbal-, spatial-, or object-based material. We manipulated task difficulty within every WM domain by varying the *memory load*, which is – as already mentioned in section 2.5 – the number of items to be remembered, and designed WM tasks to be highly demanding for every subject. More specifically, we first measured our subjects' WM spans outside the scanner to match levels of subjective task difficulty between young and old subjects. Then, based on the individual estimates of the WM span obtained in this pretest, we created memory load sets for the actual fMRI experiment for each subject and for each WM domain, separately. These sets typically consisted of the following five memory load levels: the load level that represented the individually estimated WM span – later on referred to as the central load level – plus two easier and two more difficult load levels. This procedure should guarantee that subjective task difficulty was comparable across individuals and age groups. We thereby considered all relative load levels as rather demanding because they closely ranged around the critical WM span of a subject. Moreover, all three WM domains and their five respective difficulty levels were presented in a randomly interleaved way. Participants could therefore not anticipate the load level of an actual trial and they had to be prepared for the most difficult tasks. For these reasons, we expected a recruitment of the other hemisphere across all load levels to be likely in DLPFC and aPFC in this main experiment.

6.1 Material and Methods

In the next sections, I will illustrate the specific material and methods of the main experiment in more detail by presenting information about subjects, the memory paradigm, stimuli of the fMRI experiment and their presentation, the procedures, data acquisition and analysis.

6.1.1 Subjects

Twelve young and 11 older subjects completed all sessions of the main experiment. We excluded two of the young participants and one of the older ones from data analysis due to strong movement artifacts in the fMRI recordings, lack of oral responses, or falling asleep

during scanning, respectively. Consequently, we were left with 10 young subjects (3 males; age range: 19–27 y; mean age: 24.3 y; standard deviation (*SD*): 2.7 y) and 10 old subjects (4 males; age range: 59–70 y; mean age: 65.2 y; *SD*: 3.8 y) for our final analyses. All subjects were native German speakers and scored higher than 27 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). Young and old participants did not show significant differences (all *p* > 0.45) in the age-corrected scores of the applied subtests "picture completion," "vocabulary," "similarities," "block design," "arithmetic," and "digit span" of the Wechsler Adult Intelligence Scale (Tewes, 1991). One subject of each age group was regularly taking thyroxin, but no other participants were on any medication, suggesting that the BOLD-signals were not modulated by drugs. Moreover, none of our subjects had any Japanese or Chinese language skills, which was important to ensure that the object items were perceived as objects and not linguistically-based material. All subjects had normal or corrected-to-normal visual acuity, were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), and participated in the experiment for monetary compensation, and none suffered from chronic, neurological, or psychiatric diseases. All participants gave written consent in accordance with the declaration of Helsinki, and the study was approved by the ethics committee of the University of Tübingen.

6.1.2 Memory paradigm, stimuli of the fMRI experiment, and stimulus presentation

Participants worked on three versions of a delayed match-to-sample task (Sternberg, 1966), in which participants memorized either verbal-, spatial-, or object-based material that consisted of consonants of the Latin alphabet, dots within a grid, and Japanese Kanji signs, respectively (see below for more details and figure 8).

Each trial started with a random *baseline period* (15 or 16 s), during which subjects were asked to maintain fixation on a white cross that was presented in the center of the otherwise black screen. In the *encoding period*, various randomly selected white WM items were centrally presented one after the other for 1 s each. There was an interstimulus interval (ISI) of 200 ms between items. During the random *maintenance period* (16 or 15 s), subjects again maintained fixation on a white fixation cross in the center of the screen while trying to keep the encoded items in memory. In the *response period*, we simultaneously showed all previously presented items of the encoding phase except for one, which was replaced with a novel item. The participants' task was to identify this new target item by verbally indicating its corresponding number. We manipulated task difficulty within every WM domain by varying the memory load. Figure 8 exclusively illustrates trials with a memory load of 3.
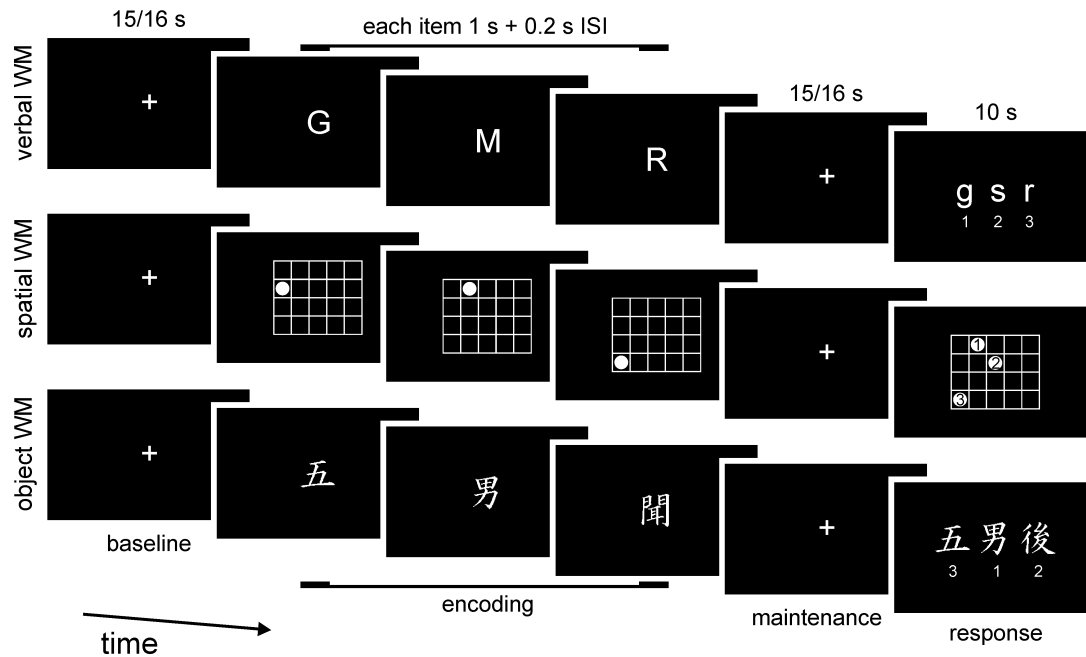
Figure 8. The memory paradigm of the main fMRI experiment.

This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA*, 2017, 114(5), E830-E839.

We used consonants of the Latin alphabet (uppercase letters in the encoding phase and lowercase letters in the response phase) as memory items in the verbal domain to ensure that subjects focus on the verbal content of a letter and not its shape. All letters were presented in Arial font and a 50-pixel font size. In the spatial domain, dots (ø: 30 pixels) within a grid (192 × 240 pixels) that consisted of 20 squares (4 rows × 5 columns; each square: 48 × 48 pixels) served as memory items. Twenty Japanese Kanji signs (~50 × 50 pixels) that had been randomly chosen from the Japanese Language Proficiency Test were the memory items in the object WM domain (compare figure 9). We displayed the numbers indicating the stimuli in the response phase in Arial font and a 30-pixel font size and the fixation crosses of the baseline and maintenance phases in a 50-pixel font size.

Figure 9. The memory items of the object WM domain.

This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA*, 2017, 114(5), E830-E839.

The visual stimuli were created on a Windows based personal computer using MATLAB R2007b (The MathWorks) and Cogent Graphics, developed by John Romaya at the Laboratory of Neurobiology at the Wellcome Department of Imaging Neuroscience. A video projector (frame rate: 60 Hz; resolution: 1,024 × 768 pixels) projected them onto a translucent screen (size of the projected image: 28° × 37° visual angle). A mirror was mounted on the head coil, which allowed the subjects to watch the projected stimuli on the translucent screen behind them with a viewing distance of 92 cm.

6.1.3 Procedures

As mentioned earlier, the aim of the main experiment was to control for subjective task difficulty between the two age groups by using WM load sets for the subjects in the fMRI measurements that had been created on the estimates of their individual WM spans. To achieve this goal, we divided the main experiment into various sessions, including a pretest, in which we assessed our subjects' WM spans and fMRI sessions, in which we measured BOLD responses reflecting WM maintenance. Altogether, the whole main experiment consisted of five sessions, which were conducted on five separate days. I will describe each of these sessions in more detail in the following sections.

6.1.3.1 Session 1

As mentioned in section 6.1.1, our subjects worked on six subtests of the German version of the Wechsler Adult Intelligence Scale (Tewes, 1991), the Edinburgh Handedness Inventory (Oldfield, 1971), and the Mini-Mental State Examination (Folstein et al., 1975) on the first day.

6.1.3.2 Session 2: pretest

The aims of the second session were to assess our participants' WM spans and to create individual load sets on the basis of these assessments in order to guarantee that levels of subjective task difficulty are matched between young and old subjects in the fMRI sessions.

In the purely psychophysical pretest of the second session, subjects sat in front of a monitor and dealt with the same general delayed match-to-sample WM tasks of the fMRI experiment (compare figure 8). However, these tasks differed from the tasks of the fMRI experiments in the following aspects. First, we presented four memory load levels per WM domain in this pretest. Young subjects worked on memory loads 5, 6, 7, and 8 in the verbal domain; 4, 5, 6, and 7 in the spatial domain; and 3, 4, 5, and 6 in the object domain, whereas

old participants dealt with tasks that were one load level easier (i.e., 4, 5, 6, and 7 in the verbal domain, etc.). These load levels were chosen on the basis of a pilot study looking at the typical WM spans of young and old subjects in our memory task. Second, the length of the baseline and maintenance periods also differed from the fMRI paradigm and lasted 2 and 3 s, respectively, instead of ~15 s. Finally, subjects identified the new target item during the response phase of the pretest by pressing a key that represented its corresponding number. In contrast, participants verbally reported this number in the fMRI paradigm. There were 8 consecutive blocks with 24 trials each in the pretest. Each of the 12 conditions (3 WM domains × 4 absolute load levels) was repeated twice per block in a randomized way resulting in 16 repetitions of each condition. Contrary to the fMRI experiment, subjects watched the visual stimuli on a cathode ray tube (CRT) monitor (frame rate: 60Hz; resolution: 1,280 × 1,024 pixels) that was directly placed in front of them with a viewing distance of 57 cm. The screen size of the CRT monitor (30° × 40° visual angle) was roughly identical to the projected image of the fMRI experiment (compare page 37).

Contrary to the usual approach of defining the WM span in reading span or operation span tasks (compare section 2.5), we followed the rationale of Schneider-Garces et al. (2010) and directly assessed our subjects' WM spans by means of delayed match-to-sample tasks. These authors used a delayed match-to-sample task to simultaneously reveal WM task-related brain regions and assess their subjects' WM spans. Schneider-Garces et al. (2010) argued that common procedures of assessing WM spans are limited in their specific paradigm due to the fact that they do not "directly estimate WM capacity within the same task used to assess brain activity (in this case, the Sternberg task). It is therefore difficult to exactly scale the scores obtained by each individual subject in these span tests so that they are made consistent with the memory loads used in" (Schneider-Garces et al., 2010; p. 657) their delayed match-to-sample task.

Based on Schneider-Garces et al. (2010) and Cowan (2000), we assessed our subjects' WM spans in the pretest for each WM domain also by means of a measurement termed *throughput*[2]. This term captures how many of the presented WM items a person is able to successfully keep in memory. The following equation 1 that was adapted from Schneider-

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[2] Please note that we did not define memory span as the highest load level at which a person reproduces all trials correctly as it is usually done in simple span tasks which are in principal similar to our delayed match-to-sample tasks (compare section 2.5). As described above, such approaches determine the STM span neglecting executive processes of WM. Thus, creating individual WM tasks on the basis of STM capacity limits might result in tasks that are not difficult enough to engage brain regions that are associated with WM-related executive processes. Support for this assumption comes from studies showing that patients with lesions in PFC perform as well as normal controls in simple span tasks while they show deficits in more demanding WM tasks (D'Esposito & Postle, 1999).

Garces et al. (2010) defines the throughput in our experiment as a function of the *objective memory load*, the *subjective performance* (hits) and *chance level*:

$$\text{throughput} = \frac{(\text{hits-chance level})}{(1\text{-chance level})} \times \text{memory load} \qquad \textbf{[1]}$$

If a person answers a task perfectly (hits = 1), the throughput value will equal the memory load. The assumption is that the throughput increases with further increases in memory load until the person reaches his or her personal capacity limit, which is the WM span. Figure 10 illustrates this assumption by means of a fictitious example of how we defined a subject's WM span in the pretest.
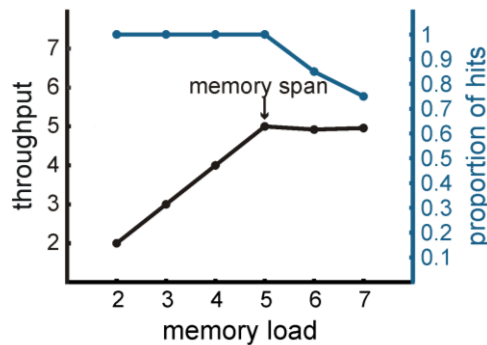
Figure 10. **A fictitious example of how we defined a subject's WM span in the pretest.**

In this example, proportion of hits (blue) and throughput values (black) are displayed as a function of the memory load level. The fictitious subject answers all trials belonging to memory loads 2-5 correctly (proportion of hits = 1). This performance results in throughput values that equal the memory loads and expresses that the person stores all presented items and is able to memorize an increasing amount of information up to a memory load of 5. Here, the hit level drops and the WM span is reached because throughput saturates despite increasing memory load. This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

We calculated throughput values for each of the four load levels of the pretest based on equation 1. Individual WM spans were determined to be the memory load having the maximum throughput value separately for each WM domain (Schneider-Garces et al., 2010). Based on these estimates of the WM span, we created individual load sets for the fMRI experiment to balance subjective task difficulty. Specifically, for every participant and for each WM domain, a set always consisted of five load levels: the *central load level (c)* and two easier (c-1 and c-2) and two more difficult load levels (c+1 and c+2). We typically chose the load level

representing the WM span as the central load level c. In a few exceptions, however, we modified this approach to ensure that the fMRI experiment included both load levels that subjects could solve with high accuracy (at least two load levels with >75% expected hits; criterion 1) and load levels at which a subject's WM span was reached or even exceeded (criterion 2). First, in cases where using the estimated WM span as the central load level c would predict too poor performance and violate criterion 1, we reduced the originally assessed central load level by one item. We repeated this procedure until performance criterion 1 was fulfilled and used the adjusted central load level as the actual central load level c in the fMRI experiment. Second, in cases where subjects answered all trials correctly in the pretest, and their estimated WM span consequently corresponded to the largest load level of the pretest, we increased the originally assessed central load level by one. We applied this procedure because the true WM span might have been larger than the estimated WM span, and thus our original procedure could have produced too simple WM load sets (compare criterion 2). Third, in contrast to verbal and spatial memory items, the object material was unfamiliar to our participants during the pretest. It was therefore possible that subjects could specifically improve their performance for the object WM domain in the fMRI experiment due to learning, making the load levels of the object domain in the fMRI experiment too simple (compare criterion 2). To prevent this putative problem, we increased a subject's originally assessed central load level of the object domain by one item as long as this load level was more than one item smaller than the person's central load level c of the verbal domain (the latter level served as a proxy for the upper bound of performance for a well-trained task). As before, also in the object domain, the central load level was only adjusted if our performance criterion 1 was not violated.

6.1.3.3 Sessions 3-5: fMRI scanning sessions

In the last three sessions of the study, subjects worked on the individualized fMRI versions of the memory task (compare figure 8 and the previous section), while they were scanned using fMRI. Each scanning session consisted of five consecutive blocks between which subjects were allowed to take a break. Within a block, each of the 15 conditions (3 WM domains × 5 relative load levels) was presented once in a randomized way. Consequently, each condition was repeated 15 times across days.

6.1.4 Data acquisition

In the following sections, I will explain how we acquired the behavioral and fMRI data of our main experiment.

6.1.4.1 Behavioral data acquisition

In the pretest of the main experiment, participants' answers were recorded by means of a mini number pad keyboard. In contrast, subjects orally responded in all fMRI sessions. We recorded their verbal answers by using a MRI (magnetic resonance imaging) compatible microphone (sampling rate: 8 kHz; Optoacoustics Dual-Channel Microphone; Optoacoustics) and analyzed them off-line using self-written scripts in MATLAB R2007b (The MathWorks).

6.1.4.2 fMRI data acquisition

Magnetic resonance (MR) images were acquired using a 3-Tesla MR-scanner Trio gradient system and a 12-channel head coil (Siemens). We collected a T1-weighted magnetization-prepared rapid-acquisition gradient echo structural scan of the whole brain from each subject on each day they were scanned [number of slices: 176; slice thickness: 1mm; gap size: 0 mm; in-plane voxel size: 1 × 1 mm; repetition time (TR): 2,300 ms; echo time (TE): 2.92ms; field of view (FOV): 256 × 256 mm; resolution: 256 × 256 voxels]. Furthermore, we measured T2*-weighted gradient-echo planar imaging (EPI) scans for our fMRI analyses [slice thickness: 3.2 mm; gap size: 0.8 mm; in-plane voxel size: 3 × 3 mm; TR: 2,000 ms; TE: 30 ms; flip angle: 90°; FOV: 192 × 192 mm; resolution: 64 × 64 voxels; 32 axial slices]. Cerebral cortex and most subcortical structures were completely covered by the EPI volume, but we did not record from the most posterior parts of the cerebellum in several of our subjects due to brain size.

6.1.5 Data analysis

I will describe how we analyzed the behavioral and functional data of the main experiment in the following sections.

6.1.5.1 Behavioral data analysis

We statistically analyzed all behavioral data using SPSS (version 22; IBM SPSS Statistics). To investigate whether our two age-groups differed in essential cognitive processes, we conducted six independent-samples *t*-tests – one on each of the six age-corrected scores of the subtests of the Wechsler Adult Intelligence Scale. For details of the behavioral data analysis of WM performance in the verbal, spatial, and object delayed match-to-sample tasks of the fMRI sessions, please also refer to section 6.2.1 in the results part of the main experiment.

6.1.5.2 fMRI data analysis

Functional data were analyzed using Statistical Parametric Mapping version 8 (SPM8, Wellcome Department of Cognitive Neurology, London) and SPSS (version 22; IBM SPSS Statistics). In the next paragraphs, I will explain in detail how we analyzed the fMRI data.

Preprocessing of the functional data. We preprocessed our functional images using SPM8. First, we realigned all functional images from all 15 blocks by using the first scan of the first block as a reference. We coregistered and averaged the three T1 anatomical images of the three sessions to create a mean anatomical image. Next, all functional images were aligned to this mean anatomical image based on a coregistration of the mean functional image to the average T1 scan. Then, we normalized subjects' mean anatomical images to the SPM T1 template in Montreal Neurological Institute (MNI) space (mean brain). The resulting normalization parameters were also applied to all functional images for spatial normalization. Finally, all functional images were smoothed by using a Gaussian filter ($7\times7\times7$ mm^3 full-width at half-maximum) and high-pass-filtered (cutoff period: 128 ms).

First-level analysis. On the single subject level of our main experiment, we created a general linear model (GLM) with 45 regressors that were comprised of a combination of 15 memory conditions (3 WM domains × 5 relative load levels) and 3 task phases (encoding period vs. maintenance period vs. response period). We convolved all 45 regressors with the default canonical hemodynamic response function offered by SPM. The movement parameters that were calculated during the realignment procedure served as covariates of no interest in this GLM. The fixation periods in the beginning of a trial and the intertrial intervals were not specifically modeled and were consequently treated as the baseline phase. For each subject, we generated 15 statistical *t*-contrast images – each of them representing one of the 15 memory conditions (3 WM domains × 5 relative load levels) in the maintenance period (image set 1) – and three statistical *t*-contrast images – each of them representing one of the three WM domains in the maintenance period while considering all five load levels simultaneously (image set 2). All analyses described in the following were conducted independently for verbal, spatial, and object WM domains.

Analyzing fMRI lateralization patterns of the ROIs. The aim of the main experiment was to investigate whether areas that are involved in WM processes show a bilateral or unilateral activation pattern in younger and older adults when they work on subjectively very demanding tasks. To answer this question, (i) we first searched for potential task-relevant brain areas by means of a second level contrast in SPM. (ii) We next determined a left and a right hemispheric counterpart in each of these ROIs. (iii) Then, we assessed for all participants their individual peak coordinates within the two hemispheric counterparts of all predefined ROIs (for further details, see below) to extract event-related time courses (ERTs) and estimates of percentage

of BOLD-signal change (derived from the respective beta weights of our GLMs) from these individually assessed coordinates. We decided for this subject-based ROI approach due to the fact that the brains of elderly adults typically exhibit structural changes (Raz, 2000; Schneider-Garces et al., 2010). Consequently, we could not be sure – even after spatial normalization of the brains – that the same group-based coordinates would occupy the same functional locations in different age groups (and perhaps also not in different individuals of the same age group). (iv) We illustrated the results by means of ERTs and (v) finally conducted our statistical analyses on the acquired individual beta weights. Below, I describe all steps in more detail.

(i) To reveal potential task-relevant brain areas that might play a role in the maintenance phases of the experiment, we established a full-factorial model on the second level with the factors "age" (two levels: young vs. old) and "load" (five levels: 1-5), separately for every WM domain, by entering the appropriate first-level contrast images in SPM (image set 1). Then, we applied an *effects of interest* (EOI) contrast with a minimal cluster-size criterion of $k \geq 10$ voxels and a statistical threshold of $p < 0.05$ that was corrected for multiple comparisons using the familywise error (FWE) correction. This *F*-contrast investigated which voxels show significantly different activation strengths from baseline in any of the 10 factor combinations (2 age groups × 5 relative load levels) during the maintenance period. Areas that were displayed by the EOI contrast (see table 1 and figure 13) were considered candidates for potential task relevant areas and/or for areas showing age-related differences because the BOLD-signal was modulated by the memory tasks and/or by the age of the subjects in these regions. Areas that exhibited stronger activation during baseline than during the maintenance period were not considered, because we have no biologically plausible reason supporting the assumption that a negative BOLD response during the maintenance phase could reflect a neural correlate of WM maintenance.

(ii) In a next step, we defined the voxels with the highest *F*-values within left and right counterparts of the ROIs as their representative group coordinates (table 1). Because we wanted to find out whether our ROIs show bilateral activation patterns in young and old subjects, it was crucial to compare the activation strengths of spots that are cross-hemispheric functional counterparts of each other. We frequently found significant voxels in the left and right counterparts of these ROIs across all three WM domains by means of the described EOI approach. In case of identifying significant voxels within a ROI in only one hemisphere, we mirrored the representative group coordinate of this

hemisphere to the other hemisphere. Then, we searched for significant spots within a 20-mm radius sphere around the mirrored coordinate while changing the statistical threshold ($p < 0.05$, FWE correction on cluster-level at $p < 0.001$, $k \geq 10$). If we succeeded in finding significant voxels according to this latter small-volume approach, we chose the voxel with the highest F-value that anatomically matched its equivalent in the other hemisphere as the representative group coordinate (underlined voxels in table 1). If we did not succeed, we accepted the mirrored coordinate as the representative group coordinate (empty field in one of the two hemispheric counterparts in table 1). Because, only for the spatial domain, we did not find significant voxels in one of the ROIs, namely the calcarine sulcus, we used the representative group coordinates of this ROI of the verbal domain in the spatial domain for further analyses.

(iii)   Then, we applied the contrast that represented the maintenance phase independent of load level (image set 2) in all subjects ($p < 0.001$, uncorrected, $k \geq 10$ voxels). We placed a 20-mm radius sphere separately for each hemispheric counterpart of all ROIs around the representative group coordinate and determined the voxel with the highest t-value that anatomically matched the respective ROI. Whenever we were not able to find any matching voxel in a subject, we assigned the representative group coordinate to this person. For instance, for DLPFC and aPFC we only assigned the representative group coordinate in up to one case per age group and hemispheric counterpart, with the exception of aPFC in the object domain. Here, the group coordinate was assigned twice in each hemispheric counterpart in the young group, whereas it was assigned to one old subject in the left hemispheric counterpart. Also, in almost all other ROIs, we found individual coordinates in the majority of our subjects of both age groups except for calcarine sulcus, PMv, and SMA. On a group level, we did not find representative group coordinates in calcarine sulcus in the spatial domain, so we instead used the ones of the verbal domain for further analyses (compare table 1). It is thus not surprising that we had to assign the group coordinate in ~ 50 % of the cases in this ROI but we did so for both age groups and for both hemispheres. Importantly, across ROIs, there was no systematic difference in how often we assigned group coordinates to a specific age group or to a specific hemisphere, with two exceptions: In case of PMv, we assigned the group coordinate in ~ 50% of young and old subjects to the right hemispheric counterpart in the spatial and object domain. Also, we did so in ~ 50% of the young participants for the left counterpart, whereas we found an

individual coordinate for left PMv in each subject of the old group and in both WM domains. Moreover, in case of SMA, the group coordinates were frequently assigned to the right counterpart of young subjects in both the verbal (five times) and the object domain (seven times), whereas we did not have to do such assignment in old subjects and in the left counterparts of both age groups. Despite these differences in the assignment of group coordinates, we did not reveal any differences in PMv and SMA lateralization between both age groups in our ROI-based analyses of percentage of BOLD-signal change (see below).

Separately for every subject, ROI, and WM domain, we then extracted ERTs of signal intensities and estimates of the percentage of BOLD-signal change for each of the five regressors (load levels 1-5) of the maintenance period and averaged them across a sphere with a radius of 3 mm (and 9 mm) around the individually determined voxel.

(iv) The ERTs of signal intensities illustrate how the BOLD-signal developed across a trial and were extracted by means of scripts that were adapted from the Nod Lab ERT for SPM toolbox (NERT4SPM; by Axel Lindner and Christoph Budziszewski; https://svn.discofish.de/MATLAB/spmtoolbox/NERT4SPM). We generated ERTs from every individual subject across load levels and trials, aligned them to the onset of the maintenance phase and filtered (high pass filter: cutoff period, 128ms) and normalized them by an estimate of overall baseline activity across all conditions. This baseline activity represented the mean image intensity at the very end of the baseline period (between -5 and -2 s relative to the onset of the encoding period). In the end, we averaged ERTs across subjects within each age group.

(v) We extracted the GLM-based beta estimates expressed as percentage of BOLD-signal change during the maintenance period for all conditions and all subjects by means of self-written scripts in MATLAB R2007b (The MathWorks). We calculated three-way repeated measures analyses of variance separately for each WM domain with the factors "hemisphere" (two levels: left vs. right), "age" (two levels: young vs. old), and "load" (five relative load levels: 1-5) for each of our ROIs and used the extracted estimates of percentage of BOLD-signal change as dependent variables. As previously mentioned, we were mainly interested in investigating whether our ROIs were bilaterally or unilaterally involved in the memory tasks. When an analysis of variance (ANOVA) revealed a significant main effect of "hemisphere" in an area, we interpreted this region to be more unilaterally involved in the task because one

hemisphere showed stronger activation than the other one. Note that – with the exception of DLPFC and aPFC – I only report main effects of "hemisphere" and interactions between "hemisphere" and "age" for all ROIs because these statistical effects provide information about the lateralization pattern and about putative differences of the pattern between young and old subjects (but see table 2 for an overview about all effects).

We additionally calculated *Bayes factors* for every ROI on the acquired estimates of percentage of BOLD-signal change independently for young and old subjects according to Dienes (Dienes, 2011). These factors quantified how probable the alternative hypothesis (there are differences in ROI activity between the hemispheres) is versus the null hypothesis (there are no differences in ROI activity between the hemispheres). We modeled the prediction of our alternative hypothesis as a uniform distribution. In every ROI, we determined which of the two hemispheric counterparts showed the higher estimate of percentage of BOLD-signal change and used this as an upper limit of the model and we chose a value representing 5% of this value as the lower limit. We decided to use varying lower and upper limits depending on the ROIs to take into account the individual activation strengths in different brain areas. When the resulting Bayes factor turned out to be above 1 for a given ROI, the experimental data supported the alternative hypothesis; on the contrary, when the Bayes factor was below 1, the experimental data spoke in favor of the null hypothesis and when the Bayes factor equaled 1, the experimental data were not sensitive enough to say which of the two hypotheses was more likely.

6.2 Results

In this section, I will present the behavioral data of the main experiment before introducing the fMRI results of this experiment which illustrate the lateralization patterns of the ROIs in younger and older subjects separately for highly demanding verbal, spatial, and object WM tasks.

6.2.1 Behavioral results

Concerning behavioral measurements, we analyzed on the one hand if the two age groups worked on different objective difficulty levels in the fMRI experiment and on the other hand if we succeeded in creating individual load sets that were matched for subjective task difficulty between the two age groups.

6.2.1.1 Analyzing objective task difficulty

To investigate whether younger and older adults worked on different objective difficulty levels in the fMRI experiment, we compared the mean central load levels (level 3) of young and older participants (see figure 11) by means of a two-way repeated measures ANOVA with the factors "age" (two levels: young vs. old) and "domain" (three levels: verbal vs. spatial vs. object).

This analysis revealed that young subjects had higher mean central load levels and therefore could cope with objectively more difficult WM tasks than old subjects in all WM domains [main effect of "age": $F(1,18) = 17.71$; $p = 0.001$]. This result is in accordance with previous reports showing that WM performance decreases with increasing age (Hultsch et al., 1999; Nyberg et al., 2014; Park et al., 2002). Furthermore, the ANOVA yielded a main effect of "domain" [$F(2,36) = 18.21$; $p < 0.00001$], but no significant interaction between "age" and "domain" [$F(2,36) = 1.44$; $p = 0.250$]. Post hoc paired t-tests revealed that across age groups, verbal tasks were objectively more difficult than spatial tasks [$t(19) = 4.40$; $p = 0.0003$; uncorrected; survives Bonferroni correction for multiple comparisons] and object tasks [$t(19) = 5.54$; $p = 0.00002$; uncorrected; survives Bonferroni correction for multiple comparisons], whereas spatial and object domains did not differ in objective difficulty [$t(19) = 1.10$; $p = 0.287$].
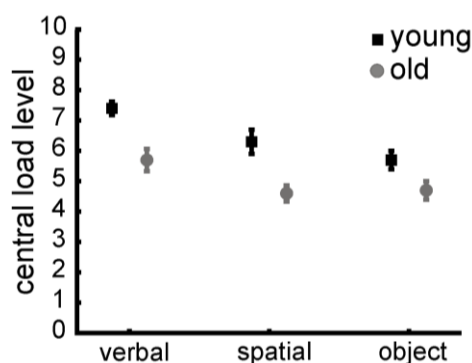
***Figure 11*. Objective task difficulty in the main fMRI experiment.**

To illustrate the objective difficulty of the tasks that were used in the main fMRI experiment, I present mean central load levels (the third relative load levels of the load sets) of the fMRI experiment and their standard errors (*SE*), separately for age groups (black: young, *n* = 10; gray: old, *n* = 10) and WM domains (verbal vs. spatial vs. object). This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

6.2.1.2 Analyzing the success of matching subjective task difficulty

As written in the Material and Methods section of the main experiment, throughput values were calculated for every load level according to equation 1, separately for each person and for each WM domain. Figure 12 illustrates that the profiles of the throughput curves as

function of the relative load levels look quite similar for young and old adults in the verbal WM domain: they increase with similar slopes up to the central load level before reaching a plateau. Hence, it seems that subjects in both age groups reached their WM spans equally fast and at the same relative load level, guaranteeing the same subjective task difficulty despite the differences in objective task demands (see previous section). Similar profiles of the throughput function of young and old subjects were also observed for the spatial domain; however, in the object domain the initial increase of the throughput curves seems to differ with age.
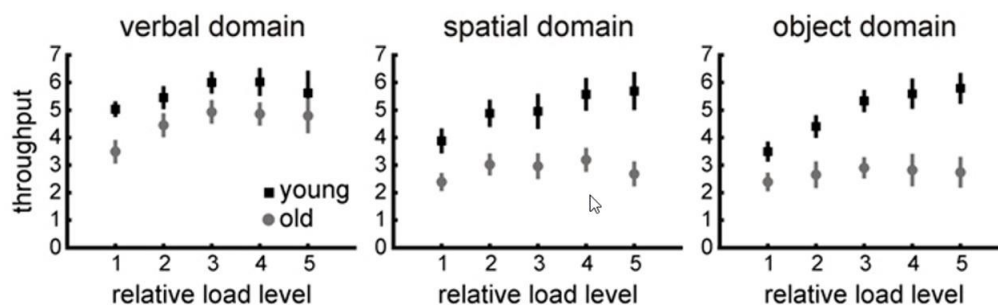
Figure 12. **Subjects' behavioral performance in the main fMRI experiment.**

To demonstrate our subjects' behavioral performance in the main fMRI experiment, mean throughput values of this experiment and their *SE*s are shown, separately for age groups (black: young, *n* = 10; gray: old, *n* = 10), WM domains (left: verbal; center: spatial; right: object), and relative load levels (1-5). This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

To statistically examine whether we had indeed been successful in matching subjective task difficulty between age groups in the fMRI experiment, we tested whether the profiles of the throughput curves were comparable between young and old participants. We calculated two-way repeated measures ANOVAs with the factors "age" (two levels: young vs. old) and "load" (five levels: 1-5) on throughput values separately for each WM domain and examined whether the interactions between "age" and "load" were significant. The results indicate that we were successful in controlling for subjective task difficulty in the verbal [interaction "age" × "load": $F_{(1.9,34.3)} = 0.38$; $p = 0.678$] and spatial [interaction "age" × "load": $F_{(2.6,46.3)} = 2.65$; $p = 0.068$] domain because the interactions were not significant. In contrast, the way the throughput varied with load differed between young and old participants in the object domain [interaction "age" × "load": $F_{(2.6,46.6)} = 5.71$; $p = 0.003$]. Inspection of figure 12 suggests that young subjects did not reach their capacity limits in the object domain, whereas old participants did. Moreover, the ANOVAs revealed that, as expected, young participants achieved higher throughput values than old subjects in all WM domains by showing significant main effects of "age" [verbal: $F_{(1,18)} = 5.75$, $p = 0.028$; spatial: $F_{(1,18)} = 16.19$, $p = 0.001$; object: $F_{(1,18)} =$

20.51, *p* = 0.0003]. Furthermore, the main effects of "load" expressed that throughput values significantly varied across relative load levels in all WM domains [verbal: $F_{(1.9,34.3)}$ = 5.15, *p* = 0.012; spatial: $F_{(2.6,46.3)}$ = 7.14, *p* = 0.001; object: $F_{(2.6,46.6)}$ = 11.68, *p* = 0.00002].

6.2.2 fMRI results: analyzing fMRI lateralization in young vs. old subjects

The main purpose of our fMRI analyses was to investigate whether the BOLD-signal amplitudes of cross-hemispheric counterparts of task-relevant prefrontal and language-related areas differ during WM maintenance in young and older subjects when they work on subjectively equally difficult tasks. As written in the "aims and hypotheses" section of this dissertation, we specifically focused on the prefrontal regions DLPFC, aPFC, and VLPFC. The two cross-hemispheric counterparts of each of these "main" ROIs were identified in each individual based on anatomical and functional criteria: cross-hemispheric pairs were identified by their anatomical location and by the presence of WM maintenance-related activity during the instructed delay of our stimulus sequence (compare also figure 13 and page 44).
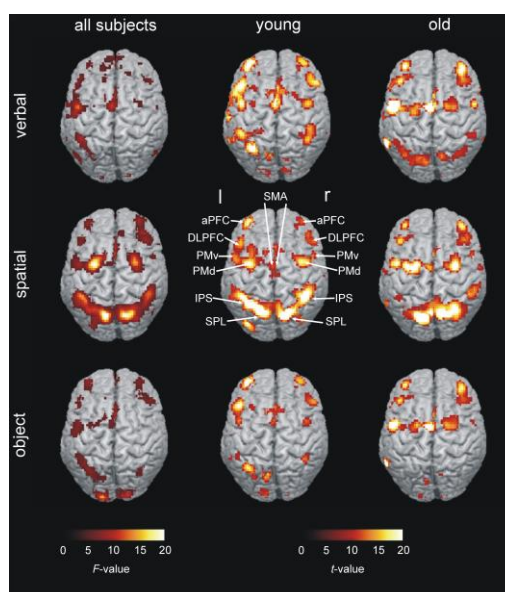
Figure 13. **WM maintenance-related brain activity in the main experiment.**

In the first column, I present the EOI group maps of the main experiment for WM maintenance, namely for the verbal (first row), spatial (second row), and object (third row) domain (*p* < 0.00001, uncorrected). In the second and third column, I show WM maintenance-related activation across all load levels for two representative subjects of the young and old group, respectively (*p* < 10^{-11}, FWE correction for multiple comparisons). This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

Apart from our main ROIs (DLPFC, aPFC, and VLPFC), a number of additional brain areas did exhibit maintenance-related activity, namely anterior insula, dorsal premotor

cortex/frontal eye fields (PMd/FEF), ventral premotor cortex (PMv), supplementary motor area (SMA), intraparietal sulcus (IPS), superior parietal lobule (SPL), calcarine sulcus, and lobule VI/crus1 of lobule VII of the cerebellum. Here, I also describe the results for these additional task-related areas because they have been consistently reported to be involved in WM processes in young subjects (Baddeley, 2003; D'Esposito et al., 1998; Eriksson et al., 2015; Fiez et al., 1996; Reuter-Lorenz et al., 2000; Schneider-Garces et al., 2010; Smith & Jonides, 1999; Wager & Smith, 2003). However, we had no prior hypotheses with respect to their pattern of lateralization. Table 1 displays representative coordinates of all ROIs.

Table 1. **List of ROIs and their representative group coordinates.**

			MNI group coordinates of representative voxels, mm								
			Verbal			Spatial			Object		
ROI	BA	Hem	x	y	z	x	y	z	x	y	z
Frontal regions											
Mid-frontal gyrus (DLPFC)	46/9	L	−39	30	27	−39	27	36	−36	30	27
		R	48	30	33	42	30	39	36	33	27
Mid-frontal gyrus (aPFC)	46/10	L	−33	51	18	−33	51	18	−33	51	18
		R	_33_	_54_	_18_	33	57	18	33	54	21
Inferior frontal gyrus (VLPFC)	44/45	L	−45	12	30	−48	6	33			
		R				48	6	33	_42_	_9_	_30_
Insula		L	−30	21	3	−30	18	6	−30	24	3
		R	33	24	0	36	24	6	36	27	0
Premotor regions											
PMd	6	L	_−27_	_−3_	_60_	−27	−3	63	_−33_	_−3_	_60_
		R	_33_	_0_	_60_	27	0	60	_33_	_−9_	_66_
PMv	6	L	−48	−6	57	−48	−3	51	−48	0	48
		R	_57_	_−6_	_51_				54	−6	_48_
SMA	6	L	−6	6	54	−6	12	51	−3	15	51
		R	6	15	48	6	15	48	6	18	45
Parietal regions											
IPS	40	L	−33	−57	45	−45	−45	51	−33	−57	48
		R	_36_	_−54_	_42_	45	−42	51	33	−63	48
SPL	7	L	_−18_	_−69_	_54_	−12	−69	57	_−15_	_−75_	_54_
		R	_12_	_−69_	_54_	15	−72	60	_12_	_−72_	_48_
Occipital and subcortical regions											
Calcarine sulcus	17	L	−12	−93	0				−12	−93	−3
		R	15	−90	0				12	−90	0
Cerebellum (l6/crus 1)		L	_−30_	_−57_	_−30_	−30	−66	−27			
		R	30	−60	−27	_36_	_−63_	_−27_	_27_	_−60_	_−21_

BA = Brodmann's area, Hem = hemisphere, L = left, R = right. ROIs were selected with corrected significance thresholds, either based on a full-brain analysis [p < 0.05, FWE correction for multiple comparisons (k ≥ 10)] or based on a small-volume analysis [p < 0.05, FWE correction on cluster level at p < 0.001 (k ≥ 10); see Material and Methods of the main experiment for further details; underscored coordinates]. We did not find any significant voxels by applying corrected significance thresholds in case of empty fields. See Material and Methods of the main experiment for information about how we proceeded in such a case. Note that the coordinates in this table represent the location of the ROIs exhibiting maintenance-related activity on a group level. However, these coordinates are slightly different from the average of the individual coordinates from which we finally extracted event-related time-courses and estimates of percentage of BOLD-signal change for our statistical analyses. This table is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, Proc Natl Acad Sci USA, 2017, 114(5), E830-E839.

For every subject and for each ROI, we assessed the WM maintenance-related BOLD activity in the respective cross-hemispheric counterparts across a sphere of 3-mm radius in terms of the estimated percentage of BOLD-signal change. In cases in which the estimated percentage of BOLD-signal change was indistinguishable between both cross-hemispheric counterparts of an area in at least one WM domain, we refer to this area as *bilateral*. In turn, an area is labeled as *unilateral* when one hemispheric counterpart is activated more strongly than the other in each WM domain. Accordingly, we grouped our ROIs in four respective categories: a) *domain-general bilateral ROIs* (i.e., areas that showed a bilateral activation pattern across all WM domains); b) *domain-specific bilateral ROIs* (i.e., areas that were bilateral in at least one WM domain but unilateral in others); c) *domain-general unilateral ROIs* (i.e., the same pattern of unilateral activation was exhibited across all three WM domains); and d) *domain-specific unilateral ROIs* (i.e., lateralization was present throughout but the dominant hemisphere varied across WM domains). Note, however, that none of our ROIs fell in the latter category. In the following sections, I will separately present the functional results for the remaining three categories.

6.2.2.1 Domain-general bilateral ROIs

I first report the results of the prefrontal areas that had been shown to exhibit age-related differences in lateralization, namely DLPFC and aPFC. The averaged ERTs of the BOLD-signals in these areas are depicted in figure 14 A and B, respectively. Separate time courses are shown for the two hemispheres (brighter color: left hemisphere; darker color: right hemisphere), for young (upper rows) and old (lower rows) subjects, and for verbal (red), spatial (green), and object (blue) domains. These figures indicate that there was hardly any difference in activation between the cross-hemispheric counterparts of DLPFC and aPFC – in both age groups and in all three WM domains.

To statistically test this impression, we first conducted – independently for each ROI and WM domain – three-way repeated-measures ANOVAs with the factors "hemisphere" (two levels: left vs. right), "age" (two levels: young vs. old), and "load" (five levels: 1-5) on our estimates of percentage of BOLD-signal change during the WM maintenance phases (figure 15 A and B). These analyses revealed that left and right hemispheres of DLPFC and aPFC were indeed similarly engaged in the maintenance phases in all three WM domains [absence of main effects of "hemisphere" in DLPFC: verbal: $F(1,18) = 0.27$, $p = 0.609$; spatial: $F(1,18) = 0.22$, $p = 0.649$; object: $F(1,18) = 0.83$, $p = 0.373$; absence of main effects of "hemisphere" in aPFC: verbal: $F(1,18) = 0.25$, $p = 0.624$; spatial: $F(1,18) = 0.13$, $p = 0.724$; object: $F(1,18) = 0.24$, $p = 0.633$]. Both areas are thus considered domain-general bilateral ROIs. Furthermore,
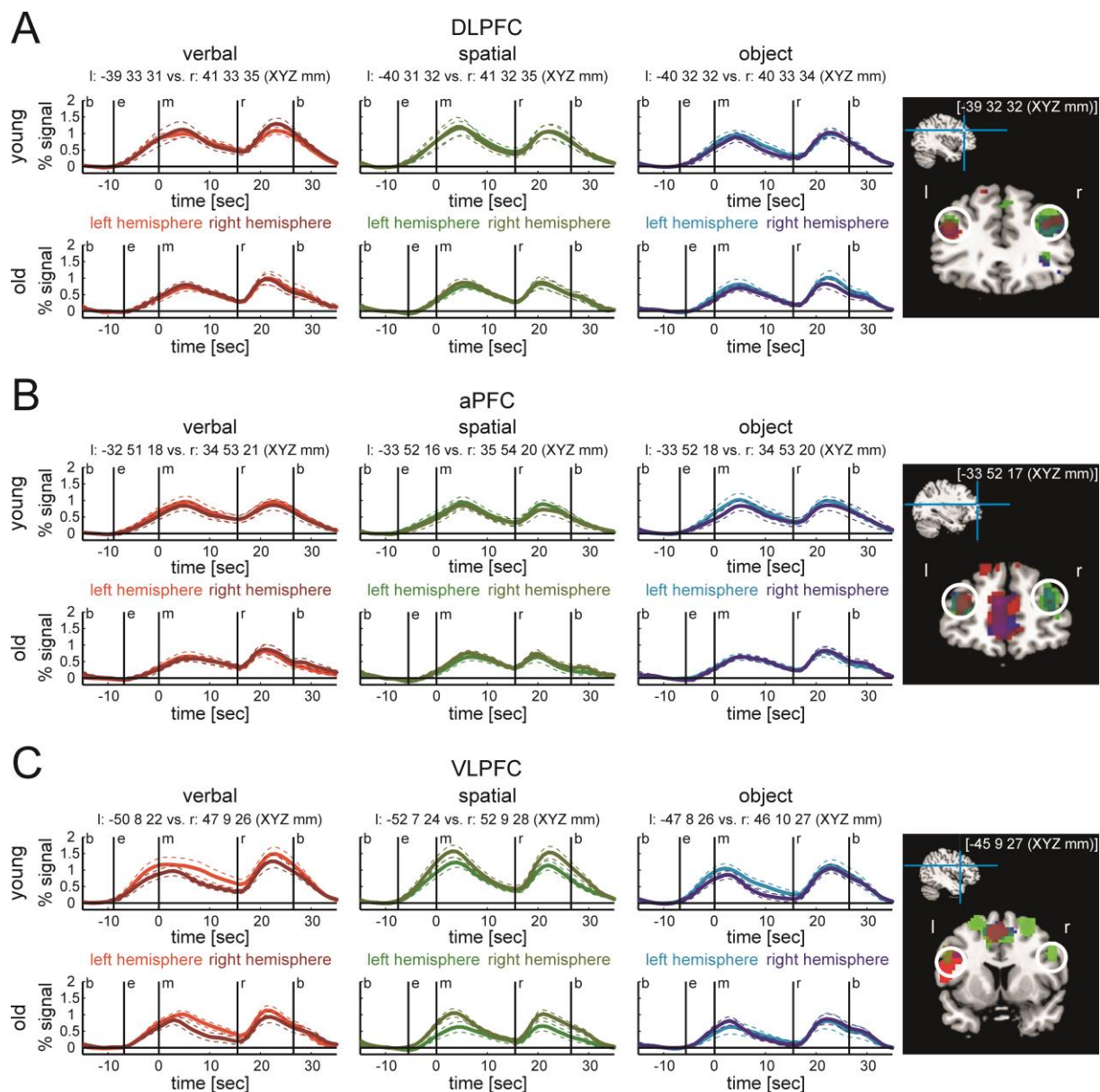
***Figure 14.* Time-resolved fMRI activity in both hemispheres of young vs. old subjects in the main experiment.**

The time courses of the BOLD-signals of DLPFC (A), aPFC (B), and VLPFC (C) are presented separately for the left (brighter color) and right (darker color) hemispheres, young subjects (upper rows, *n* = 10) and old subjects (lower rows, *n* = 10) and verbal (red), spatial (green), and object (blue) WM domains. Each time course refers to the across-subjects average of all trials of all five load levels. Dotted lines represent *SE*s. Vertical solid lines indicate the onsets of the individual phases of a trial: baseline (b), encoding (e), maintenance (m), response (r). Time courses are aligned to the onset of the maintenance phase. Consider that we did not extract time courses of a ROI from the same representative group coordinate of this ROI but from individual coordinates. The coordinates above the time courses are the mean coordinates of these individual coordinates. All coordinates are in MNI space. Whereas DLPFC (A) and aPFC (B) represent domain-general bilateral ROIs, VLPFC (C) represents a domain-specific bilateral ROI. To illustrate the locations that we considered as DLPFC, aPFC, and VLPFC, respectively, I separately present the group maps for memory maintenance (EOI contrast; see Material and Methods of the main experiment) in the verbal (red), spatial (green), and object (blue) domains (*p* < 0.00001, uncorrected) and highlighted them with white circles. Note that colors mix

additively when the same spots were activated in two WM domains, whereas dark reddish stains refer to spots that were recruited in all three domains. l, left; r, right. This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA*, 2017, 114(5), E830-E839.

the ANOVAs indicated that in both areas, the BOLD-signal was significantly modulated by the load level in verbal and spatial domains during the maintenance period – as it was expected – but not in the object domain [main effects of "load" in DLPFC: verbal: $F(2.8,50.1) = 10.34$, $p = 0.00003$; spatial: $F(4,72) = 11.47$, $p < 0.00001$; object: $F(4,72) = 1.36$, $p = 0.255$; main effects of "load" in aPFC: verbal: $F(2.4,43.7) = 8.39$, $p = 0.0004$; spatial: $F(4,72) = 14.62$, $p < 0.00001$; object: $F(4,72) = 2.24$, $p = 0.073$]. The missing load effect in both ROIs in the object domain could refer to the fact that we were not successful in controlling subjective task difficulty in this domain (see above section 6.2.1.2) and that load levels encompassed a difficulty range in which the BOLD-signal was not yet (young group) or no longer (old group) modulated by the load level. Finally, the main effects of "age" and, most importantly, the interactions between "age" and "hemisphere" were not significant in DLPFC and aPFC in all three WM domains (all $p > 0.17$). Hence, in both prefrontal ROIs neither the age groups nor the hemispheres had any differential influence on BOLD-signal amplitudes in any of the three WM domains. Please also refer to the black filled circles in table 2 for an overview of all significant main effects and interactions revealed by the ANOVAs of all ROIs and WM domains of the main experiment.

I would like to highlight that our analytical approach used the same fMRI data set for ROI selection and ROI analyses. Such an approach can principally introduce circularity and biased activity estimates in neuroimaging studies (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). We took specific care to meet the criteria described by Kriegeskorte and colleagues to avoid such negative effects on our results (as will be discussed later in section 6.3.2). In addition, we resorted to an a priori definition of the cross-hemispheric counterparts of our main ROIs based on previous WM research (Fiez et al., 1996). More specifically, we repeated our analyses for these ROIs on the percentage of BOLD-signal changes extracted from meta-coordinates reported in a WM study by Fiez et al. (1996), although neither circularity nor biased activity estimates seem to be present in our approach (compare section 6.3.2 for a more detailed discussion of these issues). These analyses again revealed the same patterns of hemispheric lateralization like the ones obtained by our main analytical approach (compare gray empty circles in table 2).
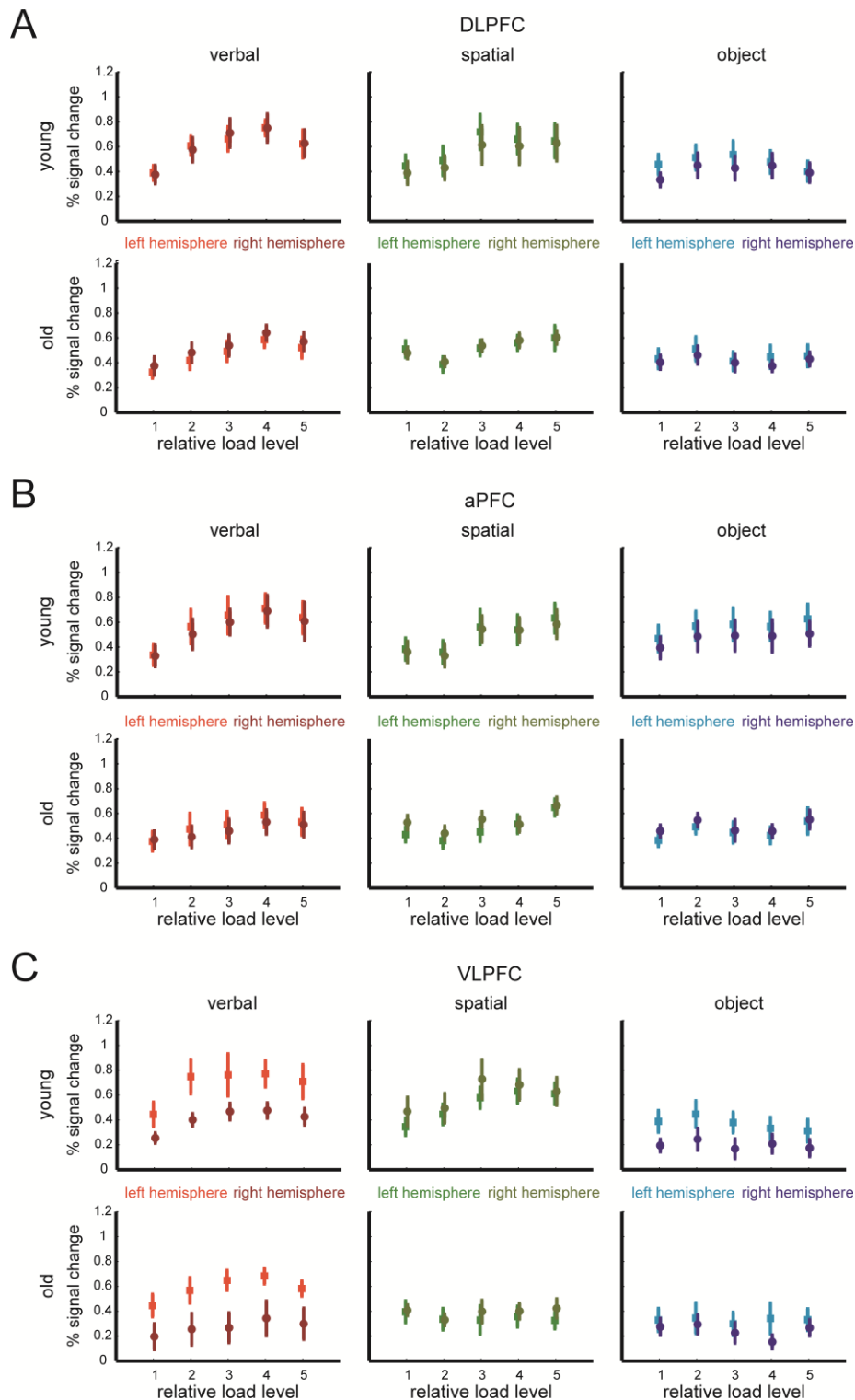
Figure 15. Percentage of BOLD-signal change of the relative load levels in the maintenance phases of the main experiment.

Mean percentage of BOLD-signal change and *SE*s of DLPFC (A), aPFC (B), and VLPFC (C) are presented separately for hemispheres (brighter color: left; darker color: right), age groups (upper rows: young subjects, *n* = 10; lower rows: old subjects, *n* = 10), WM domains (red: verbal; green: spatial; blue: object), and relative load levels (1-5). This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

Table 2. **Significant main effects and interactions of the main experiment revealed by the three-way repeated-measures ANOVAs with the factors "hemisphere," "age," and "load" on percentage of BOLD-signal change.**

ROI	Verbal Hem	Verbal Load	Verbal Interaction	Spatial Hem	Spatial Load	Spatial Interaction	Object Hem	Object Load	Object Interaction
Frontal									
DLPFC		•••			•••				
		•••			•••				
		○			○○				
aPFC		•••			•••				
		•••			•••				
VLPFC	•••	•••	h × l: •		••	l × a: ••	•		
	•••	••	h × l: •••		•	l × a: •	•		
	○○○	○	h × l: ○				○○○		
Insula		•••			•••				
		••			•••				
Premotor									
PMd		••			•••				
		•			•••				
PMv	•••	•	h × l: •	••			••		
	•••	•	h × l: •	••			••		
SMA	•••	••			•••			••	
	•••	•			•••			••	
Parietal									
IPS	•••	•••		••	•••	l × a: ••	••		
	•••	••		•	•••	l × a: ••	••	•	
SPL		•••	h × l: •		•••	l × a: •	•••		h × a: •
		•	h × l: •		•••	l × a: •	••		h × a: •
Occipital									
Calcarine salcus								••	
								••	l × a: •
Subcortical									
Cerebellum (l6/crus1)	••	•••			•		•		
	•	•			•		•		h × l: •

Main effects of "age" never were significant (all $p > 0.05$); results of the ANOVAs on the percentage of BOLD-signal change averaged across the volume of a 3-mm radius sphere are depicted in black; ANOVAs that considered average activation within a 9-mm radius sphere are illustrated in gray. Finally, we averaged the percentage of BOLD-signal change of our subjects across a volume of a 9-mm radius sphere around a priori defined locations of DLPFC and VLPFC as were specified in Fiez et al. (1996) as common sites of activation across various WM studies and repeated the ANOVAs for these areas. Fiez et al. did not report such locations for aPFC. The respective results, which are depicted in the third rows of DLPFC and VLPFC as gray unfilled circles, are in close correspondence to those revealed by our main analyses. Hem, main effect of "hemisphere"; h × a, interaction between "hemisphere" and "age"; h × l, interaction between "hemisphere" and "load"; l × a, interaction between "load" and "age"; Load, main effect of "load". • $p < 0.05$; •• $p < 0.005$; ••• $p < 0.001$. This table is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

Our failure to reveal significant differences in activation strength between the hemispheric counterparts of DLPFC and aPFC does not allow us to conclude that these cross-hemispheric pairs were indeed equally activated. The reason is that we did not control for type II errors as strictly as for type I errors, a common tradeoff in orthodox statistics like in the ANOVAs performed here. To account for this limitation, we additionally calculated *Bayes factors* (Dienes, 2011) to probe whether the two counterparts of our ROIs were similarly active (null hypothesis) in the maintenance phases of the memory tasks or not (alternative hypothesis). Figures 16 A and B illustrate Bayes factors of DLPFC and aPFC for young and old subjects, respectively, separately for all WM domains (red: verbal; green: spatial; blue: object). A Bayes factor below 1 represents evidence in favor of bilaterality and a Bayes factor above 1 denotes evidence in favor of unilaterality. Although the Bayesian approach typically refrains from using thresholds, Bayes factors that have values above 3 and below 1/3 provide substantial evidence for more unilateral vs. bilateral activation, respectively (Jeffreys, 1961). In cases in which the Bayes factors equal 1, the experimental data are not sensitive enough to decide which lateralization pattern is more likely.

Figure 16. **Bayes factors of the main ROIs acquired from the main experiment.**

Bayes factors of the 10 young (A) and 10 old (B) subjects of the main experiment are shown separately for DLPFC, aPFC, and VLPFC and WM domains (red: verbal; green: spatial; blue: object). A Bayes factor below 1 denotes evidence in favor of bilaterality, a Bayes factor above 1 represents evidence in favor of unilaterality, and a Bayes factor that equals 1 expresses that the experimental data are not sensitive enough to decide which lateralization pattern is more likely. The horizontal dashed lines represent the thresholds that provide – according to Jeffreys (1961) – substantial evidence for unilateral (upper line, y = 3) vs. bilateral (lower line, y = 1/3) activation patterns. I logarithmized the y-axis to ensure that the two thresholds have the same distance from 1. This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

The Bayes approach supported the preliminary conclusions suggested by the above-described ANOVA results: in all WM domains, left and right hemispheres were equally activated in DLPFC and aPFC in both young subjects (Bayes factors of DLPFC: verbal, 0.15; spatial, 0.33; object, 0.45; Bayes factors of aPFC: verbal, 0.29; spatial, 0.20; object, 0.52) and old subjects (Bayes factors of DLPFC: verbal, 0.32; spatial, 0.07; object, 0.31; Bayes factors of aPFC: verbal, 0.26; spatial, 0.33; object, 0.22). Note that in the object domain there is generally less evidence in favor of bilaterality in young compared with old subjects. This finding may reflect the abovementioned fact that young participants worked on object-based WM items that did not push them to their capacity limits as opposed to the other WM domains and to the group of older subjects. In summary, all abovementioned results clearly speak in favor of the idea that bilateral activation patterns are associated with high WM task demands in DLPFC and aPFC and are independent of age and WM domain.

Our methods of analyzing the fMRI data only considered the height of activation in a relatively small area (a 3-mm radius sphere), whereas the extent of the activation has not reported so far. However, it might be possible that subjects would lack differences between the left and right hemisphere in peak activations in DLPFC and aPFC but exhibit hemispheric differences with respect to the spatial extent of activation. To tackle this issue, we repeated our original analyses while sampling from a much larger area (a 9-mm radius sphere). The respective analyses led to the same basic findings like our original analyses (see gray filled circles in table 2), suggesting that there are no differences in lateralization with respect to the spatial extent of activation in our prefrontal (and all other) ROIs. Please also refer to the outlook section 8.5.1 for further considerations about this issue.

Further areas that were engaged in WM maintenance and in which the main effect of "hemisphere" was not significant across all three WM domains were the *anterior insula* [verbal: $F(1,18) = 2.36$, $p = 0.142$; spatial: $F(1,18) = 0.86$, $p = 0.365$; object: $F(1,18) = 0.16$, $p = 0.698$], *PMd* [verbal: $F(1,18) = 0.01$, $p = 0.919$; spatial: $F(1,18) = 1.66$, $p = 0.213$; object: $F(1,18) = 1.53$, $p = 0.232$], and the *calcarine sulcus* [verbal: $F(1,18) = 0.0003$, $p = 0.988$; spatial: $F(1,18) = 0.64$, $p = 0.433$; object: $F(1,18) = 0.38$, $p = 0.548$]. Considering these results, the corresponding Bayes factors (compare figure 17 A and B) and the fact that we did not find any "hemisphere" × "age" interactions in the respective ANOVAs (all $p > 0.10$), we assume that in addition to DLPFC and aPFC, the anterior insula, the PMd, and the calcarine sulcus are regions that exhibit a bilateral activation pattern during the maintenance phases of all three WM domains and thus reflect a domain-general bilaterality that is independent of age[3].

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[3] As I already wrote on page 46, I only indicate main effects of "hemisphere" and interactions between "hemisphere" and "age" for all ROIs (apart from DLPFC and aPFC) because these statistical effects provide information about the lateralization pattern of a ROI and about putative differences of the pattern between young and old subjects. Compare table 2 for an overview of all effects.
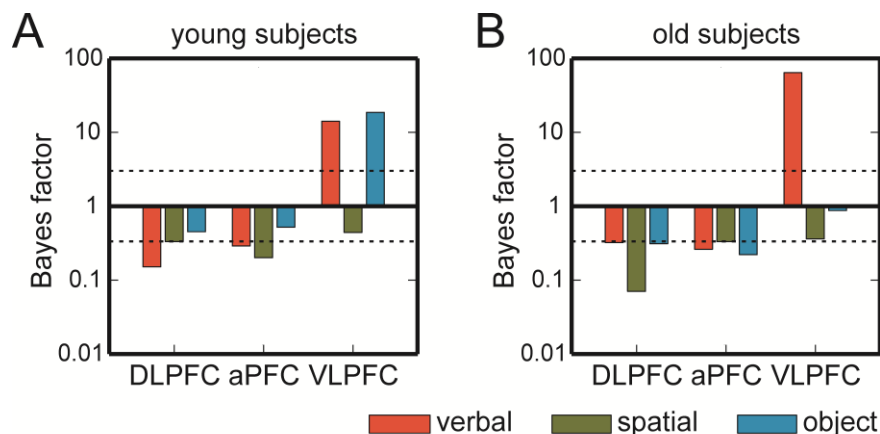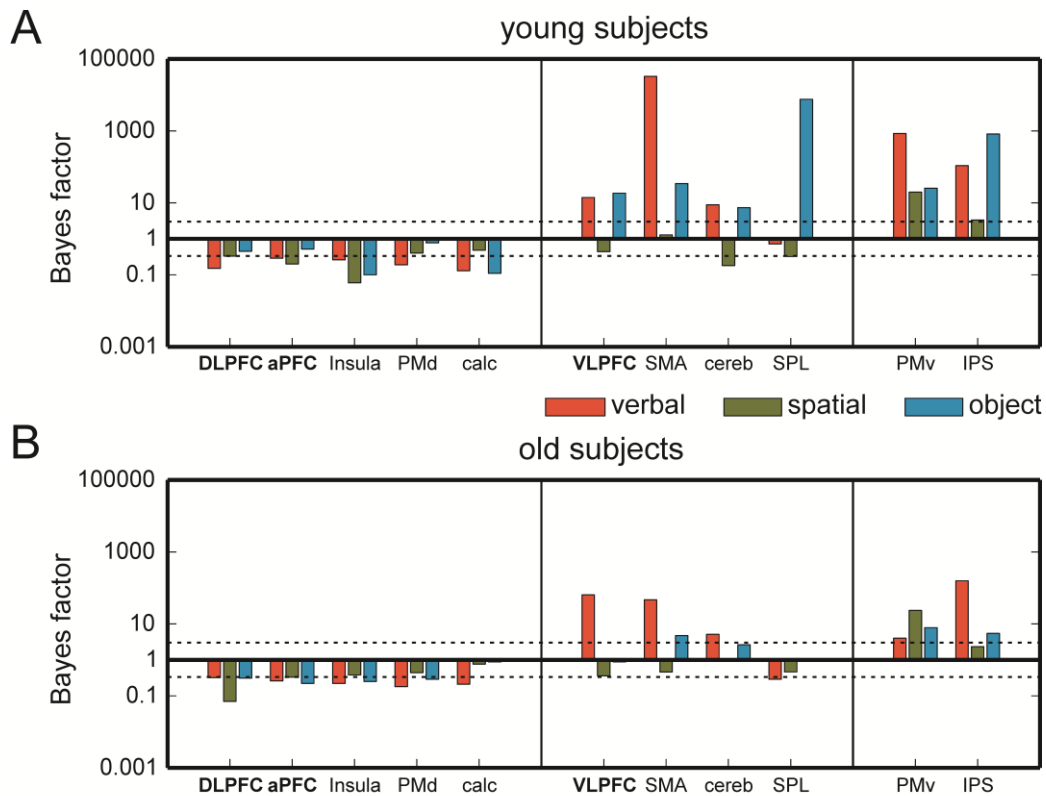
Figure 17. **Bayes factors of all ROIs acquired from the main experiment.**

Bayes factors of the 10 young (A) and 10 old (B) subjects of the main experiment are shown separately for all ROIs and WM domains (red: verbal; green: spatial; blue: object). A Bayes factor below 1 denotes evidence in favor of bilaterality, a Bayes factor above 1 represents evidence in favor of unilaterality, and a Bayes factor that equals 1 expresses that the experimental data are not sensitive enough to decide which lateralization pattern is more likely. The horizontal dashed lines represent the thresholds that provide – according to Jeffreys (1961) – substantial evidence for unilateral (upper line, y = 3) vs. bilateral (lower line, y = 1/3) activation patterns. I logarithmized the y-axis to ensure that the two thresholds have the same distance from 1. Vertical lines separate ROIs according to their lateralization pattern revealed by the main experiment: leftmost ROIs reflect domain-general bilateral ROIs that showed bilaterality across all WM domains; in the middle, I depict domain-specific bilateral ROIs exhibiting bilaterality in at least one WM domain; rightmost are domain-general unilateral ROIs that exhibited stronger activation in the left hemisphere across all WM domains. Our main ROIs, which are also depicted in figure 16, are marked in bold. calc, calcarine sulcus; cereb, lobule VI/crus1 of lobule VII of the cerebellum. This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

6.2.2.2 Domain-specific bilateral ROIs

Contrary to DLPFC and aPFC, we had predicted that *VLPFC* should rather exhibit a unilateral pattern of activation, at least in those WM domains that build on language-related processes. In fact, VLPFC – along with the *SMA* and the *cerebellum* – exhibited a unilateral pattern in the verbal and object domains but a more bilateral one in the spatial domain. Hence, these ROIs exhibited a domain-specific bilaterality. Whereas *VLPFC* and *SMA* showed

stronger activation in the left than in the right hemisphere in the verbal domain [main effects of "hemisphere" in *VLPFC*: $F(1,18) = 16.82$, $p = 0.001$; in *SMA*: $F(1,18) = 31.58$, $p = 0.00003$] and in the object domain [main effects of "hemisphere" in *VLPFC*: $F(1,18) = 4.91$, $p = 0.040$; in *SMA*: $F(1,18) = 14.43$, $p = 0.001$] across age groups, right lobule VI/crus1 of lobule VII of the *cerebellum* was stronger activated than its left-hemispheric counterpart in these WM domains [main effects of "hemisphere": verbal: $F(1,18) = 10.27$, $p = 0.005$; object: $F(1,18) = 6.25$, $p = 0.022$]. In contrast, the left and right cross-hemispheric counterparts were similarly engaged in all three ROIs in the spatial domain [main effects of "hemisphere" in *VLPFC*: $F(1,18) = 0.71$, $p = 0.410$; in *SMA*: $F(1,18) = 3.82$, $p = 0.066$; in *cerebellum*: $F(1,18) = 0.96$, $p = 0.341$]. Importantly, all effects were independent of age and thus identical across age groups (all interactions between "hemisphere" and "age": $p > 0.24$). The Bayes factors of young and old subjects further support the aforementioned findings (compare figure 17 A and B). The time courses of the BOLD-signal changes (figure 14 C) and the Bayes factors (figure 16) show that the activation in *VLPFC* matched our predictions.

Another brain region that exhibited domain-specific bilaterality was area *SPL*. ANOVAs of SPL showed no main effects of "hemisphere" in the verbal [$F(1,18) = 0.33$; $p = 0.573$] and spatial [$F(1,18) = 1.60$; $p = 0.222$] domains, whereas they revealed a significant main effect of "hemisphere" in the object domain [$F(1,18) = 18.10$; $p = 0.0005$]. We did not find significant interactions between "hemisphere" and "age" in these ANOVAs (verbal and spatial: $p > 0.40$), apart from the object domain [$F(1,18) = 4.45$; $p = 0.049$]. The Bayes factors of young and old subjects further support these findings (compare figure 17 A and B). These statistical results suggest that, except for the object domain, the described lateralization patterns were similar in young and old subjects. Here, young subjects showed a stronger activation of the left hemisphere across load levels [a two-way repeated-measures ANOVA with the factors "hemisphere" (two levels: left vs. right) and "load" (five levels: 1-5) on the estimates of percentage of BOLD-signal change during the WM maintenance phases of only young subjects found a significant main effect of "hemisphere": $F(1,9) = 20.10$; $p = 0.002$; uncorrected; survives Bonferroni correction for multiple comparisons]. In contrast, old subjects did not show this hemispheric difference [the respective ANOVA including the data of only old subjects did not reveal a main effect of "hemisphere": $F(1,9) = 2.32$; $p = 0.162$]. Because the object task was subjectively easier for young subjects (as described above), this result leaves ambiguous whether the difference in lateralization patterns in SPL in the object domain is a function of task difficulty or age.

6.2.2.3 Domain-general unilateral ROIs

The three-way repeated measures ANOVAs yielded significant main effects of "hemisphere" for all WM domains in *PMv* [verbal: $F(1,18) = 15.76$, $p = 0.001$; spatial: $F(1,18) = 14.20$, $p = 0.001$; object: $F(1,18) = 12.38$, $p = 0.002$] and in *IPS* [verbal: $F(1,18) = 23.59$, $p = 0.0001$; spatial: $F(1,18) = 10.88$, $p = 0.004$; object: $F(1,18) = 13.81$, $p = 0.002$], whereas, in each case, activation was stronger in the left hemisphere. Therefore, these areas are considered domain-general unilateral ROIs. The additional absence of significant interactions between the factors "hemisphere" and "age" (all $p > 0.35$) indicate that this hemispheric difference is independent of age. This conclusion is supported by Bayes factors of young and old subjects (compare figure 17 A and B). In sum, *PMv* and *IPS* are regions that maintain left-lateralized activation patterns during the maintenance phases of all three WM domains in the face of high subjective task loads and independently of age.

6.3 Discussion of the main experiment

In this section, I will first summarize and interpret the results of the main experiment. Then, I will discuss specific analytical issues and important limitations of this experiment. As will be seen in the next chapter, we also conducted a control experiment which was supposed to address some of these limitations. Also note that there will be a general discussion of the results in the last chapter of this dissertation.

6.3.1 Summary and interpretation of the results

The goal of the main experiment was to investigate if young and elderly subjects equally show bilateral recruitment of cross-hemispheric counterparts in DLPFC and aPFC when they work on highly-demanding verbal, spatial, and object-based WM tasks that are matched for subjective task difficulty. As previously described, we were specifically interested in these two brain regions because they have shown a unilateral vs. bilateral contribution to memory tasks in young and older adults, respectively, in former research (Cabeza et al., 2002; Rossi et al., 2004). Moreover, we wanted to find out whether bilaterality is a general mechanism that the brain employs to cope with challenging tasks. Therefore we asked whether not only the DLPFC and aPFC but also whether task-relevant brain regions that are known for their highly lateralized processing of language-based information – like Broca's area in VLPFC – show bilateral activation patterns during difficult tasks (Belger & Banich, 1998; Berker et al., 1986).

The results of the main experiment clearly demonstrate that cross-hemispheric counterparts of DLPFC and aPFC are simultaneously recruited in our demanding WM tasks in

young and elderly participants and across all WM domains. In accordance with Banich's and Belger's notion (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998) and CRUNCH (Reuter-Lorenz & Cappell, 2008), I interpret the bilateral activation patterns of these prefrontal regions as an age-independent mechanism of the brain to cope with increased cognitive task demand (for further discussion of this interpretation, please refer to the general discussion in chapter 8).

As previously described in chapter 4, Belger and Banich suggested that almost all tasks can be processed by both hemispheres in their specific modes, with the exception of certain phonetic tasks whose linguistic contents are assumed to be exclusively processed by the left hemisphere in right-handed people (Belger & Banich, 1998). In accordance with this notion, VLPFC shows – in contrast to DLPFC and aPFC – a left-lateralized activation pattern in the verbal and object domains (and a more bilateral activation pattern in the spatial domain) despite our high task demands. As many of our participants reported that they had stored the object items partly by maintaining names which they had associated with them, I suspect that unilaterality of VLPFC in the object domain also represents verbal mnemonic strategies. In addition to VLPFC, the SMA and cerebellum maintained unilaterality in the verbal and object domains and may also be considered language-relevant areas because – like VLPFC – these areas are involved in preparing and executing speech as well as in verbal WM processes (Smith & Jonides, 1999; Stoodley & Schmahmann, 2009) (compare also chapter 3). Furthermore, Broca's area (which overlaps with our left ROI in VLPFC) and left SMA are anatomically interconnected with right lobule VI and crus1 of the cerebellum (Leiner, Leiner, & Dow, 1991; Schmahmann, 1996). The unilateral activation pattern of VLPFC, SMA, and cerebellum could reflect subvocal rehearsal during the maintenance phase of the verbal and object WM tasks (Ben-Yehudah, Guediche, & Fiez, 2007; Smith & Jonides, 1999).

Moreover, PMv showed stronger activation in the left hemisphere than in the right across all three investigated WM domains and in both age groups, a pattern consistent with the idea that left PMv plays a role in language (Duffau et al., 2003). Since this unilateral lateralization pattern was not domain-specific for the verbal (and object) material but was also present in the spatial domain, I assume that the function of a lateralized pattern of PMv during the maintenance phase of our study may reflect an unspecific preparation of the verbal report that was required during the response epochs of all three WM domains (Duffau et al., 2003).

In summary, the results of the main experiment speak in favor of the idea that recruiting the contralateral counterpart in the other hemisphere is not a general strategy of the human brain to compensate for high task demands. Instead, brain regions that are probably related to language-based processes (VLPFC, SMA, cerebellum, and PMv) demonstrate a unilateral activation pattern despite high WM task demands.

6.3.2 Justification of our fMRI analysis approach

It is important to highlight that we used the same fMRI dataset for both ROI definition and ROI analysis, which may involve certain risks in neuroimaging studies (Kriegeskorte et al., 2009). Kriegeskorte et al. (2009) proposed that ROIs should rather be defined a priori on the basis of the existing literature. In the following paragraphs, I will first briefly explain and justify our analytical approach, and then I will also detail the reasons why this approach does not involve any risks in our case. Finally, I will also refer to our additional analytical approach based on an a priori definition of our main ROIs which led to the same principle findings of the main analyses.

In brief, our ROI-based analysis was performed as follows: we used a second level contrast to identify memory maintenance-related brain areas as candidate ROIs. Next, for each candidate ROI, the voxel that exhibited the most reliable activation during WM maintenance was separately selected in each individual and for each hemisphere. Based on the averaged activity estimates that were retrieved from a 3-mm radius sphere around the individually selected voxel for each hemispheric counterpart of a given ROI we then determined the actual pattern of lateralization in that ROI. Our approach to map task-related ROIs in each individual closely followed the procedures proposed by Schneider-Garces et al. (2010). We preferred this particular approach because we wanted to apply a ROI-based approach that would consider age-related anatomical changes in the brain and would thus make for a more fair comparison across age groups (Schneider-Garces et al., 2010).

Despite the advantage of mapping task-related ROIs in each individual instead of using the same coordinates for all subjects in aging-studies, using the same fMRI dataset for both ROI definition and ROI analysis may (i) involve the general danger of circularity and (ii) lead to biased activity estimates in neuroimaging results (Kriegeskorte et al., 2009). In the following, I will detail the reasons why, in the context of our study, both concerns can be dispelled:

(i)   According to the criteria specified in Kriegeskorte et al. (2009), our approach did avoid any circularity: the tests for the functional selection of brain regions (both within and across subjects) exclusively focused on memory maintenance-related brain activity *within* a given part of the brain (or voxel) and merely served to identify regions for later ROI analyses. Our actual ROI analyses instead focused on activity differences *between* voxels of cross-hemispheric pairs of regions. In other words, the earlier selection of regions (or voxels) was based on maintenance-related activity – independent of hemisphere – and thus did not make any prediction about whether or not the level of activity differed between the hemispheric counterparts of a ROI. Hence, our tests for the functional

selection of brain regions and our ultimate ROI analyses were in fact statistically independent and thus not circular.

(ii)   According to Kriegeskorte et al. (2009), an approach like the selection of our peak voxels could – in the presence of noise – bias activity estimates toward larger values. However, this bias should have been likewise present for both hemispheric counterparts of a ROI, and thus, potential cross-hemispheric differences in activation should have been preserved (Schneider-Garces et al., 2010). Indirect evidence in support for this assumption comes from our alternative ROI analyses that considered information across spheres of 9-mm radius (compare page 57). These analyses of much larger spherical spaces should have significantly attenuated the aforementioned biasing effect and – as is illustrated in table 2 – still produced the same cross-hemispheric patterns of activation.

Although neither circularity nor biased activity estimates seem to play a role in our approach, we still conducted further analyses for our main ROIs DLPFC and VLPFC for which we had formulated a priori hypotheses (see chapter 5). We repeated our analyses for these ROIs on the percentage of BOLD-signal changes during the maintenance phase extracted from meta-coordinates reported by Fiez and colleagues (1996). These analyses demonstrated the same lateralization patterns as our original analyses (table 2, gray unfilled circles in the third rows of DLPFC and VLPFC) and thus further validate our results. The reason we chose the coordinates of Fiez and colleagues (1996) is that they reported average coordinates for DLPFC and VLPFC, which were calculated across various WM studies. Using these averaged meta-coordinates for the new analyses seemed a reasonable approach because there are no studies with a task design comparable to ours (e.g., with a long maintenance phase, different WM domains, etc.). Unfortunately, however, Fiez et al. (1996) did not offer averaged coordinates for aPFC. The respective analyses for aPFC are therefore lacking.

6.3.3 Limitations of the main experiment

I will discuss various limitations of the main experiment in this section. First, there were several limitations in the object-based WM task that could affect the interpretation of our experimental findings. On the one hand, many subjects maintained not only "pure" object information but resorted to a verbal mnemonic strategy, as reported by the majority of our subjects after the experiment. On the other hand, subjective task difficulty was not successfully matched between young and old subjects. Figure 12 demonstrates that young subjects most likely did not reach their memory spans in the object domain. Thus, they experienced the object

WM task as subjectively easier than did our older subjects. This may have resulted from the fact that older adults learn new material more slowly (Hultsch & Dixon, 1990). Future studies could use Kanji signs in the object domain if they make sure to use new items in every trial to prevent learning effects and to complicate the usage of verbal mnemonic strategies for maintaining items of the object domain. The shortcomings in the object domain offered us the possibility to see whether these "imperfections" are reflected in the activation of our ROIs in a meaningful way. For example, whereas the Bayes factors in DLPFC and in aPFC clearly indicated bilaterality in young and old subjects in both verbal and spatial domains, in the object domain, there was less evidence for bilaterality in young compared with old subjects. The fact that the object domain was not as difficult for the young as for the old subjects might underlie this finding. Furthermore, we found a significant "age" × "hemisphere" interaction in SPL in the object domain: whereas young subjects clearly showed a stronger activation of the left hemisphere, older subjects did not. This finding could suggest that beyond PFC, SPL might also respond to increased task difficulty by recruiting its cross-hemispheric counterpart. However, this issue requires further research (please refer also to the outlook section 8.5.2 of this dissertation).

Second, it is crucial to report that there was a statistical trend in the behavioral analyses for the interaction between the factors "age" and "load" ($p = 0.068$) in the spatial WM domain. Despite this trend, I assume that we successfully controlled for subjective task demand in the spatial domain because the trend was evoked by load level 5 – the most difficult level (the trend for the interaction disappeared when including only load levels 1-4 in an ANOVA: $p > 0.30$). Contrary to young subjects, the elderly subjects seem to have failed in sustaining their WM performance for the most difficult level that surpasses their memory spans by two items (compare figure 12). Since both age groups reached their performance limits within the range of load levels we offered, I still think that the tasks were subjectively comparable in difficulty between the age groups.

Third, our main experiment lacked an easy control condition which would have allowed us to see unilateral activation in DLPFC and aPFC that would have become bilateral activation as we increased the load level. Although we had included a range of five load levels, we did not reveal a significant "load" x "hemisphere" interaction on percentage BOLD-signal change in DLPFC and aPFC in neither WM domain in the ANOVAs, which would have spoken in favor of such a lateralization shift depending on task demand. Instead, bilateral recruitment of DLPFC and aPFC was present at all load levels in all three WM domains and in both age groups (compare figure 15 A and B). This result is not surprising because, as was mentioned above, all relative load levels closely ranged around a subject's WM span. Thus, even the easiest load levels were subjectively demanding as they were not substantially easier than the

critical memory span (only two items less). Furthermore, since participants could not anticipate the load level of the current trial, they always had to be prepared for a load level up to two items above their estimated memory span. Either of these two factors could have triggered the recruitment of the other hemisphere irrespective of the actual load.

To demonstrate that DLPFC and aPFC do in fact exhibit lateralized patterns of activity in easier versions of our WM tasks and to further substantiate the notion that young individuals also shift from a lateralized mode of prefrontal processing to a bilateral processing mode when WM tasks get more difficult, we conducted an additional control experiment with 11 young adults. This experiment allowed us to contrast easy vs. difficult WM tasks and is described in more detail in the next chapter.

7 Control experiment

In the control experiment, we engaged the same WM tasks as in our main experiment but resorted to the verbal and spatial domains (figure 8). In this experiment, both verbal and spatial domains consisted of one easy and one difficult load level. The experiment was conducted in four subsequent sessions and we tested only one experimental condition (e.g., verbal easy, etc.) per session to make it clear to the subjects whether any given trial would be easy or difficult.

7.1 Material and Methods

I will describe the materials and methods used in the control experiment in more detail in the next sections by referring to subjects, the memory paradigm, procedures, data acquisition, and data analysis. Since the stimuli used in the control experiment were identical to the ones of the verbal and spatial WM domains of the main experiment and since the stimulus presentation in the fMRI scanning sessions was also identical in the two experiments, I won't explicitly describe these topics again in this section. Please refer to section 6.1.2 of the main experiment for these details.

7.1.1 Subjects

In the control experiment, we measured a total of 12 young subjects while ultimately including 11 subjects (6 males; age range: 21-30 y; mean age: 25.1 y; *SD*: 3.2 y) who had not participated in the main experiment. One subject was excluded due to strong movement artifacts. All participants had normal or corrected-to-normal visual acuity, were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), participated in the experiment for monetary compensation, and gave written consent in accordance with the declaration of Helsinki, and none suffered from chronic, neurological, or psychiatric diseases. The study was approved by the ethics committee of the University of Tübingen.

7.1.2 Memory paradigm and procedures

For the control experiment, we used an easy and a difficult version of the verbal and spatial WM tasks of the main experiment (figure 8). The respective load levels in the easy conditions were three items in the verbal domain and two items in the spatial domain. Load levels were chosen one item lower than those engaged in the study by Reuter-Lorenz and colleagues (2000), who demonstrated lateralized activation of DLPFC in young subjects in

both WM domains. For the difficult conditions, we used the average WM capacity of young subjects revealed in the verbal domain (load level: 7) and the spatial domain (load level: 6) in our main experiment (compare figure 11).

We dropped the object domain because, in our main experiment, we had failed to control for subjective task difficulty in this domain and because subjects reported to have used verbal mnemonic strategies, making a qualitative differentiation between verbal and object domains disputable (compare section 6.3.3). The control experiment included four sessions that were conducted one after another on the same day. Each session comprised 20 repetitions of a single experimental condition (verbal easy, spatial easy, verbal hard, and spatial hard). All subjects worked on the easy conditions in the first and second session before coping with the difficult tasks in the third and fourth session. This order was chosen to avoid a carryover of compensation strategies from difficult to easy tasks. We randomized the order of WM domains across subjects, so that some subjects first worked on verbal tasks and others on spatial tasks, respectively.

7.1.3 Data acquisition

As in the main experiment, participants orally responded in the fMRI sessions of the control experiment and we recorded their verbal answers by means of the MRI-compatible microphone (sampling rate: 8 kHz; Optoacoustics Dual-Channel Microphone; Optoacoustics). We analyzed these answers off-line using self-written scripts in MATLAB R2007b (The MathWorks).

We acquired MR images using a Prisma system and a 20-channel head coil in the control experiment (Siemens) and collected a T1-weighted magnetization-prepared rapid-acquisition gradient echo structural scan of the whole brain from each subject [number of slices: 176; slice thickness: 1mm; gap size: 0 mm; in-plane voxel size: 1×1 mm; TR: 2,300 ms; TE: 2.96 ms; FOV: 256×256 mm; resolution: 256×256 voxels]. Furthermore, we measured T2*-weighted gradient-EPI scans for our fMRI analyses [slice thickness: 3.2 mm; gap size: 0.8 mm; in-plane voxel size: 3×3 mm; TR: 2,000 ms; TE: 35 ms; flip angle: 90°; FOV: 192×192 mm; resolution: 64×64 voxels; 32 axial slices]. Comparable to the main experiment, cerebral cortex and most subcortical structures were completely covered by the EPI volume, but we did not record from the most posterior parts of the cerebellum in several of our subjects due to brain size.

7.1.4 Data analysis

We statistically analyzed behavioral data using SPSS (version 22; IBM SPSS Statistics) and functional data using SPM8 (Wellcome Department of Cognitive Neurology, London) and SPSS (version 22; IBM SPSS Statistics).

Preprocessing of the functional data. To preprocess our functional data, we first realigned all functional images from all four blocks by using the first scan of the first block as a reference. Then, all functional images were aligned to the anatomical image based on a coregistration of the mean functional image to the T1 scan. Next, we normalized subjects' anatomical image to the SPM T1 template in MNI space (mean brain). The resulting normalization parameters were also applied to all functional images for spatial normalization. Finally, all functional images were smoothed by using a Gaussian filter ($7 \times 7 \times 7$ mm^3 full-width at half-maximum) and high-pass-filtered (cutoff period: 128 ms).

First-level analysis. We created a GLM on the single subject level with three regressors that comprised the encoding, maintenance, and response phases separately for every experimental condition (e.g., verbal easy). Then, independently for every experimental condition, we convolved all three regressors with the default canonical hemodynamic response function offered by SPM and used the movement parameters that were calculated during the realignment procedure as covariates of no interest in the respective GLM. The fixation periods in the beginning of a trial and the intertrial intervals were not specifically modeled and were consequently treated as the baseline phase. For each subject, we generated four statistical *t*-contrast images separately representing the maintenance period of easy and difficult conditions of the verbal and the spatial domain.

Analyzing fMRI lateralization patterns of the ROIs. The procedure of analyzing lateralization patterns of our ROIs in the control experiment was identical to the one described in the main experiment (compare section 6.1.5). We used the representative group coordinates of the main experiment (see (ii) on page 43) to determine individual peak voxels within our ROIs (see (iii) on page 44). However, for the latter step, we used, separately for the verbal and spatial domain, the statistical *t*-contrast images representing the maintenance period of the difficult condition of the control experiment.

7.2 Results

In the following sections, I will present behavioral results and fMRI results that illustrate lateralization patterns of our ROIs in young adults working on the easy and difficult verbal and spatial WM tasks of our control experiment.

7.2.1 Behavioral results

The analysis of the hit rate showed that we were successful in creating an easy and a more difficult condition in both domains: firstly, almost all trials were answered correctly in the easy conditions of the verbal domain (proportion of hits: mean, 0.996; standard error (*SE*), 0.005; throughput: mean, 2.980; *SE*, 0.021) and the spatial domain (proportion of hits: mean, 0.984; *SE*, 0.008; throughput: mean, 1.938; *SE*, 0.033). Secondly, the proportion of hits was significantly lower in the difficult conditions of both the verbal (proportion of hits: mean, 0.841; *SE*, 0.036; throughput: mean, 5.701; *SE*, 0.296) and spatial (proportion of hits: mean, 0.833; *SE*, 0.039; throughput: mean, 4.797; *SE*, 0.282) domain (both tests revealed almost the same statistical values: $U = -2.81$, $p = 0.005$; we conducted Wilcoxon tests because simple conditions were not normally distributed in both WM domains due to ceiling effects in performance).

7.2.2 fMRI results: analyzing fMRI lateralization shift between easy and difficult tasks

The aim of the control experiment was to investigate whether there is lateralized activation of DLPFC and aPFC in easy tasks that shifts to bilateral activation of corresponding counterparts in difficult tasks. To this end, we calculated two-way repeated-measures ANOVAs – independently for DLPFC and aPFC and for the verbal and the spatial domain – with the factors "hemisphere" (two levels: left vs. right) and "load" (two levels: easy vs. difficult) on the estimates of percentage of BOLD-signal change during the maintenance phase (compare figure 18) and also determined the corresponding Bayes factors (figure 19 C and D).

For *DLPFC*, the ANOVAs revealed significant interactions between "hemisphere" and "load" in both the verbal [$F(1,10) = 6.79$; $p = 0.026$] and spatial [$F(1,10) = 5.88$; $p = 0.036$] domains. Bayes factors supported these findings (verbal easy: 30.94; verbal difficult: 0.08; spatial easy: 2.26; spatial difficult: 0.11; compare also figure 19 C and D). These results indicate that left DLPFC was more activated than its right counterpart in the easy conditions of verbal and spatial domains. This lateralization disappeared in the difficult conditions due to an increase in activation of the right hemisphere in both domains (compare figure 18 A).

For *aPFC*, the "hemisphere" × "load" interactions were not significant [verbal: $F(1,10) = 2.13$, $p = 0.175$; spatial: $F(1,10) = 0.01$, $p = 0.940$; figure 18 B]. However, at least in the verbal domain, the corresponding Bayes factors again indicated a unilateral lateralization pattern in the easy condition (verbal: 3.06; figure 19 C) that transforms into a bilateral activation pattern in the difficult condition (verbal: 0.31; figure 19 D), whereas a clear trend in the same direction was also present in the spatial domain (spatial easy: 2.63; spatial difficult: 0.55; figure 19 C and D).
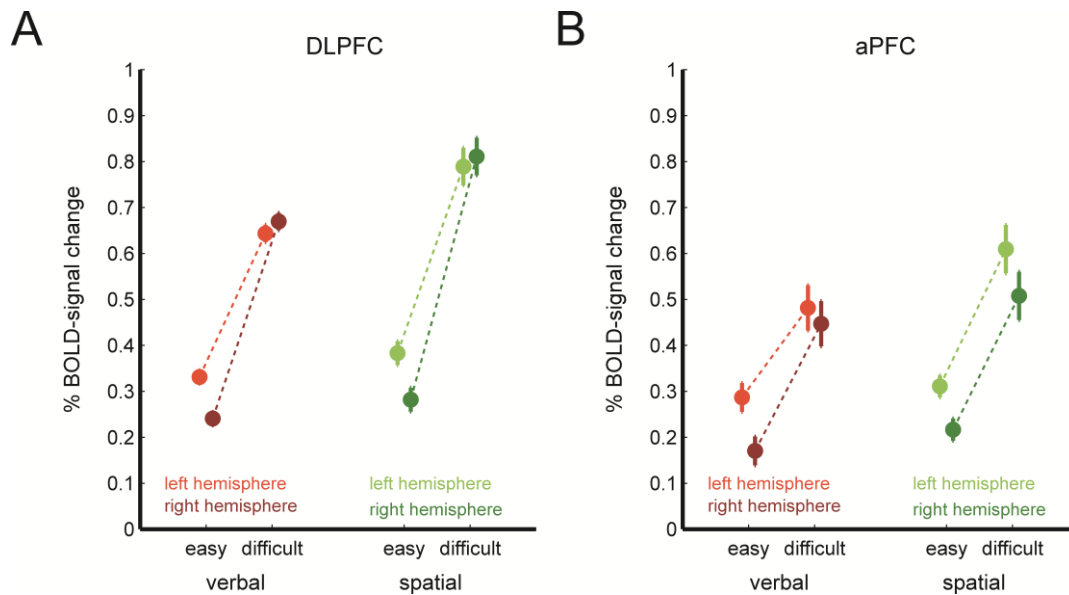
Figure 18. **Percentage of BOLD-signal change of DLPFC and aPFC in easy vs. difficult tasks of the control experiment.**

This figure shows mean percentage of BOLD-signal change of the 11 young subjects of the control experiment and their *SE*s, separately for DLPFC (A) and aPFC (B), for easy and difficult tasks, for the left (brighter color) and right (darker color) hemisphere, and for verbal (red) and spatial (green) WM domains. Due to the within-subjects design, we adjusted error bars by removing the between subjects variance within one condition according to the procedures described by Masson and Loftus (Masson & Loftus, 2003). This figure illustrates the findings described in the main text that left DLPFC and left aPFC were more strongly activated than their right counterparts in the easy verbal and spatial tasks and that this lateralization difference disappeared in the difficult tasks because of an increase in activation of the right hemisphere. This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

Moreover, we conducted – separately for DLPFC and aPFC – repeated-measures ANOVAs with the factors "domain" (verbal vs. spatial) and "hemisphere" (left vs. right) on the percentage of BOLD-signal change in easy WM tasks to more directly test the notion that these prefrontal regions do exhibit a unilateral pattern of activation during memory maintenance in such easy tasks. In fact, in both verbal and spatial domains left DLPFC and left aPFC were more strongly activated during WM maintenance than their right counterparts [main effect of "hemisphere" in *DLPFC*: $F(1,10) = 10.05$, $p = 0.010$; interaction between "domain" and "hemisphere" in *DLPFC*: $F(1,10) = 0.034$, $p = 0.857$; main effect of "hemisphere" in *aPFC*: $F(1,10) = 7.68$, $p = 0.020$; interaction between "domain" and "hemisphere" in *aPFC*: $F(1,10) = 0.07$, $p = 0.792$].
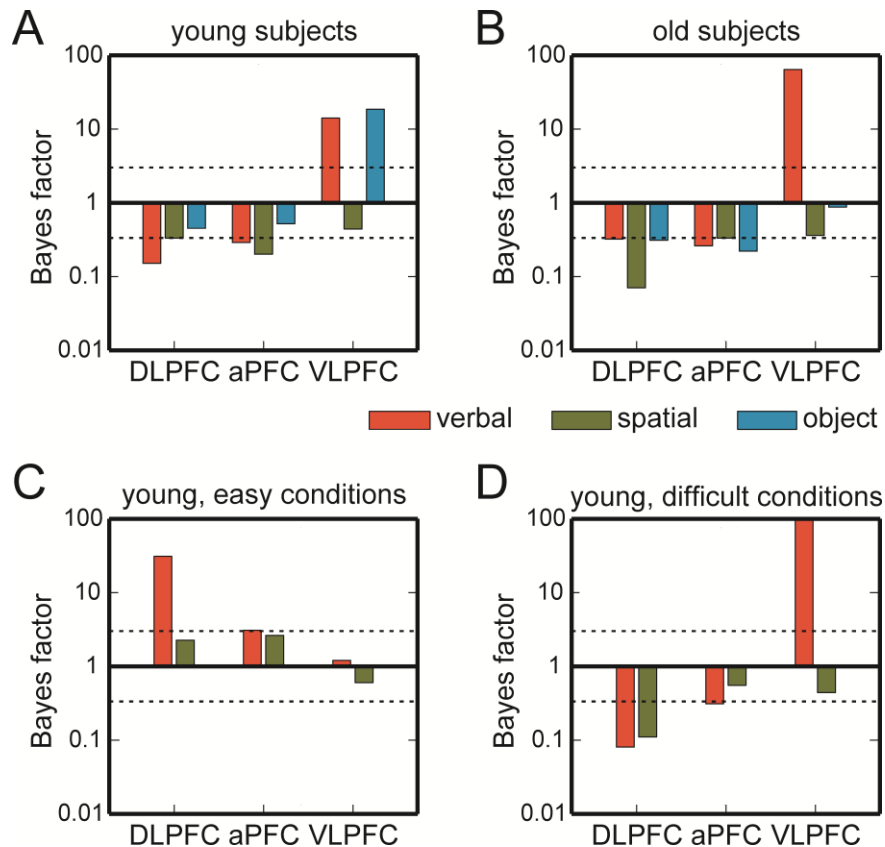
Figure 19. Bayes factors of the main ROIs acquired from the main and control experiments.

I illustrate Bayes factors of the 11 young subjects of the control experiment separately for easy (C) and difficult (D) tasks, for the main ROIs DLPFC, aPFC, and VLPFC and for the verbal (red) and spatial (green) WM domains. Bayes factors of the 10 young (A) and 10 old (B) subjects of the main experiment are also shown once more for the same ROIs and all WM domains used in this experiment (red: verbal; green: spatial; blue: object; compare figure 16) to provide a better overview of the lateralization patterns of the main ROIs across the main and control experiments. As previously mentioned, a Bayes factor below 1 denotes evidence in favor of bilaterality, a Bayes factor above 1 represents evidence in favor of unilaterality, and a Bayes factor that equals 1 expresses that the experimental data are not sensitive enough to decide which lateralization pattern is more likely. The horizontal dashed lines represent the thresholds that provide – according to Jeffreys (1961) – substantial evidence for unilateral (upper line, y = 3) vs. bilateral (lower line, y = 1/3) activation patterns. I logarithmized the y-axis to ensure that the two thresholds have the same distance from 1. For better general visibility, I set the upper limit of the y-axis to 100. As a consequence, the bar depicting the Bayes factor of VLPFC in the verbal domain was cut in D because its value amounts to 241 (compare figure 20). Note that, whereas VLPFC generally exhibited unilaterality in difficult conditions of the verbal domain (A, B, and D), this pattern was less pronounced in the easy condition (C), which could relate to a floor effect, because the easy verbal task may have been too simple to drive left VLPFC. This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

Further effects of the aforementioned ANOVAs with the factors "hemisphere" and "load" referring to DLPFC and aPFC and the results of the respective ANOVAs of *VLPFC* and of all

additional ROIs taken from the main experiment are in table 3. Moreover, corresponding Bayes factors are depicted in figure 20 C and D. In summary, the findings of our control experiment support the notion that DLPFC and aPFC show left-lateralization during memory maintenance in easy verbal and spatial WM tasks but which recruit their right-hemispheric counterpart when tasks get difficult. The results of the main experiment suggest that this support mechanism operates in a domain-general and age-independent manner.

Table 3. **Significant main effects and interactions of the control experiment revealed by the two-way repeated-measures ANOVAs with the factors "hemisphere" and "load" on percentage of BOLD-signal change.**

ROI	Verbal			Spatial		
	Hem	Load	Interaction	Hem	Load	Interaction
Frontal						
DLPFC		•	h × l: •	•••		h × l: •
aPFC					•	
VLPFC	•	•	(h × l: •)		•	
Insula		•			•	
Premotor						
PMd		••			•••	
PMv	•	••	(h × l: •)	•	•••	
SMA	•	•	(h × l: ••)		•••	
Parietal						
IPS	•••	•			•••	
SPL		•			•••	
Occipital						
Calcarine salcus	•••				•	
Subcortical						
Cerebellum (l6/crus1)	•	•	(h × l: •)	••	••	

Interactions in parentheses did not express increased bilaterality with increasing load but the opposite: lateralization in the verbal domain became stronger with increasing load in areas that I interpreted as language-related areas (namely, VLPFC, SMA, cerebellum, and PMv; compare section 6.3.1). Note that, contrary to the main experiment (table 2), the main effect of "load" in aPFC did not reach the conventional significance threshold in the verbal WM domain of the control experiment (p = 0.114). Hem, main effect of "hemisphere"; h × l, interaction between "hemisphere" and "load"; Load, main effect of "load". • p < 0.05; •• p < 0.005; ••• p < 0.001. This table is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.
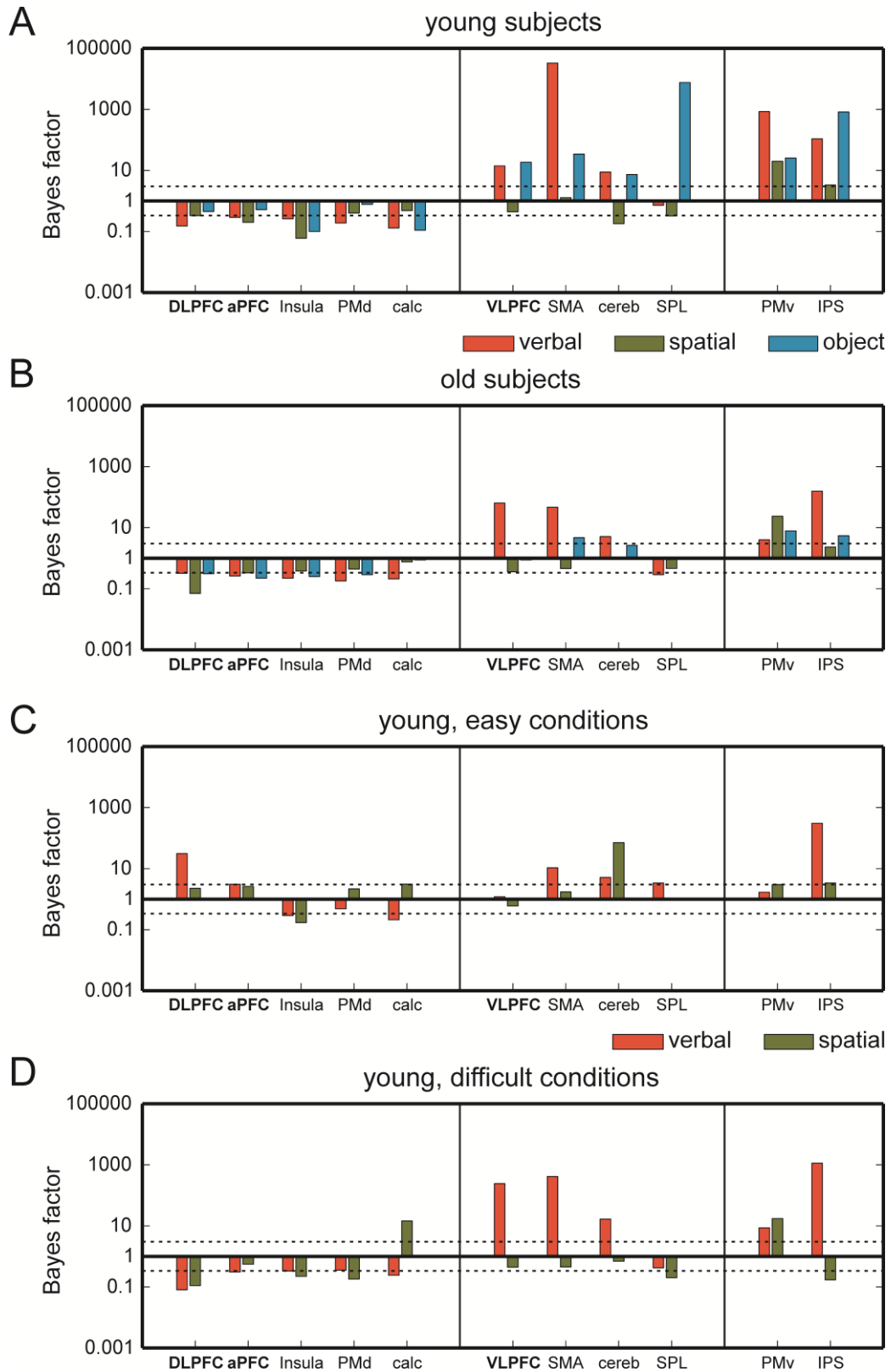
Figure 20. Bayes factors of all ROIs acquired from the main and control experiments.

The aim of this figure is to provide a general overview of the lateralization patterns of all ROIs across the main and control experiment. Thus, Bayes factors of the 10 young (A) and 10 old (B) subjects of the main experiment – that were already presented in figure 17 – are shown again separately for all ROIs and WM domains (red: verbal; green: spatial; blue: object). Furthermore, Bayes factors of the 11 young subjects of the control experiment are illustrated for easy (C) and

difficult (D) tasks separately for all ROIs and verbal (red) and spatial (green) WM domains. Again, a Bayes factor below 1 denotes evidence in favor of bilaterality, a Bayes factor above 1 represents evidence in favor of unilaterality, and a Bayes factor that equals 1 expresses that the experimental data are not sensitive enough to decide which lateralization pattern is more likely. The horizontal dashed lines represent the thresholds that provide – according to Jeffreys (1961) – substantial evidence for unilateral (upper line, y = 3) vs. bilateral (lower line, y = 1/3) activation patterns. I logarithmized the y-axis to ensure that the two thresholds have the same distance from 1. Vertical lines separate ROIs according to their lateralization pattern revealed by the main experiment (A and B): leftmost ROIs reflect domain-general bilateral ROIs that showed bilaterality across all WM domains; in the middle, I depict domain-specific bilateral ROIs exhibiting bilaterality in at least one WM domain; rightmost are domain-general unilateral ROIs that exhibited stronger activation in the left hemisphere across all WM domains. Our main ROIs, are marked in bold. Note that the lateralization patterns in the difficult conditions do also well generalize across experiments (compare A and D), with the only exceptions of calcarine sulcus and IPS in the spatial domain (compare section 8.3.2 for a more detailed discussion of this issue). calc, calcarine sulcus; cereb, lobule VI/crus1 of lobule VII of the cerebellum. This figure is reprinted from Höller-Wallscheid et al., Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age, *Proc Natl Acad Sci USA,* 2017, 114(5), E830-E839.

7.3 Discussion of the control experiment

I will begin the discussion of the control experiment with a summary and interpretation of its results. Afterwards, I will discuss the limitations of this experiment and provide suggestions for improving such an experiment for further research. Please note that I will also discuss further issues concerning both, the main and the control experiment, in a general discussion in the next chapter.

7.3.1 Summary and interpretation of the results

The aim of the control experiment was to investigate if young adults show a lateralized activation pattern of DLPFC and aPFC in easy verbal and spatial WM tasks that transforms into a more bilateral activation pattern when WM tasks become more demanding. Our results demonstrate that DLPFC is activated more strongly in the left hemisphere during easy WM tasks of both WM domains, and that this lateralized activation pattern shifts to bilateral recruitment in the more difficult task variants due to a stronger engagement of the right hemisphere. These activation patterns tend to be also present in aPFC. Thus, the control experiment provides empirical evidence that young individuals shift from a rather lateralized processing mode in DLPFC and aPFC during WM maintenance to a bilateral one when WM tasks get more difficult. Inspired by the ideas of Banich's group (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998) and CRUNCH (Reuter-Lorenz & Cappell, 2008) and by also considering the results of the main experiment, I interpret the lateralization shift in DLPFC and aPFC as a support mechanism of the human brain that compensates for task difficulty in

a domain-general and age-independent fashion by recruiting cross-hemispheric counterparts of these prefrontal brain areas. For further discussion of this interpretation, please also refer to section 8.5.3 of this dissertation.

7.3.2 Limitations of the control experiment

The intent of this dissertation was to investigate whether bilateral activation patterns in PFC represent an age-specific compensation mechanism or an age-independent response of the human brain to subjectively difficult WM tasks. The main experiment showed that there is bilateral recruitment of PFC in young and old participants in the face of subjectively highly demanding WM tasks. Bilaterality in prefrontal regions of elderly adults during cognitive tasks is a well-established experimental finding that has been frequently reported in the literature (Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000) and the main experiment obviously replicated this general finding. The major contribution of this experiment is the novel finding that – contrary to previous studies – we exhibited bilateral activation patterns in these prefrontal areas also in our young group during demanding WM tasks. Furthermore, there is empirical evidence for the idea that older adults have a behavioral advantage in memory tasks when they activate PFC bilaterally instead of unilaterally (Cabeza et al., 2002; Reuter-Lorenz et al., 2000), which speaks in favor of a compensatory interpretation of bilateral activation patterns in PFC for older adults (Cabeza et al., 2002). Thus, what has been lacking to investigate the hypothesis if bilateral activation patterns of PFC represent an age-independent response of the brain to cope with increased task demand is empirical evidence for a shift from unilateral to bilateral activation patterns in PFC of young adults with increasing task demand. Consequently, we decided to include only young subjects in our control experiment. Indeed, we were successful in demonstrating such a lateralization shift in PFC for young adults in our control experiment and, thus, limiting subjects to a young age group was sufficient to inspect our hypothesis. Nevertheless, one can argue that for the sake of completeness, we should have also included elderly subjects to be able to show that both young and older adults similarly shift from a unilateral to a bilateral activation pattern in our specific WM paradigm. Future studies could tackle this issue by including subjects of varying age groups.

As was already discussed in section 6.3.3, we encountered some problems with the object WM domain in the main experiment. Consequently, the interpretation of the results of this domain was ambiguous in the main experiment, and therefore we decided to omit the object WM domain in the control experiment. Thus, I cannot provide any information about potential lateralization shifts of task-related brain regions depending on task difficulty for the object domain. Researchers who would like to investigate this question may include the object

WM domain in their experiments while making sure to use new Kanji or other abstract signs (that are not linguistically coded) in every trial to prevent learning effects and to complicate the usage of verbal mnemonic strategies. As also mentioned earlier on page 64, this approach might help to solve the problems that we encountered with the object WM domain in the main experiment.

I will describe a further peculiarity of the control experiment in the following paragraph: the control experiment demonstrates a change in lateralization as a function of task difficulty for both the verbal and the spatial domain by means of significant interactions between "hemisphere" and "load" in young adults for DLPFC. In contrast, we failed to reveal such significant interactions in the respective ANOVAs for aPFC, suggesting that this lateralization shift is not as obvious for aPFC as it is for DLPFC. Nevertheless, given the overall pattern of results of the main and control experiments, there are still convincing reasons to assume that also in aPFC there are changes in lateralization as a function of task difficulty and that these changes are comparable to those in DLPFC. This is for the following two reasons: *first*, we could clearly show bilaterality in the very demanding verbal and spatial tasks of the main experiment in aPFC. This was not only true for the group of elderly subjects – matching the results of former research (Cabeza et al., 2002) – but also for the group of young subjects. However, based on this main experiment I could not conclude that bilaterality arises from task difficulty. This is because it was unclear whether aPFC would exhibit unilaterality in easier tasks. This limitation led us to perform the control experiment which also included easier tasks. While this experiment failed to reveal a significant interaction between "load" and "hemisphere" in aPFC, we did however demonstrate that aPFC is activated unilaterally in easy tasks. This was shown by the repeated measures ANOVA with the factors "domain" (verbal vs. spatial) and "hemisphere" (left vs. right) on the percentage of BOLD-signal change in aPFC of the easy tasks of the control experiment. This ANOVA revealed that the left aPFC is more strongly activated than its right counterpart during the maintenance of easy verbal and spatial WM items. Of course, this analysis does not mean that the lateralization pattern in aPFC would change as a function of task difficulty. Yet, it at least demonstrated that the easy tasks of the control experiment are sufficient to elicit unilateral patterns of activation in aPFC, which is a crucial prerequisite for our main experiment. *Second*, when focusing on the results for aPFC in the control experiment in the verbal domain, the corresponding Bayes factors reached the threshold for unilaterality in the easy condition and that for bilaterality in the difficult condition. While the respective Bayes factors did not meet these thresholds in the spatial domain, they nevertheless indicated evidence for the same general pattern of lateralization (please compare figure 19 C & D).

Still the question remains why the control experiment failed to reveal more clear-cut evidence for bilaterality in aPFC for the difficult tasks and most probably due to this reason also a significant interaction between "hemisphere" and "load." This could be due to the following reason: while we were successful in presenting both easy and more difficult tasks in the control experiment (compare behavioral results of the control experiment), we cannot guarantee for this experiment that all our subjects worked at their capacity limit in the demanding tasks. This is because, unlike the main experiment, we did not match task difficulty on an individual level in the control experiment. Thus, our control experiment seems to have been less reliable in recruiting the cross-hemispheric aPFC to respond to increased task difficulty[4].

This may suggest that DLPFC and aPFC have different thresholds of task difficulty before recruiting cross-hemispheric counterparts and support different compensatory functions. The latter assumption matches the notion that human lateral PFC supports executive control processes which enable us to coordinate thoughts and actions with internal goals and that such control processes are hierarchically organized in the posterior-to-anterior direction in lateral PFC with respect to the level of abstraction at which task rules and goals are represented (Badre & D'Esposito, 2007; D'Esposito & Postle, 2015; Koechlin, Ody, & Kouneiher, 2003; Koechlin & Summerfield, 2007). Empirical evidence for this idea comes from neuroimaging studies showing that activation is shifted from posterior parts of the lateral PFC to anterior parts when action representations become less specific/ more abstract (Badre & D'Esposito, 2007; Koechlin et al., 2003; Koechlin & Summerfield, 2007). For instance, Badre and D'Esposito (2007) demonstrated that the lowest abstraction level predominantly activated the premotor cortex and increasing levels of abstraction coincided with a shift of activation more anteriorly from premotor cortex to DLPFC and to aPFC. Due to such a general hierarchical organization of lateral PFC, it may not be surprising that aPFC shifts from unilaterality to bilaterality at more demanding load levels than DLPFC which is situated more posteriorly in PFC. However, further investigations are needed to examine this question. Please also refer to the outlook section 8.5.2 for a description of a possible experiment to address this issue.

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[4] The fact that – contrary to the main experiment – task difficulty did not significantly modulate brain activation in aPFC across hemispheres in the verbal domain of the control experiment (see missing main effect of "load" in table 3) might support the idea that the difficult verbal task of the control experiment was not as subjectively demanding as the respective difficult tasks of the main experiment.

8 General discussion

In the general discussion of this dissertation, I will focus on a variety of topics that are associated with this work – either directly with the main and the control experiment or with unanswered questions that are raised by these experiments. More specifically, at the beginning of this chapter, I will summarize the results of the two experiments of this dissertation and integrate them with the scope of recent empirical research. Then, I will discuss important strengths and limitations of this work and deal with two issues that the reader might have come across in the course of this work. Namely, I will provide possible reasons for the fact that WM capacity decreases with increasing age and speculate about potential functions of bilateral activation patterns of our ROIs in demanding WM tasks. At the end, I will provide an outlook for potential future studies – which might clarify some of the unsolved topics of this dissertation – and concluding remarks.

8.1 Summary of the results

The aim of this dissertation was to examine if bilateral recruitment of DLPFC and aPFC during WM tasks represents an age-specific compensation mechanism or, alternatively, an age independent strategy of the human brain to increased task demands. Secondly, we asked whether recruiting cross-hemispheric counterparts is an option available to all task-relevant brain areas, even those that are known for their highly lateralized processing of language-based material like, e.g., Broca's area in VLPFC (Berker et al., 1986). Lastly, we investigated if the recruitment of cross-hemispheric counterparts represents a domain-general support mechanism and could therefore be observed across verbal, spatial, and object WM domains.

The results of the main experiment clearly indicate that in DLPFC and aPFC the simultaneous recruitment of cross-hemispheric counterparts during highly demanding WM tasks is present in both young and old subjects and in all WM domains. In the control experiment, in which a group of young subjects completed both easy and difficult WM tasks in both the verbal and spatial domain, we found further evidence that young individuals also shift from a lateralized processing mode to a bilateral one when WM tasks become more demanding. In this experiment, DLPFC shows left-lateralization during memory maintenance in easy verbal and spatial WM tasks and bilateral recruitment when WM tasks become more difficult due to a stronger engagement of the right hemisphere. aPFC tends to show the same lateralization shift depending on task difficulty. Consequently, the results of the two experiments provide empirical evidence that bilateral activation patterns in DLPFC and aPFC do not represent an age-specific compensation mechanism. Rather, they speak in favor of a

general age-independent support mechanism that compensates for task difficulty in a domain-general manner. Finally, in answer to our second question, the two experiments demonstrate that the cross-hemispheric recruitment is not a general response to difficult WM tasks because specific brain regions (VLPFC, SMA, cerebellum, and PMv) retain their lateralized activation pattern in demanding verbal and object WM tasks when they most probably process language-based information.

8.2 Integration of the results into the existing literature

This section integrates the results of this dissertation into the existing literature and is divided into two parts: the first part relates the results of the main and control experiments to former research studies and the second part introduces the *scaffolding theory of aging and cognition* (Park & Reuter-Lorenz, 2009) – a contemporary theory of the field of the cognitive neuroscience of aging which is supported by our results.

8.2.1 Relating the results to former research

Previous work demonstrated that younger adults show unilateral activation of prefrontal cortical regions, whereas older adults exhibit a bilateral activation pattern of these areas during the execution of cognitive tasks. Different to our main experiment, however, these studies kept *objective task difficulty* constant across subjects and age groups (Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000). Because these bilateral activation patterns were found in high-performing older adults but neither in young adults nor in low-performing older individuals (Cabeza et al., 2002), Cabeza interpreted them as an age-specific compensation mechanism (Cabeza et al., 2002; Cabeza et al., 1997). In our main experiment, we used a task that was subjectively very demanding and matched *subjective task difficulty* across young and old participants. In these conditions, we saw bilateral activation patterns in DLPFC and aPFC in all investigated WM domains and in both age groups, suggesting that bilateral activation is not age-dependent.

Thus, our results are in agreement with the CRUNCH model (Reuter-Lorenz & Cappell, 2008) which proposes that, independently of age, neural activity increases in subjectively demanding tasks. This increase can be local but can also spread to other brain regions, including an area's cross-hemispheric counterpart (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2010). Support for the prediction of CRUNCH which pertains to local increases of activation levels comes from fMRI studies demonstrating that brain activation increases within specific prefrontal brain regions with increasing WM task demand also in young subjects

(Braver et al., 1997; Callicott et al., 1999; Glahn et al., 2002). Moreover, there is evidence for the concrete predictions of CRUNCH coming from neuroimaging studies that varied memory load in WM tasks and compared the performance and activation levels within specific brain regions of PFC between young and older adults at varying load levels (Cappell et al., 2010; Mattay et al., 2006). As already mentioned in chapter 5, these studies showed that older subjects developed stronger vs. weaker activation levels in these prefrontal brain regions than young subjects at easier vs. more difficult WM tasks, respectively. The overactivation in older adults at lower task levels was associated with task performance comparable to younger subjects, whereas underactivation was associated with decreased task performance in older compared to younger adults (Cappell et al., 2010; Mattay et al., 2006). In accordance with the notion of CRUNCH, overactivation of specific brain regions seems to be an age-independent response of the human brain to increased task demand. More specifically, CRUNCH proposes that seniors have to apply this overactivation at lower objective task difficulties to maintain good task performance because they experience these lower task loads as subjectively more demanding due to neurocognitive decline. However, young adults can show the very same activation patterns when the task demands are objectively (and also therefore subjectively) higher (Reuter-Lorenz & Cappell, 2008). Consequently, a specific prediction of the CRUNCH model is that differences in brain activation strength between age groups should disappear once subjective task difficulty is matched between age groups (Schneider-Garces et al., 2010). The first evidence supporting this prediction came from an fMRI experiment by Schneider-Garces and colleagues (2010). In this work, all young and old subjects worked on the same objective WM load sets in a verbal delayed match-to-sample task comparable to ours. Importantly, apart from WM load, Schneider-Garces et al. also considered individual WM span as a factor influencing brain activity. They demonstrated that the BOLD response was larger in older subjects when it was expressed as a function of *objective WM load* – both in single ROIs and after averaging all ROIs (considered as "total activation strength"). However, this age-related difference disappeared when total activation strength was expressed as a function of *normalized WM load*. The *normalized WM load* represented a normalization of the *objective WM load* to the subjects' WM spans and thus could be conceived of as a *subjective WM load* estimate. Interestingly, Schneider-Garces et al. did not report any results for DLPFC and aPFC, although at least DLPFC should support WM tasks like the verbal task used in their study (Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 1999). We here also used "subjective WM loads" that were tailored to each individual's WM capacity. Yet, going beyond the study of Schneider-Garces et al., we focused on both DLPFC and aPFC and used not only a verbal WM task but also spatial and object tasks. Moreover, these authors did not focus on differences in lateralization patterns in their analyses.

In fact, all previously mentioned neuroimaging studies dealt with the question of how activation strength increases with growing task demand within specific prefrontal brain regions in younger and older participants. Therefore, none of the authors analyzed differences in lateralization patterns to investigate how a lateralization shift of cross-hemispheric counterparts is associated with increasing task demand, which is also a central part of CRUNCH (Reuter-Lorenz & Cappell, 2008). At this point, the results of this dissertation make a valuable contribution to the research fields of WM and the cognitive neuroscience of aging because we directly tested whether or not individual ROIs were bilaterally activated in the face of challenging WM tasks. We showed that lateralization patterns of the prefrontal areas DLPFC and aPFC depend on the difficulty of WM tasks: in the control experiment, and in agreement with former research (Cabeza et al., 2002; Reuter-Lorenz et al., 2000), both areas were unilaterally activated in young adults during easy WM tasks. In contrast, in our main experiment DLPFC and aPFC exhibited bilateral activation patterns in both young and old subjects and in either WM domain when subjective task difficulty was high. Moreover, our control experiment allowed us to directly demonstrate this change in lateralization as a function of task difficulty in DLPFC for both the verbal and the spatial domain by means of significant interactions between "hemisphere" and "load". Thus, in accordance with CRUNCH, our results demonstrate that not only is the increase of activation within a brain region an age-independent response of the brain to growing task demands – which had already been shown in the described neuroimaging studies – but so is the spread to additional brain regions, more specifically, the recruitment of cross-hemispheric counterparts in the other hemisphere.

Further support for the predictions of CRUNCH in the context of lateralization shifts comes from a behavioral aging study from Reuter-Lorenz and colleagues (1999), in which young and older subjects worked on three letter-matching tasks with varying difficulty levels. As already described on page 26, subjects had to decide whether a target letter matched one of various probe letters in these tasks. In some trials, the target and the matching probe letter were projected to the same visual hemifield/hemisphere ("within-hemisphere processing") and in other trials, these letters were presented to opposite left and right visual hemifields/hemispheres ("across-hemisphere processing"). The results of this study clearly demonstrate that elderly subjects were better in the across-hemisphere processing trials than in the within-hemisphere processing trials at all difficulty levels. In contrast, younger subjects showed such an across-hemisphere advantage only in the most difficult task. These results support the predictions of CRUNCH in that they indicate that older adults have a behavioral advantage from bilateral processing at lower objective task difficulties at which unilateral processing is supposedly sufficient for younger adults. However, when task difficulty further increases, young adults can also profit from across-hemisphere processing (Reuter-Lorenz et al., 1999). Since this study is purely behavioral, it does not provide any information about brain

regions that might support across-hemisphere processing. Here, our experiments supply evidence that bilateral processing in PFC indeed plays an important role in maintaining performance independently of age in demanding WM situations. Hence, our results also support Banich and Belger's hypothesis that across-hemisphere processing is an age-independent beneficial strategy of the brain to adapt to demanding cognitive situations (Banich, 1998; Banich & Belger, 1990; Belger & Banich, 1992, 1998) (please also refer to section 4.3 for a more detailed explanation of this hypothesis). We complement their research by demonstrating that PFC is a key brain structure associated with this strategy.

Last but not least, we found that VLPFC, SMA, cerebellum, and PMv maintain a lateralized activation pattern even in the face of high task demands while these regions presumably process language-based information. This result matches former research demonstrating that specific language-based processes are not divided across the two hemispheres (Belger & Banich, 1998; Gazzaniga, 1995, 2000).

8.2.2 The scaffolding theory of aging and cognition

The *scaffolding theory of aging and cognition* (STAC) (Park & Reuter-Lorenz, 2009) integrates the most important findings of the field of the cognitive neuroscience of aging and is one of the most influential current theories in the field (Reuter-Lorenz & Park, 2010). The CRUNCH model (Reuter-Lorenz & Cappell, 2008) is compatible with this theory and, as I will point out in the end of this section, the results of this dissertation also provide empirical evidence for STAC.

The basic ideas of STAC (Park & Reuter-Lorenz, 2009) – which are also illustrated in figure 21 – can be summarized as follows: with increasing age, the human brain has to cope with a series of detrimental structural changes (e.g., shrinkage of brain structures, white matter deterioration, cortical thinning, dopamine receptor depletion) and functional deterioration (e.g., dedifferentiation of the ventral visual areas, decreased activation of the medial temporal lobe, increased default network activity). Hence, an interesting question is how elderly adults continue to show a relatively high level of cognitive functioning despite these severe age-related changes of the brain. According to STAC, the aging brain achieves this through *compensatory scaffolding*, or by recruiting additional neural circuits that support the declining brain structures which no longer function properly. In other words, the scaffolding neural circuits help to adapt to age-related neurocognitive decline in a compensatory manner. They typically appear as overactivation – usually through the recruitment of contralateral counterparts – in prefrontal brain regions; however, this overactivation could theoretically occur in parietal, temporal and occipital cortices as well. Activities such as learning, engagement in

cognitively demanding tasks, physical exercise, and cognitive training result in the creation of new and more effective compensatory scaffolds. The overall level of cognitive function of an older person is influenced by an interplay between the effectiveness of compensatory scaffolding and the extent of the anatomical and functional deteriorations of the brain (Park & Reuter-Lorenz, 2009).
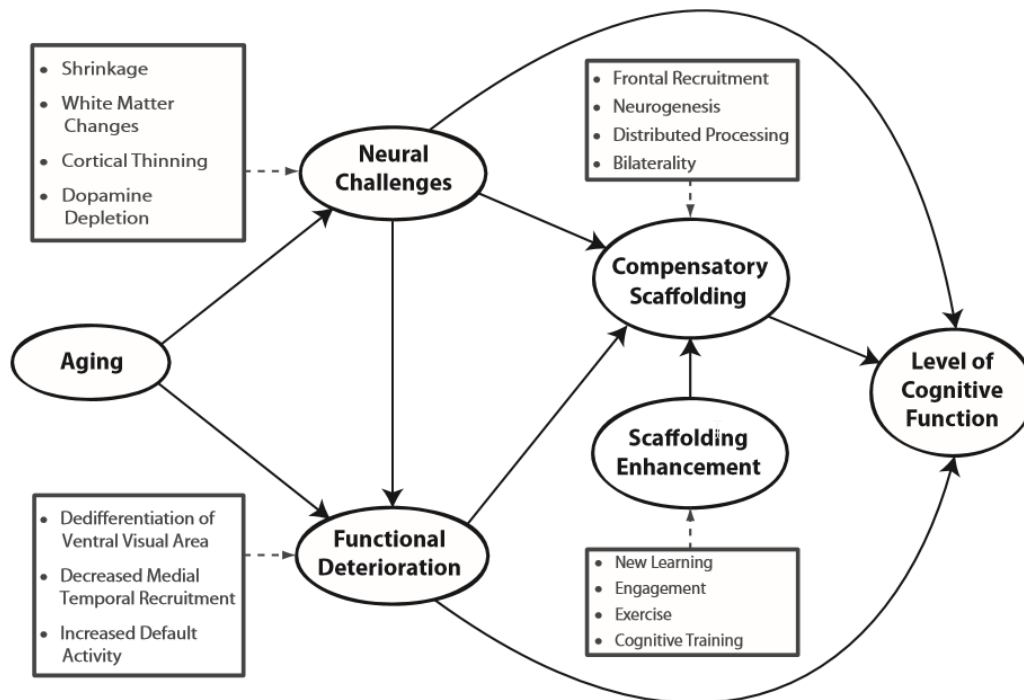
Figure 21. **An illustration of the scaffolding theory of aging and cognition.**

Our results provide new empirical evidence for the idea of this model that bilaterality in prefrontal brain regions serves compensatory scaffolding independent of age. This illustration is republished from Park, D. C. and Reuter-Lorenz, P. A., The adaptive brain: aging and neurocognitive scaffolding, *Annu Rev Psychol*, **2009, 60, p. 184, Fig. 4. Copyright © 2009 by Annual Reviews. This figure is allowed to be republished in a dissertation without obtaining additional permission from Annual Reviews according to my permission request.**

Although all the ideas of STAC (Park & Reuter-Lorenz, 2009) that I have mentioned in the previous paragraph refer to the aging brain, one central tenet of STAC is that compensatory scaffolding is not specific to old age but is instead a mechanism accessible throughout a lifetime. Hence, it allows humans of all age groups to adapt to cognitive challenges. For instance, compensatory scaffolding enables us to learn new skills during child- and adulthood: at the beginning of skill acquisition, behavior is variable, subpar, and effortful, and the underlying neural circuitry consists of a broad scaffolding network of distributed brain regions. With further training, executing the behavior becomes less and less effortful until it results in well-trained performance. At this stage, the underlying neural circuitry has transformed from a

broad set of regions to a focal, highly specialized and optimized network (Park & Reuter-Lorenz, 2009; Petersen, Van Mier, Fiez, & Raichle, 1998). Nevertheless, the regions that supported the behavior at the early stages of skill acquisition can sometimes still be reactivated, such as during execution of the well-trained skill in a challenging situation (Petersen et al., 1998).

Park and Reuter-Lorenz (2009) assume in their STAC model that younger and older adults use compensatory scaffolds usually in different situations. Young adults create new compensatory scaffolds or recruit previously established ones when they encounter new situations. On the other hand, older adults have to create or use compensatory scaffolds when coping with familiar and basic cognitive tasks because age-related structural and functional perturbances of specialized brain regions make the tasks more demanding. However, in principal, compensatory scaffolding is a general strategy of the human brain to respond to challenging situations that is similarly available for all age groups (Park & Reuter-Lorenz, 2009). The results of this dissertation support the assumption of STAC that bilateral recruitment of prefrontal brain regions is such an age-independent compensatory scaffolding mechanism (compare figure 21), since these results show that a) elderly and young adults similarly engage bilateral recruitment of DLPFC and aPFC under highly challenging verbal, spatial, and object-based WM tasks and, more specifically, that b) young adults recruit additionally to left DLPFC and aPFC in easy WM tasks the respective contralateral counterparts in the right hemisphere as a response to difficult WM tasks. To the best of my knowledge, we are the first ones to directly investigate whether cross-hemispheric pairs of specific task-related ROIs were equally activated in response to subjectively challenging WM tasks in young and old adults. In contrast, former aging studies investigating lateralization patterns during memory tasks did not control for subjective task difficulty. Those studies demonstrated that young adults show unilaterality, and old adults show bilaterality in prefrontal brain regions (Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000). Moreover, our control experiment provides new support for the STAC model by showing a lateralization shift in PFC within the same young subjects from unilaterality in easy WM tasks to bilaterality in difficult WM tasks. Such a result suggests that bilaterality indeed is a compensatory scaffolding mechanism helping to maintain performance in challenging situations. Further hints for this idea come from studies showing that bilateral recruitment of PFC is beneficial for performance in elderly subjects (Cabeza et al., 2002; Reuter-Lorenz et al., 2000). However, to finally decide whether the additional recruitment of contralateral counterparts of PFC is indeed compensatory, further research is needed (please compare the outlook section 8.5.3 for ideas of such research).

8.3 Evaluation of the main and the control experiment

The aim of this section is to introduce various important strengths and also limitations of both the main and the control experiment.

8.3.1 Strengths of the experiments

In this section, I will highlight some methodological advantages of the experiments of this dissertation which consist of a) the assessment of functionally defined ROIs in each individual, b) the control for subjective task difficulty, c) the investigation of different WM domains within the same subjects, and d) the use of a Bayesian approach in addition to conventional statistics.

As previously mentioned on page 22 and summarized by the STAC model in the previous section (Park & Reuter-Lorenz, 2009), the brains of older adults experience severe detrimental structural changes including brain volume (Raz, 2000), white matter integrity (Head et al., 2004) and dopamine receptors (Wong et al., 1997). Particularly due to the loss of brain volume (Raz, 2000), it is extremely crucial in aging studies to take care of this issue when comparing younger and older brains. This is because even after spatial normalization of the aged brains – on account of the properties of the normalization procedures – the same objective coordinates may not occupy the same functional locations in the brains of younger and older adults. Consequently, simply using the same coordinates for comparing activation levels between young and older subjects would not necessarily guarantee an apples-to-apples comparison (Schneider-Garces et al., 2010; Wilke, Holland, Altaye, & Gaser, 2008). For this reason, the choice of coordinates for extracting activation strength is very important in aging studies. An approach like ours, where we functionally determined individual peak coordinates that occupy comparable anatomical spots across subjects (compare section 6.1.5.2) is imperative when comparing functional neural activity between young and older adults (Schneider-Garces et al., 2010), even though this approach is extremely tedious because it requires identifying the respective locations in every subject – and in our case in every WM domain – separately. With this approach, we were successful in detecting congruent coordinates for all of our ROIs across subjects with the exceptions of calcarine sulcus and IPS (see below in section 8.3.2 for further details).

A further strength of the main experiment is our approach of designing individual load levels for every subject to match subjective task difficulty across subjects. In former WM studies that investigated brain activity depending on the factor "task difficulty," task difficulty was manipulated by varying the memory load between objectively easy and more difficult tasks. However, subjects always worked on the same objective memory load levels in these

studies (Braver et al., 1997; Callicott et al., 1999; Cappell et al., 2010; Glahn et al., 2002; Mattay et al., 2006; Schneider-Garces et al., 2010). This approach is comparable to the one of our control experiment and, as mentioned above, cannot ensure that the difficult tasks are actually subjectively demanding for all subjects. This is because WM capacity varies across subjects (Baddeley, 2000; Baddeley & Hitch, 1974; Cowan, 1999, 2000, 2008; Eriksson et al., 2015; Miller, 1956; Schermer, 2014) and, consequently, a specific task can bring one person to his/ her capacity limit, whereas another person can work on this task without great effort. Schneider-Garces et al. (2010) demonstrated that the factor "subjective task difficulty" is an important confounding factor in studies investigating activation strength depending on task difficulty and that one should take care of this factor – especially when comparing young and old adults because WM tasks become subjectively more difficult with increasing age (Nyberg et al., 2014; Park et al., 2002). To the best of my knowledge, we are the first ones offering individually adapted WM load sets to all subjects of our two age groups guaranteeing that both young and old participants are subjectively similarly challenged during the execution of the WM tasks.

Moreover, most previous neuroimaging studies that examined WM processes investigated only one WM domain, or when they did report results from two WM domains, the data had been collected from different subjects (see Cabeza & Nyberg (2000) and D'Esposito et al. (1998) for meta-analytical overviews of such studies), which complicates a direct comparison of domain-specific brain activation. There are only a few studies, in which the same subjects worked on two of the three main WM domains (Belger et al., 1998; D'Esposito et al., 1998; McCarthy et al., 1996; Owen et al., 1998; Salmon et al., 1996). As far as I know, there is no study measuring task-related activation elicited by verbal, spatial, and object-based WM tasks within the same sample. In contrast, all subjects of our main experiment worked on all three main WM domains assuring a direct comparison between task-related activation patterns between verbal, spatial, and object-based WM domains.

A further strength of this dissertation is the use of the Bayesian approach for assessing whether the two counterparts of a ROI are similarly active (null hypothesis) in the maintenance phases of the WM tasks or not (alternative hypothesis). This approach is beneficial because traditional statistics like ANOVAs are by definition incapable of verifying a null hypothesis. This is because traditional statistics are biased to detect type I errors with much higher sensitivity than they detect type II errors (Dienes, 2011). Bayesian analyses do not suffer from this bias (Dienes, 2011), and were therefore a fruitful and essential extension of our data analyses to allow us to confirm bilateral activation of our ROIs.

8.3.2 Limitations of the experiments

I already discussed limitations that are specific to the main and control experiments in the respective discussion sections. Namely, we encountered problems with the object WM domain and lacked an easy control condition in the main experiment (compare section 6.3.3). In the control experiment, we lacked an older subgroup and the object WM domain. Moreover, the lateralization shift depending on task difficulty was ambiguous in aPFC in the latter experiment (compare section 7.3.2). At this point, I would like to discuss two additional potential limitations that concern both experiments.

The first is the small number of subjects in both the main and control experiments (10 subjects per age group in the main experiment; 11 young subjects in the control experiment). Nevertheless, our approach should have been sensitive enough to detect hemispheric differences in lateralization for the following reasons. First, previous studies reporting the HAROLD effect also had a small n of ~10 subjects per age group and showed unilateral activation in young subjects (Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000). Second, we were able to find hemispheric differences in the 11 young subjects of our control experiment in DLPFC and aPFC when they worked on easy verbal and spatial tasks. This result shows that our paradigm was in principle suitable for detecting hemispheric differences. Third, we found an "age" × "hemisphere" interaction in SPL in the object domain of the main experiment where subjective task difficulty was not successfully controlled for. As previously mentioned in section 6.2.2.2, this interaction may have been due to the fact that the task was subjectively easier for young adults as compared to older adults, leading them to show a lateralized pattern while the older adults did not. Importantly, this interaction indicates that we are able to show age group differences with respect to lateralization patterns with our approach. Forth, despite the small number of subjects we had a relatively high number of repetitions of trials in the main experiment (5 load levels × 15 repetitions = 75 repetitions of difficult trials per WM domain; see section 6.1.3) for the important within-subject comparison between activations of the hemispheres.

Because the most important conclusion of our study builds on the finding that also young adults exhibit bilaterality during demanding tasks, we increased the n of the young group by combining the functional activation data of the difficult condition of the control experiment with the average activation (calculated across all five load levels) in the main experiment, separately for the verbal and the spatial domain. This was possible because the control experiment consisted of the same principal verbal and spatial WM tasks as were used in the main experiment. With the increased n of 21, we still did not find hemispheric differences for *DLPFC* [verbal domain: paired t-test: $t(20) = 0.31$, $p = 0.761$; Bayes factor: 0.07; spatial domain: paired t-test: $t(20) = 0.26$, $p = 0.801$; Bayes factor: 0.10] and *aPFC* [verbal domain:

paired *t*-test: $t(20) = 0.48$, $p = 0.637$; Bayes factor: 0.22; spatial domain: paired *t*-test: $t(20) = 1.01$, $p = 0.324$; Bayes factor: 0.36] in young subjects.

A further peculiarity is that, although the lateralization patterns of our ROIs generally generalize well across the difficult conditions of the two experiments, there were two exceptions: *IPS* and the *calcarine sulcus* in the spatial domain (compare figure 20 A vs. D). For example, young subjects show unilateral vs. bilateral engagement of IPS in the spatial domain of the main vs. control experiment, respectively. In contrast, they demonstrate a bilateral vs. unilateral activation pattern of the calcarine sulcus in this domain in the main vs. control experiment, respectively. A possible explanation for the inconsistent findings in the case of *IPS* might be due to how we defined the voxels belonging to an area, and the limitations of these standards when it comes to the IPS (compare section 6.1.5.2, (iii)). Our protocol was to call the voxels with the highest *t*-value along the intraparietal sulci the "individual peak coordinates" for each subject as long as they were within a 20-mm radius sphere around the respective group coordinates. Then, we extracted task-related activity from these individually assessed coordinates. In contrast to the other ROIs, we found that the relative locations of these coordinates for IPS varied quite strongly across subjects both within and also between experiments. Consequently, it is possible that the searching radius sphere of 20 mm was too large in the case of IPS and that, therefore, the individually selected locations of this ROI represent regions of varying functional properties in the main and control experiments. Actually, we chose the approach of assessing individual coordinates to cope with the issue that the brains of elderly adults undergo severe structural changes, which means that the same objective coordinate may occupy different functional locations in young and old subjects (see section 8.3.1). However, when this approach results in the selection of individual locations which strongly vary, one is not certain of comparing matching functional regions across subjects. In such a case, our approach would not be any better than the conventional approach of using the same objective coordinate for all subjects. Thus, future studies that use individually assessed coordinates should decrease the search radius for ROIs as far as possible.

Furthermore, it is important to mention again that we found individual coordinates in the majority of our participants in almost all ROIs. However, the *calcarine sulcus* was an exception, and we had to assign the general group coordinate in ~ 50 % of the participants for both age groups and for both hemispheres in the spatial domain of the main experiment. In the control experiment, we even had to assign the general group coordinate in 10 out of 11 subjects for both hemispheres in this domain. This was, however, not surprising because we also had not found representative group coordinates in the calcarine sulcus in the spatial domain on a group level. We only included this ROI in the spatial domain because we had encountered task-

related activity in the verbal and object domains[5] (compare table 1). Consequently, it is possible that the calcarine sulcus is not involved in the processing of our spatial WM task, and that the frequent artificial assignment of the group coordinate in both experiments explains why the lateralization pattern of this ROI varied in the spatial domain between experiments.

8.4 Subsequent questions

I have mentioned throughout this dissertation that cognitive capacity in general and WM capacity in particular decrease across a lifetime. However, what could be the possible underlying mechanisms for such an age-dependent development? Moreover, I demonstrated in this dissertation that bilateral recruitment of DLPFC and of aPFC is a response of the human brain to increased WM task difficulty. In what specific ways could bilaterality in these and other brain areas support humans of all ages to maintain their WM performance in challenging WM situations? In this section, I will provide some preliminary answers to these two open questions.

8.4.1 Potential mechanisms of age-related cognitive decline

There are various theories in the field of cognitive aging that suggest a single mechanism that is commonly responsible for the general age-related decline in a variety of cognitive domains like, for instance, WM, perceptual speed, episodic long-term learning, inhibition, and executive control (see also section 2.4). In the following paragraphs, I will present four mechanisms that are commonly believed to play such a role: "WM," "inhibitory functioning," "processing speed," and "sensory functioning" (Park, 2012; Park & Reuter-Lorenz, 2009). Please note that there is agreement that these mechanisms contribute to a general age-related decrease in many cognitive domains (Park, 2012). However, it is possible that it is not a single mechanism but instead a combination of them that causes age-related cognitive decline (Park, Smith, Lautenschlager, & Earles, 1996). Thus, scientific evidence supporting one of these mechanisms does not necessarily mean that the other mechanisms have no contribution (Park, 2012).

One of the theories proposing a specific cognitive mechanism responsible for age-related deteriorations in many cognitive domains states that the content of most cognitive

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[5] It is striking that we found task-related activity on a group level in the calcarine sulcus in the verbal WM domain but not in the spatial domain of the main experiment because in former studies, visual cortex had mainly been activated in visuospatial WM tasks (Cabeza & Nyberg, 2000; Wager & Smith, 2003). A possible reason for this finding may be the fact that contrary to former studies, the subjects of our main experiment worked on verbal, spatial, and object WM tasks in an intermixed design which might have motivated subjects in the verbal domain to use maintenance strategies that are otherwise typical for visuospatial domains.

operations has to be maintained in WM, which makes WM essential for almost all cognitive domains. Thus, this theory assumes that it is the reduced *capacity of WM* of elderly adults which accounts for a common age-related cognitive decline (Hasher & Zacks, 1988; Park et al., 1996). Empirical support for this theory comes, for example, from experiments comparing performance between younger and older subjects in text comprehension tasks while WM was strained to various degrees by manipulating environmental support (Hasher & Zacks, 1988). These studies showed that elderly subjects performed worse than young subjects, when WM strain was high. In this condition, the information necessary for successfully completing the task was not visually available when answering questions about a text, which required all relevant information to be in WM (low environmental support). In contrast, elderly adults performed as well as younger subjects when WM strain was reduced by visually presenting all important information (high environmental support). These results demonstrated that WM strain has an influence on task performance in other cognitive domains like text comprehension (Hasher & Zacks, 1988).

Another theory states that it is not the reduced capacity of WM but reduced *inhibitory functioning* that accounts for the age-related decline in various other cognitive domains. More specifically, the theory posits that older adults generally have problems inhibiting attention from focusing on irrelevant information, which leads to the processing of such information and, thus, also to decreased task performance in a variety of cognitive tasks (Hasher & Zacks, 1988). With respect to WM, older adults are said to demonstrate worse performance because they have problems controlling WM content. According to the theory, they can neither successfully hinder irrelevant information from entering WM nor delete information in WM that is not relevant anymore for task performance. Thus, it is likely that WM capacity does not become smaller with age but that WM performance decreases with age because irrelevant information competes with relevant information for limited space within WM (Hasher & Zacks, 1988). Empirical evidence for the assumption that old subjects have problems deleting irrelevant information from WM is provided by a study showing that older subjects recalled significantly less words and pictures than young subjects when they had been instructed to remember them (items are relevant information). In contrast, they performed as well as young subjects when they had been instructed to forget these items (items are irrelevant information). Thus, whereas old subjects remember less relevant information than their younger counterparts, they are able to maintain as much irrelevant information as the young subjects (Salthouse, Siedlecki, & Krueger, 2006).

Furthermore, Salthouse (1996) proposed that the rate at which mental operations are executed decreases with increasing age and that this reduced *speed of information processing* is a major cause for general cognitive decline. Salthouse collected empirical evidence for his

theory by demonstrating that the factor "processing speed" explains almost all of the age-related variance in a variety of cognitive tasks (Salthouse, 1996). In particular, Salthouse (1996) suggested that cognitive operations cannot be successfully completed within a necessary time frame due to the slowing of processing speed, which can negatively affect performance in a variety of cognitive domains in two independent ways: (i) the reduced speed at the beginning of information processing results in a lack of time for information processing at later stages and (ii) the result of early processing is lost before it can be used in later processing (Salthouse, 1996). Thus, in the case of WM, a reduced processing speed could mean that the brain does not encode all available information within a limited time frame because it is still coping with the encoding of specific items (compare (i)) or that operational results held in WM are lost before they can be used for further processing (compare (ii)). Both possibilities would lead to reduced WM performance because not all necessary information is processed.

A further single mechanism theory of age-dependent cognitive decline is based on the general finding that there is an age-associated decline in perception (Roberts & Allen, 2016). In particular, this theory states that decreased *sensory functioning* in older adults is responsible for their general cognitive decline, and thus also for WM decline (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994). Indeed, there is evidence that visual and auditory acuity account for a high proportion of variance in a variety of cognitive tasks, and that this relationship is especially striking in older adults (Baltes & Lindenberger, 1997; Roberts & Allen, 2016). There are various hypotheses that explain the strong relationship between sensory and cognitive functioning in older adults (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994): one hypothesis says that decreased sensory functioning evokes decreased cognitive performance in older adults because less sensory stimulation may hinder older individuals from effectively interacting with their environment, which results in less cognitive stimulation and, thus, cognitive decline in the long run (*sensory deprivation hypothesis*). Another hypothesis states that even the sensory parts of a cognitive task become more demanding for older adults due to age-related impaired perception. According to this hypothesis, cognitive performance deteriorates in older adults because cognitive operations are required for the compensation of such decreased sensory functioning, which results in less cognitive resources available for the actual cognitive operations needed to solve a cognitive task (*age-induced cognitive load hypothesis*). There is a third hypothesis that explains the increased relationship between sensory and cognitive measures in older adults. However, this hypothesis proposes that sensory functioning does not influence per se cognitive functioning in the elderly. Contrary, the neurobiological changes of the aged brain are said to independently lead to decreased sensory and cognitive functioning (*common cause hypothesis*). Please note that future research has to investigate which of these hypotheses truly explains the increased correlation between

sensory and cognitive functioning in older adults since, to date, there is no consensus (Roberts & Allen, 2016)[6].

All previously described cognitive theories explain the reduced performance of older adults in various cognitive domains by means of an impairment of a specific cognitive or sensory mechanism that takes place with increasing age. Please note, however, that biological deteriorations of the brain with age such as decline in brain volume (Raz, 2000), white matter integrity (Head et al., 2004), and dopamine receptors (Wong et al., 1997) have also been directly associated with the age-dependent negative development of cognitive functioning (Park & Reuter-Lorenz, 2009). However, I will not go into detail about these neurobiological aspects here.

In contrast to the previously described theories that explain worse cognitive performance of older adults through negative effects of age, Ramscar and colleagues provided a more optimistic interpretation of cognitive aging (Ramscar, Hendrix, Shaoul, Milin, & Baayen, 2014). More specifically, they stated that age-related decreased cognitive performance is caused by the tremendous amounts of information and knowledge that older adults keep accumulating during their life spans. In particular, computational limitations in handling these large amounts of stored information are responsible for age-related cognitive decline. Consequently, these researchers even expect elderly adults without any morbid neurocognitive decline to perform worse in cognitive tasks than their younger counterparts (Ramscar et al., 2014). Ramscar and colleagues (2014) collected empirical evidence for their theory with the aid of simulation studies presenting the performance of learning models that accumulate more and more information. Their results indeed showed that "the predictable consequences of learning on information-processing, and not cognitive decline" (Ramscar et al. (2014), page 5) explained episodic LTM performance of the elderly. How might age-related WM decline be explained in the light of Ramscar's theory? According to the state-based WM models, LTM content transforms into WM content when it is temporarily activated by attention. This may be the case when presented information enters WM and is associated with stored information in LTM (Baddeley, 2003; Cowan, 2008; D'Esposito & Postle, 2015; Eriksson et al., 2015; Petrides, 1995). In accordance with Ramscar's approach, this search through LTM may be more effortful for older adults because their LTM store usually encompasses more information, which may cause worse performance in the elderly.

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[6] I reported in section 4.1 that there are studies demonstrating that prefrontal overactivation is linked to improved cognitive performance (Cabeza et al., 2002; Davis et al., 2008; Gutchess et al., 2005; Reuter-Lorenz et al., 2000) and to occipitotemporal decreases in activation in elderly but not younger subjects (Davis et al., 2008; Gutchess et al., 2005). Such results might be considered as empirical evidence for the age-induced cognitive load hypothesis (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994).

To date, it is not clear which of the above factors contribute to age-related decreases of cognitive performance in general and WM capacity in particular. However, due to the variety of neurobiological and cognitive changes in older adults it is probable that various mechanisms mutually affect age-related cognitive decline (Park & Reuter-Lorenz, 2009). Moreover, I would like to highlight that it may also be that different mechanisms account for different cognitive domains. For instance, Ramscar's approach (Ramscar et al., 2014) makes sense for WM and episodic LTM; however, it is contradictory for semantic LTM because this part of LTM does not become worse with increasing age (Hultsch et al., 1999; Park et al., 2002), although the amount of factual knowledge certainly keeps growing across a lifetime.

8.4.2 Potential functions of domain-general bilateral ROIs and SPL in demanding working memory tasks

As described previously, both CRUNCH (Reuter-Lorenz & Cappell, 2008) and STAC (Park & Reuter-Lorenz, 2009) propose that bilateral recruitment of a brain region is an age-independent compensatory response of the human brain to increased task difficulty in cognitive tasks. The *domain-general bilateral ROIs* in this dissertation displayed bilateral activation patterns across all WM domains in the highly demanding tasks of our main experiment in young and old adults (compare figure 17). Executive WM processes are meta-storage mechanisms that operate in a domain-general manner, as opposed to storage processes which are domain-specific (Baddeley, 2000; Baddeley & Hitch, 1974; Cowan, 2008). Thus, the fact that the bilaterality was present independent of the WM domain suggests that general executive WM processes, rather than WM storage processes, underlie such bilateral recruitment. This conclusion is also in line with Reuter-Lorenz's properties of a compensatory mechanism for task demand (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). Consequently, the domain-general bilateral ROIs *DLPFC*, *aPFC*, *the anterior insula*, *PMd,* and *calcarine sulcus* might be potential loci for a compensatory mechanism as described by Reuter-Lorenz's research group. In this section, I will speculate about which specific executive functions these ROIs might fulfill during challenging WM tasks.

Park and Reuter-Lorenz (2009) claimed that compensatory scaffolding is mainly situated in the most flexible structure of the human brain, the PFC. In support of this idea, we found domain-general bilaterality in *DLPFC* and *aPFC* in young and old participants in our main experiment. Clues about the nature of this age-independent compensation mechanism might be derived from the lateralization patterns in easier tasks. For this we looked to our control experiment, where we found a left-lateralized activation for both the DLPFC and aPFC during easy tasks in both the verbal and the spatial domain. At first glance, this pattern contradicts the idea that the left and right hemisphere preferentially process verbal vs. spatial

information, respectively (Banich, 1998; Belger & Banich, 1998; Gazzaniga, 2000; Thomason et al., 2009). Such a pattern of material-specific lateralization in WM tasks has previously been reported for PFC as a whole (Nagel et al., 2013) and for DLPFC in particular (Reuter-Lorenz et al., 2000). For instance, Reuter-Lorenz and colleagues (2000) demonstrated that in a delayed match-to-sample task, DLPFC activation was left-lateralized for verbal WM but right-lateralized for spatial WM in young participants. Note, however, that their relatively short maintenance phase of 3 seconds and the temporal resolution of their imaging method (PET) did not allow them to distinguish whether the lateralization was due to encoding, maintenance, and/or retrieval processes (Fiez et al., 1996). The reported lateralization might therefore have been caused by a material-specific encoding or retrieval of the stimuli (Opitz, Mecklinger, & Friederici, 2000).

In contrast, in our study we used fMRI and exclusively focused on lateralization during WM maintenance. To this end, we used comparatively long maintenance durations (~15 seconds) allowing us to conduct a time-resolved analysis and to specifically estimate fMRI activity during the maintenance phase without any confounding influences of the encoding and retrieval phases (Curtis & D'Esposito, 2003; Lindner, Iyer, Kagan, & Andersen, 2010). Current models of WM propose that DLPFC plays an executive role during WM maintenance rather than being a mere storage buffer (Curtis & D'Esposito, 2003; D'Esposito & Postle, 2015; Eriksson et al., 2015). Therefore, any lateralization found during WM maintenance suggests a lateralization of an executive operation rather than stimulus storage. In support of this interpretation, Johnson et al. (2005) have shown that the executive WM operation of *refreshing* memory representations for WM maintenance, whereby the brain focuses and sustains attention on the memory content, engages the left and not right DLPFC and aPFC. The left-lateralization of this process was shown to be irrespective of the domain of the memorized stimulus material (Johnson et al., 2005). Our left-lateralized activation patterns expressed during the maintenance of verbal and spatial material in the control experiment could be interpreted accordingly, namely as a left-lateralized executive operation like "refreshing" that subserves the maintenance of WM across various WM domains[7].

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[7] As already mentioned in section 3.1, executive functions comprise a magnitude of varying processes (D'Esposito & Postle, 1999; Smith & Jonides, 1999; Wager & Smith, 2003). It is possible that executive functions deviating from "refreshing" are lateralized to the right PFC or that they are even bilaterally represented. There are meta-studies summarizing the results of various verbal WM studies that used different storage-only WM tasks and WM tasks that required storage plus executive functions (Smith & Jonides, 1999; Wager & Smith, 2003). These meta-studies showed a left-lateralized activation pattern of various prefrontal brain regions in storage-only tasks and a bilateral pattern of such regions in WM tasks that additionally required executive functions. Importantly, bilateral activation patterns emerged because the authors simultaneously demonstrated activation spots coming from studies which used a variety of WM tasks that required different executive functions. Thus, one cannot conclude that the bilaterality reported in these meta-studies is a result of executive functions generally being represented in both hemispheres. Another explanation of the bilateral activation pattern that emerged across studies is that various executive functions show different lateralization patterns which in sum result in the

Moreover, our research suggests that this executive operation could further recruit the right hemisphere as tasks become more difficult. This interpretation is supported by former research demonstrating that it is often not the left but the right DLPFC which shows an increase in activation in functional neuroimaging studies investigating WM and processing speed when cerebral resources are challenged (Hillary et al., 2006). However, previous studies mainly looked at verbal tasks and called for further research using nonverbal WM materials to decide whether right DLPFC recruitment in challenging tasks is domain-specific or not (Hillary et al., 2006). The results of this dissertation provide the requested empirical clues suggesting that right DLPFC involvement supports a general executive control mechanism that is domain-independent. Pardo and colleagues demonstrated that such a right-lateralized control mechanism located in DLPFC might be interpreted as "sustained attention" (Pardo, Fox, & Raichle, 1991).

Please note that besides DLPFC and aPFC, the anterior insula and PMd were also consistently mapped across all WM domains (table 1) and exhibited bilaterality in a domain-general manner in difficult tasks of both experiments in both young and older subjects (compare figure 20 A, B, and D).

Also note that, in contrast to DLPFC and aPFC, our control experiment demonstrates that bilaterality of the *anterior insula* is not modulated by task demand but that it is similarly present in easy and difficult task variants of the tested WM domains (compare figure 20 C and D). More specifically, brain activity increases with growing task difficulty in verbal and spatial tasks (compare main effects of "load" in table 3) similarly in both hemispheres (compare missing interactions "hemisphere" x "load" in table 3). Consequently, it is rather unlikely that the anterior insula is a brain structure that compensates for increased task demand in WM processes by additionally recruiting its contralateral counterpart. With respect to the potential functional role of the anterior insula in WM processes, I follow the rationale of Craig and hypothesize that it might support interoceptive meta-awareness, namely the "feeling-of-knowing" (Craig, 2009) in memory. According to my interpretation, the feeling-of-knowing is a domain-independent process that is supported by both hemispheric counterparts of the anterior insula and that results in their increased activation with growing task demand.

Moreover, we found domain-general bilaterality in both age groups of the main experiment in the *FEF* that were overlapping with our ROI *PMd*. Wager and Smith (2003) reported in their meta-study that activation in bilateral PMd/ FEF in WM tasks represents executive processes. I interpret bilaterality in PMd/FEF as a reflection of attention (Esterman

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reported bilateral pattern. The left-lateralization of the executive function "refreshing" in PFC (Johnson et al., 2005) and its right-lateralization in "manipulation" (Wager & Smith, 2003) and "updating" (D'Esposito et al., 1998) tasks support this notion.

et al., 2015; Vernet, Quentin, Chanes, Mitsumasu, & Valero-Cabré, 2014; Wardak, Ibos, Duhamel, & Olivier, 2006), which belongs to the most basic executive processes that are required for WM operations (D'Esposito & Postle, 2015; Eriksson et al., 2015; Smith & Jonides, 1999). This assumption makes PMd suitable for a compensatory support mechanism of the brain for task difficulty as it was described by Reuter-Lorenz's group (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). However, the ANOVAs of the control experiment revealed that there is no lateralization shift in PMd depending on task difficulty in both WM domains (compare missing interactions "hemisphere" x "load" in table 3). Instead, according to these statistics, activation strength similarly increases in both hemispheric counterparts of PMd when verbal and spatial WM tasks become more difficult (compare main effects of "load" in table 3) – just like in the case of the anterior insula. Interestingly, a more careful inspection of the Bayes factors (compare figure 20 C and D) suggests that there may be a lateralization shift from a unilateral to a bilateral activation pattern in easy vs. difficult tasks in the spatial WM domain. Unfortunately, this dissertation cannot provide a definite proof and the question of whether PMd is another brain structure in addition to DLPFC and aPFC that compensates for task difficulty in a domain-general or domain-specific (only in the spatial domain) manner remains open for future research (compare below section 8.5.2).

In contrast to DLPFC, aPFC, the anterior insula, and PMd, the *calcarine sulcus* was not reliably mapped across all WM domains on a group level (compare table 1). Hence, we have to use the term "domain-general" very cautiously for the calcarine sulcus. The bilateral patterns of calcarine sulcus match the results reported by Schneider-Garces et al. (2010) for their verbal WM task and may reflect the visual characteristics of the task rather than higher order WM operations (Schneider-Garces et al., 2010) making it quite unlikely that calcarine sulcus is associated with compensatory processes in demanding WM situations. I will therefore not speculate further about its function in terms of compensatory scaffolding.

Finally, although we classified *SPL* as a domain-specific bilateral ROI as it showed bilaterality in verbal and spatial WM domains but unilaterality in the object domain of the main experiment, I will also speculate about its functional role in demanding WM tasks[8]. This is because the statistical results of our experiments provide hints that also SPL might be a ROI

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[8] In my opinion, it is more probable that domain-general mechanisms underlie compensatory processes in WM than do domain-specific ones. However, I admit that I cannot exclude the possibility that there is besides a domain-general compensation strategy of the brain for task difficulty also a comparable support mechanism in the form of bilaterality that compensates for task difficulty in specific WM domains but not in others. Still, contrary to SPL, I will not discuss potential functions of the additional domain-specific bilateral ROIs VLPFC, SMA, and cerebellum in this section because I do not consider them as adequate candidates for compensatory scaffolding in the form of lateralization shifts. This is because a) as I previously discussed on page 61, I interpret these ROIs as regions being involved in language-based processes in verbal and object WM tasks and b) according to the results of the control experiment, their bilaterality does not evolve as a response to task difficulty in the spatial domain (the interactions "hemisphere" x "load" were not significant in all three ROIs).

that compensates for task difficulty by recruiting the contralateral counterpart: statistics of the main experiment showed that young participants demonstrated a stronger activation of the left than the right hemisphere in the object domain, whereas old subjects did not show this hemispheric difference (compare section 6.2.2.2). Since the object task was subjectively easier for young participants, the difference in lateralization patterns in SPL in the object domain may have been due to the fact that SPL is a brain region that develops bilaterality when WM tasks become subjectively demanding. The Bayes factors of the control experiment also suggest that SPL shows unilateral activation in easy verbal tasks which shifts to a more bilateral pattern in difficult tasks (compare figure 20 C and D). Unfortunately, this effect is not unambiguous because the interaction between "hemisphere" and "load" of the respective ANOVA was not significant (compare table 3). As in the case of PMd, further research is therefore necessary to clarify whether SPL compensates for growing task demand by recruiting the cross-hemispheric counterpart (also compare the outlook section 8.5.2). Interestingly, the functional role of SPL described in the literature supports this latter idea. For instance, Wager and Smith (2003) concluded on the basis of their meta-analytic analyses of a multitude of studies using verbal, spatial, or object-based WM tasks that SPL is associated with executive functioning in all three WM domains (see also Baddeley, 2003; Cabeza & Nyberg, 2000). According to them, SPL might play a general attentional role in WM tasks that goes beyond the control of spatial attention and eye movements for which SPL is known because this parietal region is likewise involved in both spatial and non-spatial attentional tasks (Cabeza & Nyberg, 2000; Smith & Jonides, 1999). More specifically, Wager and Smith (2003) suggested that SPL controls the focus of attention in WM processes.

In summary, our results support the idea that the bilateral recruitment of DLPFC and aPFC during WM tasks represents an age-independent, domain-general executive WM process that compensates for task difficulty. Moreover, as previously mentioned, there are hints coming from our results and previous research that beyond DLPFC and aPFC, also PMd and SPL might represent comparable scaffolds that compensate for task difficulty by recruiting contralateral counterparts. However, further research is needed to clarify this point because our statistical effects for these two brain regions could not yet provide an ultimate answer. Please also refer to the next section of this dissertation, for an illustration of how such a study could look like.

8.5 Outlook

In addition to the results of this dissertation being interesting in their own right, they also inspire new questions about the brain as it was already mentioned at various places in this

work. In this section, I will present some ideas about analyses and experiments that would address these questions by further exploring and extending the results of this dissertation. In particular, I will describe an approach to investigate the spatial extent rather than the magnitude of activation as it could serve as another critical parameter to assess compensatory brain activation in experiments comparable to ours. Next, I will describe another experiment that investigates whether PMd and SPL are brain regions that develop – besides DLPFC and aPFC and contrary to easy WM tasks – a bilateral recruitment in subjectively demanding tasks. This experiment may also elucidate whether there is a hierarchical structure underlying the aforementioned brain areas. Such a hierarchy could express itself in the development of bilaterality at various levels of task difficulty because of distinct compensatory roles of the respective areas. Then, I will introduce ideas of how one could explore whether recruiting contralateral counterparts in right DLPFC and right aPFC plays a beneficial role for WM performance by using transcranial magnetic stimulation (TMS), as this method could help to provide direct causal evidence for a compensatory role of such contralateral regions in WM. Finally, I will point out that there is need for a better comprehensive understanding of WM to get an idea of how WM truly operates in our daily lives.

8.5.1 Investigating the spatial extent of brain activation

In our main analyses, we compared the activation strength in contralateral counterparts of task-related brain regions by measuring activation magnitudes averaged across 3-mm radius spheres around individual peak coordinates. Thus, this approach focuses on the activation strength in a small area and neglects its spatial extent within the respective ROI. We opted for this approach because the activation strength was the metric consistently reported in previous studies showing the HAROLD effect (Cabeza, 2002; Cabeza et al., 2002; Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000). In this way, we can directly compare our results to these previous studies.

However, I cannot exclude the possibility that, even if the peak activations of a ROI are the same in both hemispheric counterparts, there is a difference in the spatial extent of activation. As I previously described in the results part 6.2.2.1 of the main experiment, this was the reason why we repeated our original analyses while sampling from a larger area (a 9-mm radius sphere). These analyses considering activation from a larger area within our ROIs reproduced the principle findings of our original analyses (table 2, gray filled circles). Since the comparison of averaged activity magnitudes across relatively large spheres around peak voxels should indirectly reflect hemispheric differences in spatial extent, I conclude that there are no differences in lateralization with respect to the spatial extent in our ROIs. Nevertheless, researchers who are explicitly interested in the investigation of hemispheric differences relating

to the spatial extent of activation may use appropriate analytical tools for directly counting the number of activated voxels within a predefined brain area. Please note, however, that such an approach usually depends on activation thresholds to determine which voxels are considered "activated" (Wilke & Lidzba, 2007). Using threshold criteria is problematic for comparing fMRI signals across different age groups. This is because the BOLD-signal strongly depends on neurovascular coupling, or how neural activity impacts the hemodynamic characteristics of the adjacent vasculature (D'Esposito, Deouell, & Gazzaley, 2003). Since the neurovascular system changes with age (Farkas & Luiten, 2001), age-related differences in neurovascular coupling might be responsible for age-related differences in the BOLD-signal (e.g., decreased signal-to-noise ratio, decreased amplitudes, and increased lag of the hemodynamic response in the elderly) (see D'Esposito et al., 2003, for a review). However, despite these slight age-related changes in the BOLD-signal, important characteristics (e.g., the overall shape, summation and refractory properties) are congruent across age groups (D'Esposito et al., 2003; Reuter-Lorenz & Park, 2010). Consequently, researchers in the field of the cognitive neuroscience of aging consider fMRI as a reasonable method to investigate differences in neuronal functioning between age groups (Grady, 2012). Nevertheless, one has to keep in mind possible influences of changes in the neurovascular systems of elderly adults when interpreting results acquired by means of fMRI. Importantly, these potential influences are more of a concern in approaches that measure the spatial extent of activation by setting one threshold for all young and old subjects to identify activated voxels than for our approach. This is because our main focus was on the comparison between hemispheres *within* an individual so that potential alterations of the BOLD-signal in the old subjects should be similarly pronounced in both hemispheric counterparts of a ROI and, consequently, possible cross-hemispheric differences in activation should be maintained within a person.

An appropriate toolbox for investigating the asymmetry of activation between cross-hemispheric counterparts of a ROI with respect to spatial extent in a homogeneous age group would be the *LI-toolbox* developed by Marco Wilke (Wilke & Lidzba, 2007). This toolbox calculates a lateralization index (LI) between -1 and 1 indicating whether a ROI is more right- vs. left-lateralized, respectively. The advantage of this toolbox is that one can chose among various thresholding methods when analyzing the spatial extent of activation to assess laterality within a specific ROI on the basis of counting the number of activated voxels (Wilke & Lidzba, 2007).

8.5.2 Investigating a potential hierarchy between DLPFC, aPFC, PMd, and SPL

We clearly showed in the main experiment that DLPFC and aPFC are bilaterally activated in a domain-general manner when WM tasks are highly demanding. Moreover, we

showed unilateral activation of DLPFC and aPFC in easy verbal and spatial WM tasks of the control experiment. Furthermore, we demonstrated in this experiment that activity in DLPFC shifts from unilateral to bilateral as task difficulty increases. However, for aPFC this shift was less obvious. As already explained in section 7.3.2, I believe that we did not find more convincing bilaterality in aPFC in the difficult tasks of the control experiment because we did not use individualized WM tasks that had been adapted to each subject's WM span. Consequently, we cannot guarantee that these WM tasks pushed the subjects to their capacity limits. Hence, WM tasks of the control experiment might have been difficult for our subjects but maybe not demanding enough to recruit the contralateral counterpart in aPFC. The reason why DLPFC, in contrast to aPFC, developed unambiguous bilaterality in the difficult tasks of the control experiment was explained as follows on page 77: the recruitment of the contralateral counterpart might be elicited by varying subjective difficulty levels in DLPFC and aPFC. These brain regions are generally hierarchically organized in the posterior-to-anterior direction (Badre & D'Esposito, 2007; D'Esposito & Postle, 2015; Koechlin et al., 2003; Koechlin & Summerfield, 2007). Thus, it is possible that DLPFC develops bilaterality at lower load levels than aPFC due to varying compensatory roles.

This hypothesis could be addressed with an additional fMRI experiment that would ask whether aPFC shows a lateralization shift depending on task difficulty and whether there is a hierarchy between DLPFC and aPFC. Such an experiment could use verbal and spatial WM tasks that are comparable to the respective delayed match-to-sample tasks that were used in our two experiments (Sternberg, 1966; figure 8). Importantly, this experiment must encompass both easy and subjectively highly demanding WM tasks which push the participants to their capacity limits. Moreover, the difficult tasks should consist of varying load levels and they should be presented in an ascending order with respect to difficulty (see next paragraph for more details) to be able to investigate if DLPFC and aPFC develop bilaterality at varying difficulty levels.

The specific design of the experiment would be as follows. For the easy tasks, one could use the load levels of the easy conditions of the control experiment which are three and two items in the verbal and spatial domains, respectively. In contrast, the highly demanding tasks should be individually tailored on the basis of estimated individual WM spans. Specifically, individual difficult load levels would consist of the estimated WM span plus/ minus two load levels (compare section 6.1.3). All six load levels of a WM domain should be presented block-wise in separate sessions. Subjects should start with the easy load level and proceed through the load levels in order of difficulty. This approach prevents carryover effects of compensation strategies from demanding to easy tasks and makes the difficulty level of a current trial clear to the subject. The six functional sessions of each WM domain approximately

last 75 minutes when each load level is presented 15 times. Due to time restrictions which define how long humans are allowed to stay in a fMRI scanner, subjects should work on verbal and spatial WM domains on two separate days. The order of WM domains should be randomized across subjects, so that some participants complete the verbal sessions on the first day and others start with the spatial sessions.

Depending on the questions that future researchers want to answer, they should choose whether to include the elder subject group and whether to add the object WM domain in the experiment. Importantly, as mentioned previously, researchers who decide to include the object domain should be sure to use new Kanji or other abstract signs in every trial to avoid learning effects and impede the usage of verbal mnemonic strategies.

The above described experiment would also clarify additional ambiguities of this dissertation with respect to PMd and SPL. Namely, the question of whether, in addition to DLPFC and aPFC, these brain regions also recruit their contralateral counterparts in subjectively demanding WM situations. Both PMd and SPL were considered matching candidates for compensatory scaffolds for task difficulty because the statistical evidence of our two experiments was compatible with this hypothesis albeit not conclusive (compare section 8.4.2) and because both ROIs had been associated with attentional processes in the literature (Awh et al., 2006; Eriksson et al., 2015; Esterman et al., 2015; Pardo et al., 1991; Wardak et al., 2006). Since the proposed experiment would include both easy WM tasks and tasks that push subjects to their capacity limits, it might be possible to uncover potential lateralization shifts from unilaterality to bilaterality in easy vs. highly demanding tasks, respectively, in PMd and SPL. More specifically, introducing a parametric manipulation of difficulty might identify the specific subjective difficulty levels that cause PMd and SPL and also DLPFC and aPFC to become bilaterally active. Thus, it may detect a potential hierarchy between these regions with respect to which subjective difficulty levels make them shift from a unilateral to a bilateral activation pattern.

8.5.3 Investigating the compensatory role of right DLPFC and right aPFC

As previously mentioned, there is evidence that the additional recruitment of cross-hemispheric counterparts in DLPFC and aPFC is beneficial for older adults' performance in memory tasks (Cabeza et al., 2002; Reuter-Lorenz et al., 2000; Rossi et al., 2004). Moreover, we showed that both young and old subjects recruited DLPFC and aPFC bilaterally in the very demanding WM tasks of our main experiment. In the control experiment, we even demonstrated that younger adults activated the left DLPFC and aPFC in easy WM tasks and additionally the right counterpart in DLPFC (and presumably also in aPFC) when the tasks

became more difficult. However, our results cannot prove that the additional recruitment of right DLPFC and aPFC beyond their left hemispheric counterparts actually causes improved WM performance in younger adults which would speak in favor of a compensatory role of bilaterality in PFC as it was proposed by STAC (Park & Reuter-Lorenz, 2009). This is because our experiments investigated brain activity depending on increased task demand in WM tasks in a correlative manner. However, now that we have identified the brain regions involved in performance at increased task demand, we will be able to directly test the causal role of these areas for WM performance also in young adults when they work at their capacity limits. More specifically, one might apply TMS to explore either whether the inhibition of right DLPFC and aPFC results in a decrease of WM capacity in young adults or whether the stimulation of such brain regions leads to an improvement of WM performance. In the following paragraphs, I will describe in more detail how such experiments may look like. Please note that I won't provide exact parameters defining specific TMS protocols. Typical parameters that may be used in the TMS protocols that I will mention below are stated in various review articles about TMS (Klomjai, Katz, & Lackmy-Vallée, 2015; Siebner, Hartwigsen, Kassuba, & Rothwell, 2009; Ziemann et al., 2008).

To examine the beneficial role of right DLPFC and right aPFC for young adults in the maintenance phase of demanding WM tasks, one might conduct the following experiment with healthy young subjects in which one applies a single-pulse TMS protocol that is known to inhibit neural processing (Siebner et al., 2009): all subjects' WM spans should be determined according to the approach used in our main experiment (see section 6.1.3). Then, separately for every subject, one creates a delayed match-to-sample task (compare figure 8) that uses the subject's estimated WM span as the memory load to ensure that the WM task is highly demanding for each subject. Participants should work on this task in three independent blocks which are identical apart from the fact that in two blocks single-pulse TMS inhibits separately right DLPFC or right aPFC in the maintenance phases of all trials. In contrast, there is a sham stimulation inhibiting neither DLPFC nor aPFC in the third block. Single-pulse TMS is said to modulate neural activity only during the actual application of TMS (Bagherzadeh, Khorrami, & Zarrindast, 2016; Klomjai et al., 2015; Ziemann et al., 2008) which would be restricted to the maintenance phase in this experiment. Consequently, single-pulse TMS applied in one block should not have long-lasting effects on the memory performance of the subsequent blocks. Nevertheless, one should assure that the sequence of the three blocks is randomly assigned to the subjects to control for possible positive and negative sequential effects that are independent of TMS administration, like for instance, learning or cognitive fatigue effects. The comparison of task performance (e.g., accuracy and reaction times) between the inhibitory blocks with the sham block would allow to explicitly examine whether the inhibition of right DLPFC and/ or right aPFC leads to worse behavioral performance in demanding WM tasks.

Such results combined with the results of this dissertation would speak in favor of a compensatory role of right prefrontal brain regions for increased task difficulty.

Based on such potential results, one might consider an additional experiment using high-frequency rTMS in right DLPFC and right aPFC in patient groups who are known for their problems with WM. Such groups might include older patients suffering from mild cognitive impairment or dementia and patients suffering from ADHD. Contrary to single-pulse TMS, high-frequency rTMS (> 5 Hz) can facilitate neural activity beyond the actual stimulation phase (Bagherzadeh et al., 2016; Klomjai et al., 2015; Ziemann et al., 2008). Thus, such a protocol helps to investigate if TMS in right DLPFC and right aPFC could enhance WM performance in patients suffering from WM deficits in the long run. In the experiment, patients belonging to one homogeneous patient group should be randomly assigned to one of three groups. Two groups would get high-frequency rTMS either to the right DLPFC or to the right aPFC in the course of the experiment and the third group would get a sham stimulation. Moreover, based on the experimental design used by Bagherzadeh et al. (2016), who successfully demonstrated in healthy young subjects that high-frequency rTMS in left DLPFC improves WM performance in a verbal digit span task and a visuospatial 2-back task in the long run, one should use three independent phases in the experiment. In the first and third phase, subjects would work on WM tasks, whereas the second phase would include ten sessions of high-frequency rTMS applied on ten separate days within two weeks. The third session should be conducted within five days after the last TMS session (compare Bagherzadeh et al., 2016). One could use the same WM task that I already described in the previous paragraph, namely a delayed match-to-sample task with individual memory loads that equal subjects' assessed WM spans to investigate right DLPFC and right aPFC involvement in highly demanding WM situations. More specifically, the comparison of performance in such a task between the two rTMS groups with the sham group would allow to examine if the facilitation of right DLPFC and/ or right aPFC leads to better performance of patients with WM deficits in demanding WM tasks even beyond rTMS stimulation. Such a potential long-lasting enhancement of WM performance evoked by rTMS in right DLPFC and aPFC in patients suffering from problems with WM might also be the basis for the development of intervention strategies including TMS administration to permanently help these patient groups.

8.5.4 Need for a comprehensive understanding of WM

As mentioned in section 2.3, WM research – like also the experiments of this dissertation – has usually focused on verbal, spatial, and object WM domains in the visual and auditory modalities. In contrast, the senses of olfaction, taste, and touch are very rarely

examined in the field of WM, although their modality-specific inputs can clearly also be represented in WM (Dade et al., 2001).

Moreover, various modalities are typically investigated in isolation, although outside the laboratory, we frequently encounter multisensory information coming from various senses at the same time. There is some empirical evidence that information from different modalities is integrated in WM. However, it is not clear at which processing stage the multisensory integration takes place, and how this multisensory representation is maintained in WM (Quak, London, & Talsma, 2015).

In summary, it remains open to future research to provide a comprehensive view of WM considering not only verbal, spatial, and object domains in visual and auditory modalities but also representations of other modalities and their interactions (Dade et al., 2001). More specifically, one needs to find out whether multisensory information is completely integrated and thus transformed into an holistic and/ or amodal representation in WM (Quak et al., 2015). Such results would enable us to better understand how WM realistically operates in our daily lives (Dade et al., 2001; Quak et al., 2015).

8.6 Summary and conclusions

One principle of the human cerebral cortex is its lateralized functional architecture, which supports processes such as language, precise motor control of the hands, and WM. It is well established in the field of the cognitive neuroscience of aging that in older participants such lateralized activations of DLPFC and aPFC vanish in WM tasks, which is due to the corecruitment of corresponding regions in the other cerebral hemisphere. Currently, it was not clear whether such bilateral corecruitment is an age-specific response of the human brain to increased task demand due to age-related changes or whether bilaterality in PFC is a general response to challenging WM tasks, independent of age. To clarify these alternatives, we conducted our main experiment in which young and older subjects worked on verbal, spatial, and object-based WM tasks that were matched for subjective task difficulty, so that all participants maintained large amounts of information at their capacity limits. In this experiment, we did not find any hemispheric differences in brain activation between age groups in PFC. More specifically, bilateral activation patterns of DLPFC and aPFC were present across all WM domains in both young and old adults. Moreover, we demonstrated in our control experiment that DLPFC and aPFC show unilateral recruitment in easy verbal and spatial WM tasks in young participants. Together with the results of the main experiment, the results of the control experiment provide evidence that this unilaterality shifts to bilateral recruitment during difficult task conditions in DLPFC and aPFC. These findings speak in favor of the idea that the

corecruitment of cross-hemispheric counterparts in PFC is associated with subjectively demanding WM tasks and independent of their WM domain. Yet, this corecruitment is not associated with age. Moreover, we did not detect bilaterality in all WM-relevant ROIs. For instance, areas that probably dealt with language processes (VLPFC, SMA, lobule VI and crus1 of lobule VII of the cerebellum, and PMv) maintained a unilateral activation pattern even during very demanding WM tasks.

Additionally recruiting the nonspecialized counterpart in the contralateral hemisphere in challenging circumstances and across WM domains thus seems to be an age-independent support mechanism that compensates for increased task demand so that we can maintain high performance levels. According to our results, this support mechanism seems to be largely restricted to dorsolateral and anterior parts of PFC. Since bilaterality was present in these ROIs across all WM domains, it is highly likely that the processes subserved by these areas are executive operations such as attentional control that have been described in various cognitive models of WM (Baddeley, 2000; Baddeley & Hitch, 1974; Cowan, 1995, 1999, 2008) rather than stimulus-specific maintenance procedures. Interestingly, our results also provide hints that – beyond DLPFC and aPFC – also PMd and SPL might likewise develop bilateral recruitment in response to demanding WM tasks. However, this issue remains open for further research.

In conclusion, the empirical work of this dissertation contributes to a better theoretical understanding of which strategies the human brain uses in WM processes to achieve our behavioral goals despite increased task challenges, as well as how these strategies develop across a lifetime. This contribution will become more and more important in the future as decreased birth rates and increased longevity in developed countries cause a demographic shift towards an aging population. Many adults over 80 develop dementia that, among other things, severely impairs WM processes and negatively impacts patients and their family members in their daily lives (Park & Reuter-Lorenz, 2009). Knowing how healthy young and old adult human brains work under demanding WM circumstances will help us in the future to understand how patients suffering from dementia fail to compensate for increased task demand, contributing to their extreme memory deficits. This may be a crucial basis for the development of effective interventional procedures including, for instance, specific TMS protocols that improve memory performance of these patients.

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