

# EXPLORING VISUAL VERBAL WORKING MEMORY

Neural correlates & the effect of an adaptive online training  
on brain activity and cognitive performance

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*“You have to try the impossible to achieve the possible”*

– Herman Hesse



## Summary

The ability to store and process information plays an essential role in our daily lives. The cognitive construct responsible for the processing of this information is termed working memory (WM). According to Alan Baddeley's multi-component model of this cognitive construct, one of the main types of WM is the so-called verbal WM, which is the ability to temporarily store and manipulate speech-related information (e.g., maintaining a series of numbers, such as a telephone number).

Up until now research on neural correlates of verbal WM has focused on cortical areas, underestimating other essential regions. Therefore, the first aim of this thesis was to study the neural correlates of verbal WM as well as to observe the impact of different influencing factors such as sex, age or type of task. To this end, we performed a comprehensive functional magnetic resonance imaging (fMRI) meta-analysis across 42 task-related verbal WM studies. The results of this meta-analysis demonstrated that verbal WM activated the fronto-parietal network as well as various subcortical areas such as the cerebellum, the right lenticular nucleus, and the bilateral median cingulate. Additional meta-regression analyses also suggested that age and mean reaction time of the WM task moderated activity in different brain regions. Further research is, however, required to better understand the influence of these two factors. Furthermore, a supplementary meta-analysis was performed in which we only included studies that assessed the neural correlates of an increasing verbal WM load. The results of this analysis demonstrated activation in several frontal and parietal regions as well as in subcortical regions, thereby identifying those brain regions involved during a complex verbal WM task.

The fact that WM is correlated with higher-order functions (e.g., fluid intelligence and reading comprehension) shows that WM plays a key role in a wide range of cognitive functions. Moreover, it has been found that WM capacity decreases across the lifespan. Therefore, it comes as no surprise that in the last few decades we have seen a rise in interest in the kind of

cognitive training that could increase WM capacity. Here, elderly people were a particularly popular target group for WM trainings and interventions.

However, while previous studies used a variety of different methodological approaches and tailored the training to different age groups, this made it difficult to draw any conclusions from the existing literature; therefore, the second aim of the thesis was to investigate the neural and behavioral effects of verbal WM training in middle-aged adults, who were expected to benefit more from the training than older adults, through the use of a well-defined study design aimed at overcoming previous limitations. We were able to accomplish this by providing participants with an eight-week online training which included performance feedback. The experimental group performed an adaptive training whereas the active control group was provided with a fixed low-level verbal WM task. Before and after the eight-week online training period, participants were invited to an fMRI scan in which they performed a verbal  $n$ -back task in order to observe training-related changes in brain activity. To assess the presence or absence of training-associated transfer effects, they also completed a verbal WM task (i.e., digit span task) outside the scanner. The results of this study demonstrated that the experimental group exhibited brain activity decreases in regions known to be involved in verbal WM as well as a significant performance improvement in the verbal  $n$ -back task and the forward digit span task in comparison to the active control group. This suggests that the brain became more efficient upon completing the adaptive WM online training, indicating that cognitive training of middle-aged adults can increase neural efficiency in specific brain regions.



## Resumen

La habilidad para almacenar y procesar información juega un papel fundamental en nuestro día a día. El constructo cognitivo responsable del procesamiento de la información es conocido por el nombre de memoria de trabajo (MT). Según el modelo multicomponente de Alan Baddeley sobre este constructo cognitivo uno de los principales tipos de MT es conocida como la MT verbal, que consiste en la habilidad para temporalmente almacenar y manipular la información relacionada con el habla (p.ej. mantener una serie de números en la memoria, como sería un número de teléfono).

Hasta ahora la investigación de los correlatos neurales de la MT verbal se ha focalizado en áreas corticales, subestimando otras regiones esenciales. Por consiguiente, el primer objetivo de esta tesis doctoral fue estudiar los correlatos neurales de la MT verbal así como también el impacto de posibles factores influyentes como por ejemplo sexo, edad o tipo de tarea. Para este fin realizamos un metaanálisis de imágenes por resonancia magnética funcional (IRMf) en 42 estudios que usaron tareas de MT verbal. Los resultados del metaanálisis demostraron que la MT verbal activa la red fronto-parietal así como también áreas subcorticales tales como el cerebelo, el núcleo lenticular derecho y el cíngulo mediano bilateral. Los análisis de meta-regresión sugirieron que la edad y la media del tiempo de reacción de la tarea de la MT verbal moderaban la actividad en diferentes regiones cerebrales. Sin embargo, es necesario realizar más estudios para entender mejor la influencia de estos dos factores. Además, se realizó un metaanálisis complementario en el que sólo se incluyeron estudios que evaluaban los correlatos neurales de una carga de la MT verbal en aumento. Los resultados de este análisis demostraron actividad en varias regiones frontales y parietales así como también en regiones subcorticales, identificando así las regiones cerebrales envueltas en una tarea compleja de la MT verbal.

El hecho de que la MT esté correlacionada con funciones de orden superior (p.ej. intelligen-

cia fluida y comprensión de lectura) muestra como ésta juega un papel clave en una amplia gama de funciones cognitivas. Además, se ha visto que la capacidad de la MT disminuye a lo largo de la vida. Por ello, no es sorprendente que en las pasadas décadas haya habido un aumento de interés en los entrenamientos cognitivos que puedan aumentar la capacidad de la MT. Aquí, las personas mayores han sido un grupo objetivo -particularmente popular- para realizar entrenamientos e intervenciones de la MT.

Sin embargo, si bien los estudios previos utilizaron diferentes enfoques metodológicos y dirigieron el entrenamiento a diferentes grupos de edad, esto complicó el poder realizar conclusiones de la literatura existente; por ello, el segundo objetivo de esta tesis fue investigar los efectos neurales y conductuales del entrenamiento de la MT verbal en adultos de mediana edad, los cuales se esperaba que se beneficiarían más del entrenamiento en comparación a los adultos mayores, mediante el uso de un diseño de estudio bien definido destinado a superar limitaciones pasadas. Pudimos lograrlo al proporcionar a los participantes un entrenamiento en línea de ocho semanas de duración el cual incluía retroalimentación sobre su rendimiento. El grupo experimental realizó un entrenamiento adaptativo mientras que el grupo de control activo recibió una tarea con un fijo (y menor) nivel de la MT verbal. Antes y después del periodo de entrenamiento en línea, se invitó a los participantes a un IRMf en la que realizaron la tarea *n*-back verbal para observar los cambios relacionados con el entrenamiento en la actividad cerebral. Para evaluar la presencia o ausencia de efectos de transferencia asociados con el entrenamiento, los participantes también completaron una tarea de MT verbal (es decir, el test de dígitos) fuera del escáner. Los resultados de este estudio demostraron que el grupo experimental exhibió una disminución de la actividad cerebral en las regiones que se sabe que están involucradas en la MT verbal, así como una mejora significativa del rendimiento en la tarea *n*-back verbal y en el test de dígitos en progresión en comparación con el grupo de control activo. Esto sugiere que el cerebro se vuelve más eficiente al completar un entrenamiento adaptativo de la MT, lo que indica que el entrenamiento cognitivo en adultos de mediana edad puede aumentar la eficiencia neural en regiones específicas del cerebro.

## Resum

L'habilitat per emmagatzemar i processar informació juga un paper fonamental en el nostre dia a dia. El constructe cognitiu responsable del processament de la informació és conegut com la memòria de treball (MT). Segons el model multi-component d'Alan Baddeley sobre aquest constructe cognitiu un dels principals tipus de MT és la coneguda com la MT verbal, la qual consisteix en l'habilitat per emmagatzemar temporalment i manipular la informació relacionada amb la parla (per exemple, mantenir una sèrie de números en la memòria, com podria ser un número de telèfon).

Fins ara la investigació dels correlats neurals de la MT verbal s'han focalitzat en àrees corticals, subestimant altres regions essencials. Per aquesta raó, el primer objectiu d'aquesta tesi doctoral va ésser estudiar els correlats neurals de la MT verbal així com també l'impacte de possibles factors influents com per exemple el sexe, l'edat o el tipus de tasca. Per aquest fi vàrem realitzar un meta-anàlisi d'imatges per ressonància magnètica funcional (IRMf) en 42 estudis, els quals empraren tasques de MT verbal. Els resultats del meta-anàlisi varen demostrar que la MT verbal activa la xarxa fronto-parietal així com també altres àrees subcorticals com ara el cerebel, el nucli lenticular dret i el cíngol mitjà bilateral. Els anàlisis de meta-regressió van suggerir que l'edat i la mitja del temps de reacció de la tasca de la MT verbal moderaven l'activitat en diferents regions cerebrals. Tot i així, és necessari realitzar més estudis per entendre millor la influència d'aquests dos factors. A més, es va realitzar un meta-anàlisi complementari en el que només es varen incloure estudis que avaluaven els correlats neurals d'una carga de la MT verbal en augment. Els resultats d'aquest anàlisi van demostrar activitat en varies regions frontals i parietals així com també en regions subcorticals, identificant així les regions cerebrals implicades en una complexa tasca de la MT verbal.

El fet de que la MT estigui correlacionada amb funcions d'ordre superior (per exemple, intel·ligència fluida o comprensió lectora) mostra com aquesta juga un paper clau en una

àmplia gamma de funcions cognitives. A més, s'ha vist que la capacitat de la MT disminueix al llarg de la vida. Per això, no és sorprenent que durant les últimes dècades hagi hagut un augment d'interès en els entrenaments cognitius que poden augmentar la capacitat de la MT. Per aquesta raó, les persones grans han sigut un grup objectiu particularment popular per realitzar entrenaments i intervencions de la MT.

Tanmateix, si bé els estudis anteriors utilitzaven diferents enfocaments metodològics i dirigien l'entrenament a diferents grups d'edat, això dificultava treure conclusions de la literatura existent; per tal de solucionar-ho, el segon objectiu de la tesi doctoral ha estat investigar els efectes neurals i conductuals de l'entrenament de la MT verbal en adults de mitjana edat. En aquest grup s'esperava que es beneficiessin més de l'entrenament que els adults d'avançada edat. El disseny d'estudi es va definir per tal de superar les limitacions dels estudis passats. Vam poder aconseguir-ho al proporcionar als participants un entrenament *online* de vuit setmanes seguides de duració el qual incloïa retroalimentació sobre el seu rendiment. El grup experimental va realitzar un entrenament adaptatiu mentre que el grup de control actiu va rebre una tasca amb un nivell fix (i menor) de la MT verbal. Abans i després del període d'entrenament *online*, es va convidar als participants a un IRMf en el que van realitzar la tasca *n*-back verbal per observar els canvis d'activitat cerebral relacionats amb el entrenament. Per avaluar la presència o absència d'efectes de transferència associats amb l'entrenament, els participants també van completar una tasca de MT verbal (és a dir, el test de dígit) fora del escàner. Els resultats d'aquest estudi van demostrar que el grup experimental exhibia una disminució de l'activitat cerebral en les regions que se sap que estan involucrades en la MT verbal, així com una millora significativa del rendiment en la tasca *n*-back verbal i en el test de dígit en progressió en comparació amb el grup de control actiu. Això suggereix que el cervell es torna més eficient al completar un entrenament adaptatiu de la MT, el que indica que l'entrenament cognitiu en adults de mitjana edat pot augmentar l'eficiència neural en regions específiques del cervell.

# Contents

<b>Summary</b>	<b>i</b>
<b>Resumen</b>	<b>iii</b>
<b>Resum</b>	<b>v</b>
<b>List of Abbreviations</b>	<b>x</b>
<b>List of Figures</b>	<b>xii</b>
<b>PART I: INTRODUCTION</b>	<b>1</b>
<b>1 Working memory</b>	<b>3</b>
1.1 Definition . . . . .	3
1.2 Relationship between WM and higher-order functions . . . . .	5
1.2.1 WM and reading comprehension . . . . .	5
1.2.2 WM and fluid intelligence . . . . .	6
1.3 Models of WM . . . . .	6
1.3.1 Multi-store model . . . . .	7
1.3.2 Multi-component model . . . . .	8
1.3.3 Embedded-processes model . . . . .	10
1.4 Verbal vs. visuo-spatial WM . . . . .	12
1.5 Measuring visual verbal WM capacity . . . . .	13

1.5.1	Span tasks . . . . .	13
1.5.2	<i>N</i> -back task . . . . .	14
1.5.3	Sternberg and DMTS tasks . . . . .	15
1.6	Measuring brain activity . . . . .	16
1.7	Neural correlates of visual verbal WM . . . . .	18
1.7.1	Possible influential factors . . . . .	19
1.8	Conclusion . . . . .	21
<b>2</b>	<b>WM training</b>	<b>22</b>
2.1	Introduction . . . . .	22
2.2	Visual verbal WM training effects . . . . .	23
2.2.1	Visual verbal WM training effects in aging . . . . .	26
2.3	Methodological issues . . . . .	29
2.4	Conclusions . . . . .	32
<b>3</b>	<b>Knowledge gap</b>	<b>33</b>
<b>4</b>	<b>Thesis Objectives</b>	<b>34</b>
	<b>PART II: RESEARCH ARTICLES</b>	<b>35</b>
<b>5</b>	<b>Neural correlates of visual verbal WM</b>	<b>37</b>
<b>6</b>	<b>Effects of visual verbal WM training in middle-aged healthy adults</b>	<b>57</b>

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<b>PART III: DISCUSSION</b>	<b>73</b>
<b>7 Overall key results</b>	<b>75</b>
<b>8 Integrating Results into the WM literature</b>	<b>77</b>
8.1 Training-related brain changes in activation . . . . .	77
8.1.1 Left SMG . . . . .	78
8.1.2 Cerebellum . . . . .	79
8.1.3 Cingulate . . . . .	80
8.1.4 Right angular gyrus . . . . .	81
8.1.5 Right MFG . . . . .	82
8.2 Neural efficiency and the effectiveness of WM training . . . . .	83
<b>9 Thesis achievements, limitations and future work</b>	<b>85</b>
<b>10 Conclusion</b>	<b>87</b>
<b>Acknowledgments</b>	<b>89</b>
<b>References</b>	<b>91</b>
<b>List of publications</b>	<b>106</b>
<b>Eidesstattliche Versicherung/Affidavit</b>	<b>108</b>

## List of Abbreviations

AAL	Automated Anatomical Labelling
ADHD	Attention Deficit/Hyperactivity Disorder
APM	Advanced Progressive Matrices
BA	Brodman Area
BOLD	Blood-Oxygen-Level Dependent
CBF	Cerebral Blood Flow
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
DLPFC	Dorsolateral Prefrontal Cortex
DMTS	Delayed Match-To-Sample
fMRI	functional Magnetic Resonance Imaging
$g_f$	Fluid intelligence
$g_i$	Crystallized intelligence
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
IFC	Inferior Frontal Cortex
LTM	Long-Term Memory
MFG	Medial Frontal Gyrus
PASA	Posterior-Anterior Shift in Aging
PFC	Prefrontal Cortex
RT	Reaction Time
SAT	Scholastic Aptitude Test
SMA	Supplementary Motor Area
SMG	Supramarginal Gyrus
STAC	Scaffolding Theory of Aging and Cognition
STM	Short-Term Memory
WM	Working Memory
vvWM	visual verbal Working Memory





## List of Figures

1.3.1 Multi-store model adapted from Atkinson and Shiffrin (1968) . . . . .	7
1.3.2 Multi-component model of WM adapted from Baddeley (2000) and Logie (1995)	9
1.3.3 Revised multi-component model adapted from Baddeley et al. (2011) . . . . .	10
1.3.4 Cowan’s memory model adapted from Cowan (1999) . . . . .	11
1.5.5 A schematic representation of WM paradigms. Inspired by Byrne (2018) . . . .	16
1.7.6 The working memory core network. Figure extracted from Rottschy et al., 2012, p. 839 [Fig.5] . . . . .	19
2.2.7 WM training-related activations separately analyzed for studies with verbal or spatial tasks. Figure extracted from Salmi et al., 2018, p.113 [Fig.4]. <i>Red:</i> <i>verbal working memory; Green: spatial working memory</i> . . . . .	26



## **PART I: INTRODUCTION**



# 1 Working memory

## 1.1 Definition

Imagine you are reading a really tedious Ph.D. thesis and the connection between the chapters is rather obscure. While reading it you are storing all the content in your memory and you are also trying to make sense out of the whole story. Performing this task is very demanding and it requires a specific cognitive system: working memory (WM). We can extrapolate from this example to other similar situations. Common to all is the requirement of simultaneous interplay between storage and processing of information. In fact, this is the classical definition of WM (Baddeley and Hitch, 1974; Miyake and Shah, 1999). Thereby, this psychological construct captures a cognitive capacity that we use in our daily life.

Historically, the term “working memory” has been used interchangeably with another one, namely “short-term memory” (STM) (Gonthier, 2014). This presents a problem which, in turn, shows how there is still no clear consensus on the terminology. Put shortly, STM, like WM, refers to the temporary storage of information (Chai et al., 2018); however, unlike WM, STM does not involve the manipulation of information. This means that WM includes STM but not the other way around. We could define WM as the combination of STM and additional processing. According to Baddeley (2003), the first mention of the term WM, as such, can be attributed to Miller et al. (1960):

*When we have decided to execute some particular Plan, it is probably put into some special state of place where it can be remembered while it is being executed. Particularly if it is a transient, temporary kind of Plan that will be used today and never again, we need some special place to store it. The special place may be on a sheet of paper. Or (who knows?) it may be somewhere in the frontal lobes of the brain. Without committing ourselves to any specific machinery, therefore, we should like to speak of the memory we use for the execution of our Plans as a kind*

*of quick-access, “working memory”. There may be several Plans, or several parts of a single Plan, all stored in working memory at the same time.*

Several important aspects of the modern conception of WM are already present in this first explanation: the dual function of processing and storage, the fast access to the stored information and even ideas about a cerebral localization in the frontal lobes of the brain.

Moreover, WM describes a limited capacity for simultaneous processing of information. Miller studied this limitation in his famous paper “The magical number seven, plus or minus two” (Miller, 1956). He proposed that the number of items that can be recalled in perfect order was seven (plus or minus two accounting for individual differences). This number was later questioned, and Cowan (2001) lowered the estimate to four. This difference could be due to the fact that the recalled number does not depend only on the presented stimuli but also on how the limit is measured (Miller, 1956; Cowan, 2001). The ability to store increasing amounts of information in WM is dependent on the strategy used. The most general cognitive mnemonic strategy is probably chunking, which was already introduced by Miller (1956). Accordingly, chunking is a strategy involving reorganization of the presented material into associated or familiar structures (Cowan, 2001). Thus, information can be combined to create meaningful “chunks” (or units) to improve the WM capacity (measured by the amount of information, not chunks). For example, three single digits (3, 7, 2) can be regrouped in only one (372). A precise definition of the concept of “chunk” was developed: it is a unit, which is in a maximally compressed code (Mathy and Feldman, 2012). The power of chunking is seen in special cases such as in the study by Ericsson et al. (1980). They studied an individual who learned, over the course of a year, to repeat lists of about 80 digits from memory.

In recent years, there has been an increase in interest in the inter-subject variability of the WM capacity, which accounts for the individual differences. Moreover, WM capacity has also been observed to decrease across a subject’s lifespan, demonstrating intra-subject variability (Daneman and Carpenter, 1980; Dobbs and Rule, 1989; Swanson, 1999). Specifically,

when particular tasks are performed, WM capacity has been shown to be strongly correlated with higher-level functions (Daneman and Carpenter, 1980; Kyllonen and Christal, 1990). Therefore, WM plays a key role in a wide range of higher-order functions.

## **1.2 Relationship between WM and higher-order functions**

Higher-order functions include several complex cognitive constructs, such as intelligence, reading comprehension, decision making, reasoning, and any task that is not a pure sensory process such as visual perception. In this section, we are going to explore how WM is a predictor of two different higher-order functions: reading comprehension and fluid intelligence (Gonthier, 2014).

### **1.2.1 WM and reading comprehension**

Daneman and Carpenter (1980) were the first to show that a WM task is correlated with three different reading comprehension measures (i.e. the verbal Scholastic Aptitude Test (SAT) and tests involving fact retrieval and pronominal reference). They showed that participants with higher WM capacity understood texts better. Daneman and Carpenter (1983) later also observed that higher WM capacity is correlated with the ability to resolve semantic ambiguity. They demonstrated that individual differences in WM capacity can affect the resolution of apparent inconsistencies within sentences. Afterwards, other studies further investigated the relationship between WM capacity and reading comprehension. 7- and 8-year-olds, who were accurate readers but had poor comprehensive skills, were examined by Yuill et al. (1989). This study reported that children's comprehension skills are related to their measured WM capacity. These results corroborate the idea that text processing is influenced by WM demands. A later meta-analysis by Daneman and Merikle (1996) presented data from 77 studies which investigated the relationship between WM capacity and language comprehension. They found that these two constructs were correlated in a range between  $r = .41$  and  $r = .52$ , supporting the conclusions from Daneman and Carpenter's seminal



work (Daneman and Carpenter, 1980). Moreover, they also discovered that WM is a better predictor of language comprehension than STM.

### 1.2.2 WM and fluid intelligence

General intelligence ( $g$ ) is often thought of as a composite that can be divided into crystallized intelligence ( $g_i$ ) and fluid intelligence ( $g_f$ ) (Cattell, 1963). Whereas the former,  $g_i$ , is defined as the knowledge of facts and skills that a person accumulates during their lifetime, the latter,  $g_f$  is described as the ability to solve new problems that cannot be performed automatically.  $G_f$  has been shown to be correlated with comprehension, problem solving and learning (Cattell, 1973). It is also described as independent from acquired knowledge, unlike  $g_i$ .

The first study to observe the correlation between  $g_f$  and WM was performed by Kyllonen and Christal (1990). In their study, 2144 participants performed 13 different reasoning tasks and six WM tasks. They found evidence of a strong link between individual differences in WM and  $g_f$ . In 2005, a meta-analysis on the topic was published (Ackerman et al., 2005). They observed that individual task level measures of WM correlated with  $g_f$  ( $r = .48$ ). In the same year, Kane et al. (2005) re-analyzed the data from Ackerman et al. (2005) with a different approach. They found that the correlation was substantially higher ( $r = .72$ ). Besides the ongoing debate about the actual strength of this correlation, there seems to be a consensus that these two constructs are related. As with language comprehension, WM is a better predictor of  $g_f$  than STM (Engle et al., 1999).

## 1.3 Models of WM

Since the beginning of WM research, several theoretical models have been proposed as a means of explaining this cognitive construct (Byrne, 2018). The goal of this section is to provide a brief overview of the most relevant models for the interpretation of the results discussed later in the thesis (Miró-Padilla, 2018). An exhaustive review of all the existing models in

the literature is beyond the scope of this thesis (see a review by Chein and Fiez (2010)).

### 1.3.1 Multi-store model

The multi-store model designed by Atkinson and Shiffrin (1968) could be considered the first model of WM (Barrouillet and Camos, 2015). It is also known as the Atkinson-Shiffrin model. In their proposed model, the entire human memory system is described as consisting of three parts: a *sensory system* (visual, auditory, or haptic), a *short – term store*, and a *long – term store* (see Figure 1.3.1).

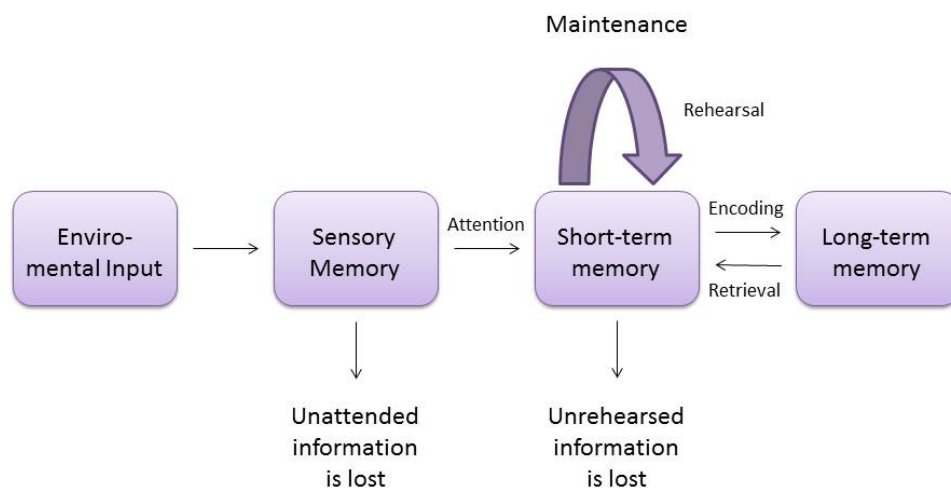


Figure 1.3.1: Multi-store model adapted from Atkinson and Shiffrin (1968)

The sensory system detects and holds information for a few milliseconds. The information is then transferred to the *short – term store* where it will only last a few seconds, unless it is maintained through active rehearsal (e.g., articulation of the items). The longer the information is rehearsed, the more likely it is to be passed on to the *long – term store*, which is a permanent storage of information where information can be held for years. The stored data can be transferred back to the *short – term store* any time in order to be manipulated. This is an obviously sequential model in the sense that the information needs to travel from one store to the other. Importantly, it also emphasizes the flow of information as being essential to the human memory system. Arguably, this model refers to STM rather than WM. However, the

authors talk about a function specific to WM (i.e., manipulation of information), albeit they attribute it to the *short – term store*. This model can be rightfully seen as the predecessor for one of the most widely adopted WM models, the so-called “multi-component model” described by Baddeley and Hitch (1974).

### 1.3.2 Multi-component model

The main goal of the multi-component model is to specify the role of the *short – term store*, which came to be called WM. In the original model proposed by Baddeley and Hitch (1974), there are three main components of WM: the *central executive*, the *phonological loop*, and the *visuospatial sketchpad*. The first is a supervisory system which coordinates the functioning of the other two components, known as the “slave systems”. The *phonological loop* stores verbal information and is believed to have evolved to support the acquisition of language (Baddeley, 2012). So far, it is the most empirically researched component of the model. It is comprised of two subcomponents: a *phonological store* which holds information—either visually or auditory—for a few seconds, and an *articulatory loop* which refreshes the incoming information from the *phonological store* using a rehearsal process (i.e., subvocal articulation). This means that data in the *phonological store* will disappear unless the *articulatory loop* works to maintain the information. It is worth mentioning that, whereas auditory verbal stimuli (e.g., hearing someone telling you the word “CUTE”) can directly enter the *phonological store*, visual verbal stimuli (e.g., seeing the written word “CUTE”) must first be coded into phonological information through subvocal articulation. Articulatory suppression prevents this specific transfer of information. The third component, the *visuospatial sketchpad*, is responsible for integrating visual and spatial stimuli. The *central executive* must control the slave systems to allow the subject to focus his attention on a specific system, depending on the circumstances. Imagine the following situation: you are piloting an airplane from Barcelona to Munich and your co-pilot is telling you an anecdote. The *visuospatial sketchpad* will process and manipulate the information regarding the direction in which you are piloting the plane whereas the *phonological loop* will process and manipulate the information from your colleague’s words.

Later, in a refined version of the model, a fourth component was added: the *episodic buffer* (Baddeley, 2000) (see Figure 1.3.2). The purpose of this new component was to bind the information from different stimuli into a single and integrated representation. It also provides the link between the slave systems and long-term memory (LTM). It works with LTM in terms of transferring the information into meaningful and chronologically distributed episodes. Before the introduction of this component, the model lacked a mechanism for interaction between the *phonological loop* and the *visuospatial sketchpad*.

Logie (1995) presented results based on which he argued that the visuo-spatial sketchpad could be also segmented into two components, just like the *phonological loop*. One component was called the *visual cache*, which acts as a visual store by retaining visual information such as color and shapes in a passive way. The other component was the *inner scribe*, which retains spatial information by controlling the directed movements in space in an active way (Logie and Pearson, 1997) (see Figure 1.3.2).

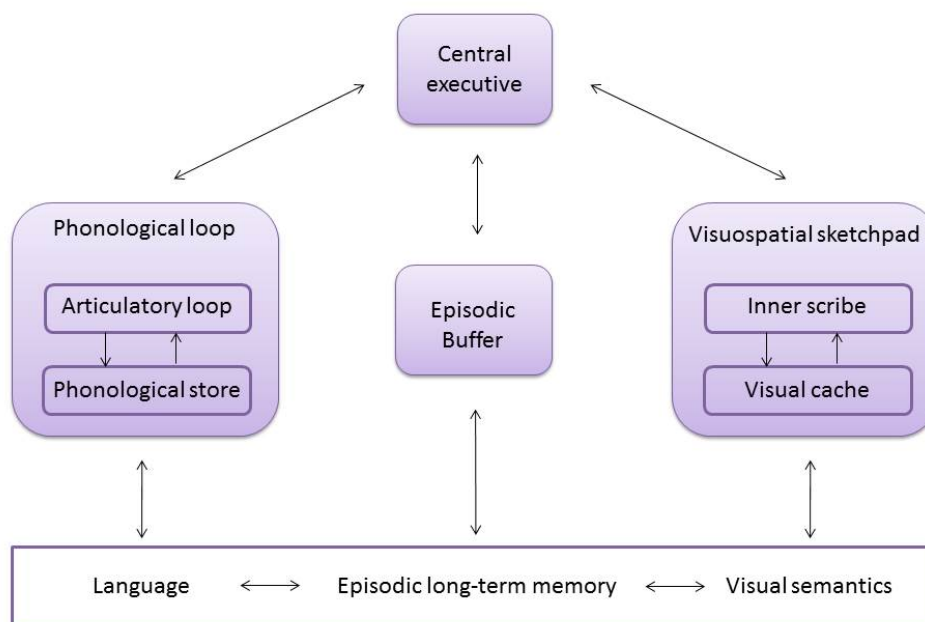


Figure 1.3.2: Multi-component model of WM adapted from Baddeley (2000) and Logie (1995)

In 2011, Baddeley, Allen, and Hitch revisited the model once more to include the missing sensory modalities (see Figure 1.3.3). In the revised model, the *central executive*

component only controls the *episodic buffer*. Therefore, the *phonological loop* and the *visuospatial sketchpad* are only connected to the *episodic buffer*, which in turn coordinates the execution of the instructions coming from the *central executive* component and binds the data from several dimensions into chunks. Moreover, the *phonological loop* and the *visuospatial sketchpad* are now considered lower level buffers. The former manipulates language-related information such as writing, speech, lip reading, and sign language whereas the latter manipulates information coming from visual, spatial, or haptic systems (Baddeley et al., 2011).

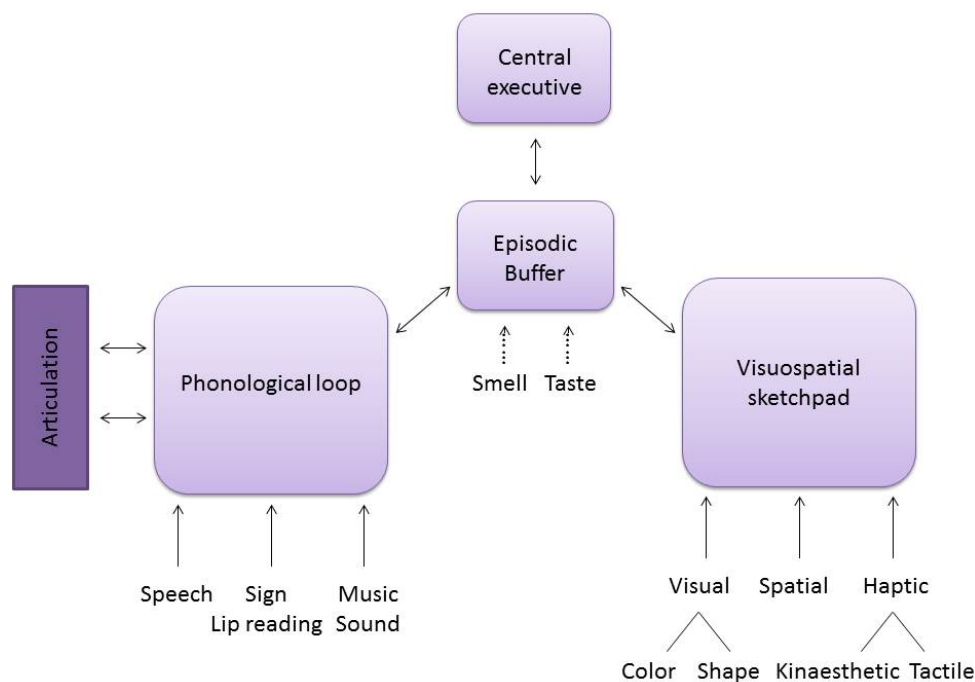


Figure 1.3.3: Revised multi-component model adapted from Baddeley et al. (2011)

### 1.3.3 Embedded-processes model

The embedded-processes model proposed by Cowan (1999, 2001) emphasizes the role of attention in WM. In this model, three organized components are distinguished: the long-term store, the activated memory, and the *focus of attention* (see Figure 1.3.4).

In contrast to Baddeley’s model, in which LTM and WM are two independent components, in Cowan’s model the activated memory component is the part of the long-term store that is in a temporarily activated state. A subset of this activated information becomes the *focus of attention* when used in cognitive operations. As in the Atkinson-Shiffrin model, it is assumed that newly arrived stimulus is first held in the sensory store for a short period and is only then transferred to the activated memory component. In this case, WM emerges as an “embedded” subset of information in the temporarily activated long-term store (Chein and Fiez, 2010). After a certain amount of time has passed, this store is deactivated. Information can not only be maintained in the *focus of attention* by subvocal rehearsal but also by searching through a set of memory items iteratively subjecting them to the *focus of attention*. The latter refreshing strategy is called attentional refreshing. Then, the central executive gathers those mental representations together for processing or manipulating.

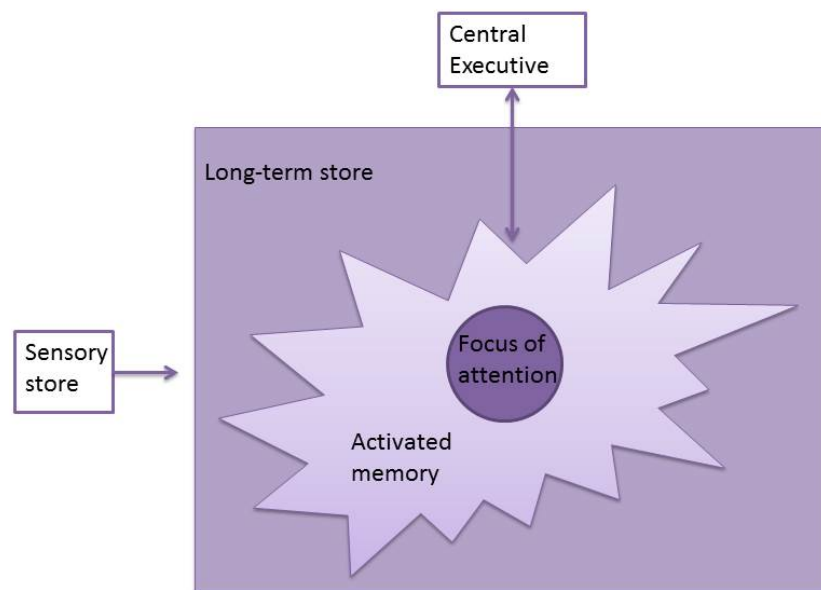


Figure 1.3.4: Cowan’s memory model adapted from Cowan (1999)

However, as mentioned above, the *focus of attention* can only cover a small amount of information at any given time. The model includes a single memory repository, comparable to the LTM system. What determines the level of performance in any kind of WM task is the (capacity-limited) span of the *focus of attention* and how the focus is directed throughout

the duration of the task (Cowan, 1995). Cowan’s model, as compared to Baddeley’s, tries to explain how memory works, regardless of the type of stimulus the person is receiving.

The models discussed are not necessarily mutually exclusive (Cowan et al., 2012). They share some features, for example they all describe a component that could generally be described as an attentional control mechanism that deals with the incoming information which sorts between what is relevant and irrelevant input.

## 1.4 Verbal vs. visuo-spatial WM

As noted when discussing the model by Baddeley and Hitch (1974), WM can be separated into verbal and visuo-spatial WM depending on the kind of incoming information. Thus, it follows from the model’s assumptions that we can differentiate between spatial and verbal WM. However, this is not a trivial conclusion. The question is, therefore, whether we should distinguish between different kinds of WM depending on the modality of incoming information. In what follows, I will consider evidence that suggests an affirmative answer to this question.

Studies show that spatial interference selectively impairs spatial WM (Vandierendonck et al., 2004; Alloway et al., 2010). In contrast, the continuous repetition of a word has shown to impair verbal serial recall but to not interfere with memory for spatial locations (Alloway et al., 2010). Moreover, several meta-analyses found different neural correlates for each type of stimuli (Owen et al., 2005; Rottschy et al., 2012). In addition, verbal WM can also be partitioned according to whether the information came from the auditory or visual system. Functional brain imaging studies using visually- and auditory-verbal WM tasks found specific activation patterns depending on the presented modality (Crottaz-Herbette et al., 2004; Rodriguez-Jimenez et al., 2009). Therefore, based on the assumption that there are different WM modalities as well as different neural correlates implicated in each one, in

the present thesis, I will specifically focus on visual verbal working memory (vvWM) (i.e., working memory for visually presented verbal stimuli).

## 1.5 Measuring visual verbal WM capacity

Several tasks can be used to measure the vvWM capacity. In this section, I will present some of the most common tests found in the WM research: span tasks,  $n$ -back task, Sternberg, and delayed match-to-sample task (DMTS) (Byrne, 2018). Some of them can also be used to assess visuo-spatial WM domain by changing the presented stimuli.

### 1.5.1 Span tasks

The first complex span task published, the reading span task, was developed by Daneman and Carpenter (1980). The task consisted of presenting a series of sentences that the participants needed to read aloud. At the end of each sentence, subjects needed to decide whether the sentence was meaningful while at the same time memorizing the last word of each sentence. After reading all of the sentences, they needed to recall all the memorized words in the presented order (see Figure 1.5.5a). It is labeled as a “complex” task because two tasks need to be performed at the same time: on the one hand, storage and processing of information of WM (namely, reading) while, on the other hand, storage of an element (namely, a word). Other complex span tasks followed a similar design, using other types of processing tasks and other types of materials to memorize (Case et al., 1982; Turner and Engle, 1989). For example, the operation span task interleaves solving mathematical operations with memorizing verbal stimuli (Turner and Engle, 1989). The WM load (i.e., task difficulty) can be increased or decreased by changing the number of items to recall.

There are also simple span tasks. To solve these tasks, as the name would suggest, a participant only needs to perform one task at once (see Figure 1.5.5b). Possibly the most well-known simple span task, is the so-called digit span task (Molz et al., 2010), which is a



subset of the Wechsler Adult Intelligence Scale (Wechsler et al., 2008). The participant is presented a visual (or auditory) sequence of digits one after the other at a speed of one digit per second. Afterwards, the subject is asked to recall the sequence of digits in the order of appearance. The investigator increases the length of the sequence of digits every time the participant answers correctly, up to nine digits. The participant's span is the length of the longest sequence of digits they can correctly recall. Once the sequence of digits is presented the participant is either asked to recall the sequence in the presented or reversed order. Thus, we usually talk about two versions of the task: the forward digit span and the backward digit span, respectively.

### 1.5.2 *N*-back task

Apart from simple and complex span tasks, vvWM can also be measured using updating tasks (Wilhelm et al., 2013). Of these, the *n*-back task is of particular interest (Kirchner, 1958). A wider adoption of the *n*-back task came only after the establishment of cognitive neuroscientific research. In this task, participants are presented with a sequence of stimuli. At each stimulus presentation, which constitutes a trial, the participant is asked to indicate whether the current stimulus matches the stimulus from *n* trials before. For instance, participants in a 2-back verbal visual task must compare the current letter with the letter displayed two trials before and determine whether the letters match (see Figure 1.5.5c). *N*-back is a highly demanding task, because it requires a temporary storage of the sequence of letters and a continuous updating of the storage by remembering new stimuli and discarding the old. WM load is increased or decreased by varying the *n*-back level. A further variation of the task reported in some studies also included “lure” trials in addition to match and non-match trials. During lure trials a stimulus is repeated, but not in the “correct” position to match (e.g., in a 3-back task, the second letter I in the sequence G I W I is a lure, but would be a match in 2-back). There exists also another variation of the task proposed by Jaeggi et al. (2003), which is known as the dual *n*-back task. This task consists of the simultaneously presentation of two independent sequences with different *n*-back modalities

of stimuli (e.g. an auditory  $n$ -back using letters and a visuo-spatial  $n$ -back using squares on different spatial locations).

Schmiedek et al. (2009) found a strong correlation ( $r = .96$ ) between the  $n$ -back task and complex span tasks (which included reading, counting, and rotation span tasks), suggesting that these two measured the same construct. However, Redick and Lindsey (2013) reported that the  $n$ -back and verbal complex span were only weakly correlated ( $r = .18$ ), whereas there was a higher correlation between  $n$ -back task and backward digit span task ( $r = .31$ ). This demonstrates that the results of WM research using different categories of tasks cannot simply be used interchangeably.

### 1.5.3 Sternberg and DMTS tasks

Another well-known task that also measures vvWM capacity is the so-called Sternberg task (Sternberg, 1966). The classic Sternberg task is comprised of three stages. First, participants need to memorize a list of letters or words (encoding period). Second, they need to maintain the list of items in their memory for a few seconds (delay or maintenance period). Third, a letter or word is presented and the participant must say whether the stimulus was in the previous list or not (recognition period) (See Figure 1.5.5d). The delay or maintenance period and/or the length of the stimulus list can be prolonged or shortened. As the delay or maintenance period and/or the list length stimuli increase, participants become less accurate and slower in the recognition period (Otani and Schwartz, 2018).

A similar task, called “delayed matching to sample” or “delayed match-to-sample” task (DMTS), is also structured in the same three-part way (Paule et al., 1998). The task starts with the presentation of a single stimulus that participants need to memorize (encoding period). This is followed by a delay or maintenance period. Then, participants are presented with a list of stimuli and they need to choose whether the previous memorized item is included in the list or not.

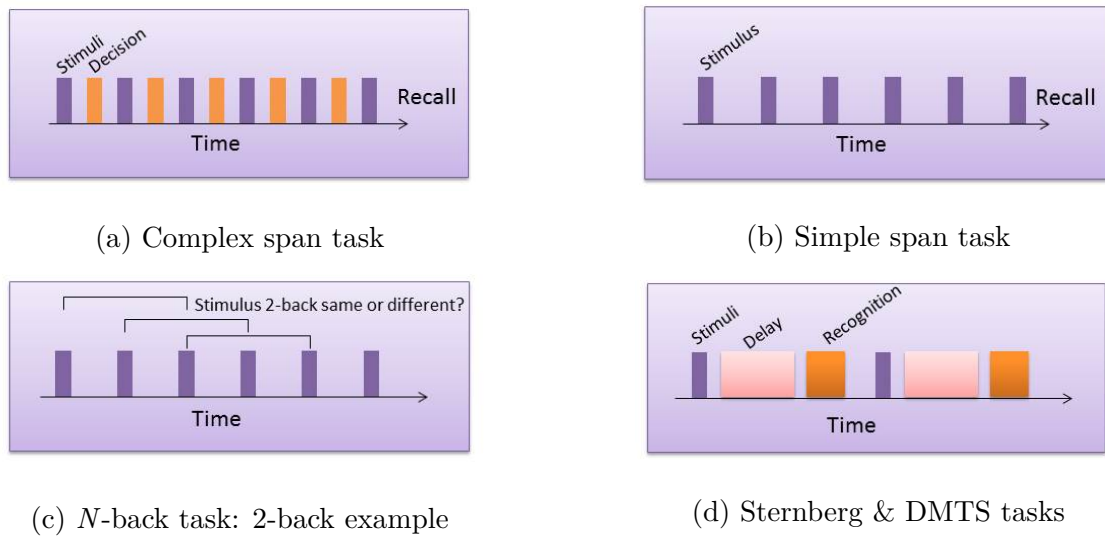


Figure 1.5.5: A schematic representation of WM paradigms. Inspired by Byrne (2018)

To sum up, there are several tasks that can be used to investigate vvWM (e.g., the complex and simple span tasks, the  $n$ -back task, the Sternberg task, and the DMTS task). Indeed,  $N$ -back and Sternberg tasks are the most suitable tasks for the scanner in order to study the brain activity related to WM. Accordingly, these two tasks are also the most frequent in the neuroimaging literature.

## 1.6 Measuring brain activity

Task-functional magnetic resonance imaging (task-fMRI) can be used to investigate the brain areas involved in vvWM tasks. This neuroimaging technique takes advantage of the blood-oxygen-level dependent (BOLD) contrast (Ogawa et al., 1990) which is based on the following principle: when a specific region of the brain is activated while solving a task, the cerebral blood flow (CBF) to that region increases. This, in turn, produces an increase in oxygenated hemoglobin and a decrease in deoxygenated hemoglobin. This change of hemoglobin type can be detected by the scanner since both types have different paramagnetic properties. Therefore, when participants lay inside the scanner, an increase in oxygenated blood flows to the regions that are being “activated” by solving the task. These

regional differences in CBF make it possible to delineate regional activity. Therefore, using task-fMRI, brain activity can be measured in an indirect and non-invasive way, making it a particularly suitable and accessible method for studying human brains.

In order to study the brain activity engaged during the cognitive component of interest—vvWM in this case—, a baseline task is also taken into consideration. This baseline needs to engage all of the same processes as the activation task with the exception of the cognitive component of interest. The neural correlates of vvWM are revealed once the activation levels recorded during the baseline task are subtracted from those recorded during the vvWM task. A hypothetical scenario will help explain this in more detail. Imagine a female subject is inside the scanner doing an  $n$ -back task comprising seven blocks of 3-back and seven blocks of X-back task. In this case the X-back task works as the baseline task. It is a pure attentional task in which participants need to press a button each time the letter “X” appears. We can only extrapolate pure vvWM activity once we subtract the brain activity observed during the X-back from the activity recorded during the 3-back task. This means that we will need to do the following contrast in order to investigate the areas that are specifically active during vvWM: 3-back - X-back. This way, we are guarding against drawing conclusions from a compound of cognitive constructs (such as activation related to visual sensory input, motor performance or attention). Therefore, the baseline (or control) task should be considered as a crucial component of the experimental design.

However, due to single imaging studies with small sample sizes, which lead to missed results, and the problems of reproducibility, it is essential to investigate the effects across individual studies (Radua and Mataix-Cols, 2009; Müller et al., 2018). In order to accomplish this we can perform a meta-analysis, which is a method that allows to summarize the results from published neuroimaging studies that tested a common hypothesis. There are two general approaches: image-based and coordinate-based meta-analyses. The first one is based on the full statistical images of the original studies, whereas the second one only uses the reported

coordinates from the published papers. To sum up, this method has evolved to help summarize and integrate the data coming from neuroimaging studies.

## 1.7 Neural correlates of visual verbal WM

Over the past years, several task-fMRI studies investigated the brain regions that are active while solving various vvWM tasks (Paulesu et al., 1993; Petrides et al., 1993; Desmond et al., 1997; Crosson et al., 1999; Lewis et al., 2004; Chang et al., 2007; Buchsbaum et al., 2011; Thürling et al., 2012; Moore et al., 2013; Chai et al., 2018). According to these studies, prefrontal and parietal cortex areas are the principal regions recruited during these kinds of tasks. However, as noted by Eriksson et al. (2015), there is still no consensus about the specific functional organization of the prefrontal cortex (PFC). During the past years, the importance of cerebellum and basal ganglia areas has been increasingly emphasized (Desmond et al., 2003; Pleger and Timmann, 2018). These regions have long been underestimated and only considered as motor control areas. Despite notable changes in the perspective, the specific contributions of these regions during the vvWM tasks are still a matter of debate. Limbic areas, such as the cingulate, have also been observed to contribute to vvWM-related neural activity, but their contribution has also been underestimated (Moore et al., 2013).

Owen et al. (2005) presented a quantitative meta-analysis of 24 studies of  $n$ -back tasks which used either verbal or non-verbal stimuli. They found a distinct fronto-parietal activation pattern depending on the stimuli used in the task. They reported that verbal tasks enhanced activation in the left ventrolateral prefrontal cortex, the medial and bilateral premotor cortex, the bilateral medial posterior parietal cortex, and the thalamus. Another meta-analysis by Rottschy et al. (2012) studied the neural correlates of WM. Their results also pointed towards a distinct brain activation pattern depending on the stimuli (e.g., Broca's area was only active when verbal stimuli were presented). They suggested that Broca's area, which is located in the left inferior frontal cortex (IFC), could be regarded as part of the *phonological loop*, specifically the *articulatory loop* (see section 1.3.2). This is in

line with the results reported in previous studies (Paule et al., 1998; Baldo and Cronkers, 2006; Aboitiz et al., 2010). The proposed neural correlates of the *phonological store* have been placed in the left supramarginal gyrus (SMG)—particularly in the left inferior parietal lobule (Paulesu et al., 1993). Regarding other components of Baddeley’s model, the *episodic buffer* has been related to the bilateral dorsolateral prefrontal cortex (DLPFC) (Balconi, 2013). Studies involving patients with different brain lesions support the notion of a *central executive* component, presumably located in frontal lobes (Smith and Jonides, 1997; Kane and Engle, 2002; Wager and Smith, 2003).

Importantly, even though there are distinct neural correlates depending on the presented stimuli, there are also brain areas activated during any kind of WM task. These are commonly referred to as the *core regions* (see 1.7.6) (Rottschy et al., 2012).

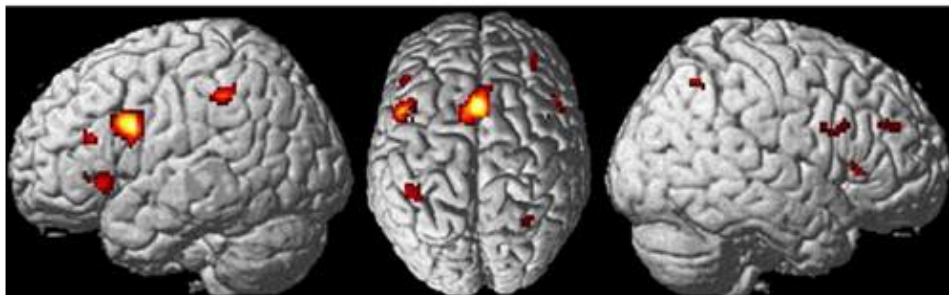


Figure 1.7.6: The working memory core network. Figure extracted from Rottschy et al., 2012, p. 839 [Fig.5]

### 1.7.1 Possible influential factors

Brain activity in response to specific vvWM tasks is likely mediated by different factors, such as age, sex, type of task (e.g., Sternberg, *n*-back...), difficulty of the task, individual performance, and others.

Age has repeatedly been identified as one of the most relevant influential factors. Several

theories have made an attempt to explain the age-related changes in WM activation. According to the “Hemispheric Asymmetry Reduction in Older Adults” (HAROLD) model by Cabeza (2002), a more bilateral pattern activation of prefrontal cortex should be observed in older as compared to younger adults. Since the appearance of this model, other theories have emerged in an attempt to explain the brain activity differences across the lifespan, such as the “Posterior-Anterior Shift in Aging” (PASA) (Davis et al., 2008), the “Compensation-Related Utilization of Neural Circuits Hypothesis” (CRUNCH) (Reuter-Lorenz and Cappell, 2008), and the “Scaffolding Theory of Aging and Cognition” (STAC) (Park and Reuter-Lorenz, 2009).

Although sex is generally regarded as a relevant influential factor and, accordingly, often added as a covariate to the analyses, its precise influence on vvWM-related neural activity remains controversial. Whereas some studies found an effect of sex on WM related activation (Bell et al., 2006; Zilles et al., 2016) others did not (Schmidt et al., 2009; Lejbak et al., 2011). The difference in observations can be partly explained by the varying influence of sex hormones involved in the control of the menstrual cycle, which have been shown to influence several cognitive functions including vvWM tasks (Mordecai et al., 2008; Joseph et al., 2012).

Finally, the type of WM task can be regarded as a relevant influential factor. Rottschy et al. (2012) meta-analysis reports that brain activity can be modulated by the WM task type or by the difficulty of the task (i.e., load). More specifically, they reported an association between task difficulty and activation intensity in the bilateral IFC. Last but not least, there is good reason to assume that mean reaction time (RT) in response to the vvWM task constitutes a relevant influencing factor since it is known to be correlated with WM load (Just and Carpenter, 1992).

## 1.8 Conclusion

As many other cognitive capacities, WM can be impaired in several mental disorders (e.g., Attention deficit/hyperactivity disorder (ADHD), depression, schizophrenia, and dementia) (Baddeley et al., 1986; Rose and Ebmeier, 2006; Forbes et al., 2009; Tillman et al., 2011). The fact that WM plays such an important role in everyday life as well as in higher-order cognitive functions (see section 1.2) raises a number of questions of both theoretical and clinical significance. Can WM capacity be increased? More specifically, can WM capacity be increased by training people in WM tasks? If yes, can such an increase be observed in elderly people showing already slight decreases in WM capacity? Does this potential increase in WM capacity transfer to similar WM tasks? I will try to answer these questions in the following chapter.



## 2 WM training

### 2.1 Introduction

The paper by Klingberg et al. (2002) is often cited as the first study to investigate the effects of WM training. Two groups participated in a computerized training consisting of four tasks: a visuo-spatial span task, a backwards digit span task, a letter span task (WM tasks), and a choice RT task. The difficulty level was adjusted in an adaptive way across trials for the experimental group. This means that the number of stimuli to be remembered by the participants changed depending on their task performance (i.e., the better the participant was, the harder the task was in the following trial). The control group performed a non-adaptive version of the tasks, meaning that the difficulty level was fixed. A strong limitation of this study is the fact that the control group performed fewer trials as compared to the experimental group. Nevertheless, the results showed that children suffering from ADHD improved their performance on trained tasks as well as on non-trained tasks requiring WM. The observed effects on performance in non-trained tasks are known as transfer effects of training. In other words, transfer effects refer to a phenomenon by which training on a particular task leads to an improvement in performance when solving another task. These effects are further specified depending on how closely they relate to the trained cognitive construct (e.g., practice-, direct-/near-/nearest-/immediate-, or far-transfer effects). This means that there are several types of transfer effect depending on the level of generalization (Linares et al., 2019). However, the standards for the different classifications are still a subject of debate.

Shortly following this study, the research on WM training underwent a rapid expansion (Nyberg et al., 2003; Olesen et al., 2004; Hempel et al., 2004; Buschkuehl et al., 2008; Jaeggi et al., 2008; Li et al., 2008; Borella et al., 2010; Redick et al., 2013; Minear et al., 2016)... Whereas some studies used updating tasks for their training (Jaeggi et al., 2008; Minear et al., 2016), others used complex span tasks (Chein and Morrison, 2010; Harrison et al.,

2013; Minear et al., 2016). In all of these studies, training interventions typically involved intensive and prolonged practice on one or more WM tasks. In a review by von Bastian and Oberauer (2014), authors claimed that improvement in WM capacity was dependent on the adequacy of the training. In the following section, I will review the literature on the behavioral and neural effects of vvWM training in healthy participants, considering younger and older populations separately.

## 2.2 Visual verbal WM training effects

Jansma et al. (2001) published one of the earliest studies to specifically investigate vvWM training effects. Fifteen healthy adult participants were trained using the Sternberg task for a total of approximately 45 minutes. After a practice session, the authors report observing a reduction in activity in the DLPFC, the right superior parietal cortex, and the supplementary motor area (SMA) during a verbal task. This study also reported that the participants' responses became faster, more stereotyped, and more accurate after practice. They hypothesized that these changes were due to a shift from controlled to automatic processing. This idea comes from the dual-processing theory, in which novel performance requires controlled processing whereas practiced performance is based on more automatic processing. Three years later, Olesen et al. (2004) published a paper in which they investigated changes in brain activity following two types of WM training in healthy human adults. Both trainings lasted for a period of five weeks. In the first experiment, three participants trained on one visuo-spatial WM task and two verbal WM tasks each day with the difficulty adaptively adjusted to the participant's performance. An increase in activity was observed in the prefrontal and parietal regions during a task-fMRI conducted after the training was completed. Moreover, a decrease in activity was also observed in the cingulate sulcus after training. Other studies investigated the neural effects of a pure vvWM training (e.g., using the  $n$ -back task) (Beatty et al., 2015; Miró-Padilla et al., 2019). On the one hand, Beatty et al. (2015) studied the effects of three 20-minute  $n$ -back training sessions (namely, 2- and 3-back levels) on healthy adults. The experimental group performed significantly better on a related task (namely, the

DMTS) and exhibited stronger brain activity in the left IFC, the right posterior parietal cortex, and the cerebellum as compared to the active control group after training. On the other hand, Miró-Padilla et al. (2019) studied the effects of adaptive verbal  $n$ -back training. They found an improvement in terms of behavioral performance in the trained task and decreased activation in the frontal superior cortex, the inferior parietal cortex, the anterior cingulate cortex, and the middle temporal cortex, all of which are believed to be WM-related areas.

There have also been studies that investigated the transfer effects of verbal WM training (Dahlin et al., 2008a; Chein and Fiez, 2010; Harrison et al., 2013; Kühn et al., 2013; Minear et al., 2016; Fellman et al., 2017). Dahlin et al. (2008a) investigated the effects of five-week long vvWM training using a letter memory task and five other updating tasks. In their first experiment, the participants were younger adults. The training group showed larger gains in a letter memory task compared to the control group. The task consisted of participants recalling the last four letters presented as quickly as possible once the presentation list ended. The control group did not receive any training (that is, a passive control group was used in the study). Before and after the updating task training, participants were also tested on a 3-back task and a Stroop task<sup>1</sup>. A significant improvement was found in the experimental group for the 3-back task, but not for the Stroop task, as compared to the control group. These results suggest near-transfer effects, given that there was an improvement in a near-transfer task. On the neural level, greater activity in the left striatum was observed in the participants that underwent training. The same participants also exhibited decreased fronto-parietal activity when performing a letter memory task. During the transfer task (namely, the 3-back) training-related brain activity increases were reported in the left striatum and frontal

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<sup>1</sup> The Stroop task is a psychological test in which participants are presented with names of colors (e.g. blue, red, green, yellow) printed in color that is either congruent or incongruent with the color word (e.g. the word “blue” printed in red ink). They are instructed to denote the color ink ignoring the names of colors. Participants take longer time to answer correctly when there is a mismatch between the color ink and the name of the colors, leading to a cognitive interference. This task measures the ability to inhibit cognitive interference.

cortex. These results suggested that transfer occurs because there has been a shift from prefrontally controlled functions to more automatized striatal functions, as predicted by Kühn et al. (2013). Regarding behavioral training effects, Chein and Morrison (2010) studied the effects of a four-week long adaptive complex WM span task training (namely, a verbal and spatially complex WM paradigm). They found that the experimental group not only showed improvement during the practiced tasks but also when solving other non-practiced tasks (e.g., Stroop task or reading comprehension). No transfer effects related to the other tasks were found (e.g., reasoning tasks or Raven's Advanced Progressive Matrices (APM)<sup>2</sup>). A similar conclusion can be drawn from the study conducted by Harrison et al. (2013). They found an improvement on similar tasks (namely, reading span and rotation span tasks) but not when considering far-transfer tasks (namely, Raven's APM, the number-series task, and the letter-sets task). Moreover, similar results were reported by Minear et al. (2016) who considered a verbal complex span training which did not yield any evidence of far-transfer effects.

In accordance with the results discussed above, Beatty et al. (2015) found an increase in brain activity in some areas following WM training, but Jansma et al. (2001) and Miró-Padilla et al. (2019) showed a decrease in brain activity in other areas after training. There are even studies reporting both increases and decreases in brain activity in some areas related to WM training effects (Olesen et al., 2004; Dahlin et al., 2008a; Kühn et al., 2013).

A recent meta-analysis by Salmi et al. (2018) reported that WM training-related areas exhibit increased activity, whereas the activity of other areas decrease, as we saw in the studies presented in this section. The verbal WM training-induced modulations reported in this meta-analysis (but no directionality) are depicted in Figure 2.2.7 below. Activation changes are wide-spread in the brain including the left IFC where the Broca's area is

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<sup>2</sup> Raven's APM is a nonverbal test that measures general fluid intelligence. It is made of 48 items and becomes increasingly difficult as progress is made throughout the test. In each item, which consists of a visual pattern, the participant needs to identify the missing element to complete the matrix.

located. This meta-analysis provides evidence of a non-uniformity in the direction in which WM trainings affect brain activity. In sum, the literature on the neural effects of vvWM in healthy young adults remains inconclusive. The observations on behavioral effects, on the other hand, are more homogeneous. Thus, most of the studies report performance improvements on the trained tasks as well as in similar (near-transfer), but not very different (far-transfer) tasks (Chein and Morrison, 2010; Harrison et al., 2013; Minear et al., 2016). Several meta-analyses were performed on studies addressing this issue, and even these came to contradictory conclusions: Melby-Lervåg et al. (2016) found no evidence of far-transfer effects and Soveri et al. (2017) found very small evidence of these effects, whereas Au et al. (2016) argued there is sufficient evidence to conclude otherwise. Hence, more research is certainly needed to draw a more final conclusion in this regard. In the following sections, I will consider training effects in older populations.

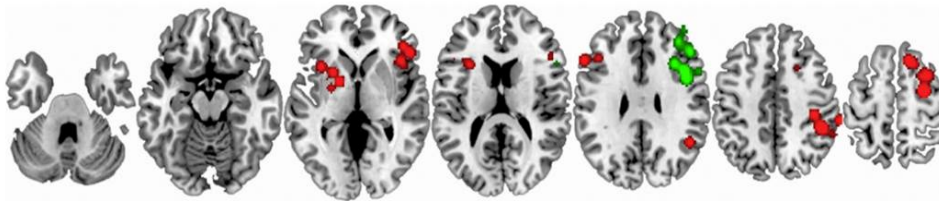


Figure 2.2.7: WM training-related activations separately analyzed for studies with verbal or spatial tasks. Figure extracted from Salmi et al., 2018, p.113 [Fig.4]. *Red: verbal working memory; Green: spatial working memory*

### 2.2.1 Visual verbal WM training effects in aging

Several studies have reported large age-related declines in verbal WM performance (Cansino et al., 2013; Pliatsikas et al., 2019). A meta-analysis by Bopp and Verhaeghen (2005) showed that older adults' complex WM capacity was only 74 % of the younger population studied. This age-related decline is accompanied by anatomical and functional brain alterations (Rajah and D'Esposito, 2005; Raz et al., 2005; Reuter-Lorenz and Sylvester, 2005). Not surprisingly, older people have become the prevalent target group for WM trainings. With

this in mind, in what follows I will provide a brief overview of the literature regarding vvWM training effects in older adults.

On the one hand, several studies report significant positive results of WM training in older adults. Borella et al. (2010) examined the effects of a vvWM training program in adults aged 65 to 75. They reported that the experimental group showed higher performance on a criterion task (i.e., a task similar to the training) as compared to the control group. Moreover, the experimental group showed prolonged beneficial effects of training at an eight-month testing follow-up compared to the control group. The researchers also found both near- and far-transfer effects of training. Brehmer et al. (2011) investigated the effects of a five-week verbal and visuospatial WM training in healthy older adults (average age: 63.2). The experimental group received an adaptive training whereas the active control group received a fixed low-level practice. They reported gains in the experimental group in both trained and non-trained tasks, showing that there were practice, direct/near-, and far-transfer effects. However, the authors' interpretation of the results is arguable, since the only far-transfer effect they report is sustained attention. It is not clear why the latter should count as a far- and not a near-transfer effect. Regarding training-related neural effects, the experimental group as well as the active control group showed a decrease in brain activation in neocortical areas during a visuospatial task performed in the fMRI, but greater activation decreases were observed in the experimental group specifically in the high load WM condition. As a follow up to the study, Brehmer et al. (2012) investigated the same training effects in younger adults (20 to 30 years old) and compared them to those in older participants (average age: 63.8). Both adaptive training groups improved their performance. However, the younger adults showed larger performance gains. Transfer effects were tested not only after the training but also three months later. Results indicated presence of practice, direct/near-, and far-transfer effects in both age groups and even in the three-month follow-up. The same limitation regarding the far-transfer effects applies to the conclusions drawn in the follow-up study, as well. Therefore, the results about far-transfer effects in older populations are far from conclusive. Near-transfer effects in older

populations were also observed in other studies (Richmond et al., 2011; Heinzl et al., 2014, 2016; Payne and Stine-Morrow, 2017). Moreover, there have been also other studies which found prolonged training benefits (Dahlin et al., 2008b; Carretti et al., 2013; Zinke et al., 2014).

On the other hand, several studies report a lack of evidence of training benefits following WM training. Dahlin et al. (2008b) investigated the effects of WM training in older adults. They report the older experimental group (average age: 68.3) revealed training-related activity increases in the left striatum as compared to the control group (average age: 68.4) during the letter memory task. However, no significant changes were found in the 3-back transfer task. It is important to note that the improvement in performance of older adults was considerably lower than the improvement in performance reached by younger adults after two weeks of training. This is in agreement with a view that older populations can benefit from training, albeit to a lesser degree than younger populations (Li et al., 2008). Finally, Tusch et al. (2016) studied the effects of a five-week adaptive verbal and visuospatial WM training (namely, Cogmed) in older adults. The experimental group (average age: 74.47) did not show transfer effects in an  $n$ -back task compared to the active control group (average age: 76.84), showing that this specific training did not yield transfer effects.

As mentioned above, there is considerable debate whether and how WM training produces far-transfer effects in older adults. Some studies demonstrate far-transfer effects to some extent (Borella et al., 2010; Brehmer et al., 2011, 2012), see a meta-analysis by Karbach and Verhaeghen (2014) but others studies do not (Dahlin et al., 2008b; Tusch et al., 2016). Therefore, the literature on the behavioral effects in older populations is also not conclusive. Regarding neural effects, literature specifically on vvWM training brain changes in older populations is sparse (Dahlin et al., 2008b; Brehmer et al., 2011; Heinzl et al., 2016). Interestingly, Heinzl et al. (2016) found a decrease in brain activity following a verbal  $n$ -back WM training in the right lateral middle frontal gyrus/caudal superior frontal sulcus during the trained task as well as during a condition in the Sternberg task.

In summary, findings on the effects of WM training both in younger and older populations are still quite heterogeneous. Methodological differences between these studies can be assumed to strongly contribute to this result heterogeneity. In the next section, I will therefore address the most relevant methodological aspects in the context of WM training studies.

## 2.3 Methodological issues

The inconsistent results regarding WM training effects can be at least partially explained by the methodological differences between studies. I will discuss the most relevant in this section.

First, a common limitation in the experimental design of several of the studies reviewed above is the lack of an adequate control group. Several studies compared the experimental group to a “no-contact” (or passive) control group (Olesen et al., 2004; Dahlin et al., 2008a,b; Chein and Morrison, 2010; Heinzl et al., 2016; Miró-Padilla et al., 2019) or even failed to have a control group at all (Jansma et al., 2001). While using a “no-contact” control group controls for test-retest effects<sup>3</sup>, it does not account for the effects of an interventional program or expectancy effects<sup>4</sup> (Morrison and Chein, 2011; von Bastian and Oberauer, 2014). This severely limits any conclusions drawn from the reported results. Thus, using an active control group would be preferable, with the participants in the active control group training on a low-demand, non-adaptive version of the training paradigm. Indeed, several studies that we discussed previously reported using this kind of control groups (Borella et al., 2010; Brehmer et al., 2011, 2012; Carretti et al., 2013; Harrison et al., 2013; Beatty et al., 2015;

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<sup>3</sup> The rest-retest effect can occur when the change in the performance is due to the repeated testing and not due to an actual improvement.

<sup>4</sup> The expectancy effect (or *Pygmalion effect*) can occur when an incorrect idea by the investigator about the participant leads the investigator to act in a specific way that elicits the expected behavior from the participant.



Minear et al., 2016; Tusch et al., 2016).

Second, the literature lacks a design standard regarding the duration, intensity and frequency of the WM training. Participants in some studies underwent a short and (presumably) intense training lasting a few days or even only one day (Jansma et al., 2001; Borella et al., 2010; Beatty et al., 2015) whereas others trained over a span of several weeks whereby the number of weeks likewise differed between the studies (Olesen et al., 2004; Dahlin et al., 2008a,b; Chein and Morrison, 2010; Brehmer et al., 2011, 2012; Carretti et al., 2013; Harrison et al., 2013; Heinzl et al., 2016; Minear et al., 2016; Tusch et al., 2016; Fellman et al., 2017; Miró-Padilla et al., 2019). It seems plausible that differences in duration and intensity of training have differential effects on both neural and behavioral levels. Jaeggi et al. (2008) argued that transfer-effects are “dose-dependent”, meaning that the longer the participants train, the longer the transfer effects will last. This hypothesis was supported by a meta-analysis, which reported that training dose and session duration moderated the effects of the WM training (Schwaighofer et al., 2015). It has been suggested that there is an initial increase of WM-related activity at the beginning of training which is followed by a decrease in activity at the end of training, showing an inverted U-shape pattern (Dahlin et al., 2008a; Kühn et al., 2013). However, this hypothesis has not been confirmed.

Third, the reported studies also differ with regard to type, modality, and adaptability of the training tasks. For example, whereas some studies used a combination of verbal and visual WM training (Olesen et al., 2004; Dahlin et al., 2008b; Chein and Morrison, 2010; Brehmer et al., 2011; Harrison et al., 2013; Tusch et al., 2016), others employed only verbal WM training tasks (Carretti et al., 2013; Heinzl et al., 2014; Beatty et al., 2015; Minear et al., 2016; Fellman et al., 2017; Miró-Padilla et al., 2019). Some studies used updating tasks and others complex span tasks. Some performed an adaptive version of the task (Olesen et al., 2004; Dahlin et al., 2008b,a; Chein and Morrison, 2010; Harrison et al., 2013; Heinzl et al., 2014; Minear et al., 2016; Fellman et al., 2017), whereas others did not (Jansma et al.,

2001; Beatty et al., 2015).

Fourth, the reported training conditions also vary across the literature. For example, in some studies, participants trained in proximity or even under direct supervision of the investigators (Jansma et al., 2001; Carretti et al., 2013; Minear et al., 2016; Miró-Padilla et al., 2019). This can lead to observer’s paradox effects (i.e., effects due to the presence of the investigator). Specifically, the meta-analysis by Schwaighofer et al. (2015) suggested that supervision of the training is a moderator that has an influence on the WM training effects.

Fifth, some studies categorize the demographic groups rather coarsely (see sections 2.2 and 2.2.1). Studies with participants from older populations did not differentiate between middle-aged, elderly, and old adults. This distinction is important given that the rate of change of neural plasticity is much lower in more advanced ages, meaning that the neural effects can differ drastically between “older adults” (Jones et al., 2006). Accordingly, it seems plausible that WM training might be more beneficial for middle-aged and elderly adults than for old adults (Buschkuehl et al., 2008; Borella et al., 2010).

Sixth, the effect of participants’ motivation is underestimated in most studies which often leads to participant drop out (Dahlin et al., 2008a; Carretti et al., 2013; Harrison et al., 2013; Minear et al., 2016; Tusch et al., 2016). It has been observed that participants’ motivation impacts training gains, especially in older populations (Carretti et al., 2011). Moreover, it seems plausible that the least motivated participants are more likely to discontinue training on harder tasks. Thus, a control group might be more likely to contain less motivated participants, which could then drive the performance difference between experimental and control group. The question could be reversed, namely, does the type of task influence motivation? For example, are participants performing a non-adaptive task more likely to get demotivated during the course of the study? However, there is no immediately apparent way to control for these possible limitations.

## 2.4 Conclusions

In this chapter, I have provided an overview of the literature on the effects of WM training and, specifically, of various tasks related to vvWM. I have discussed how WM capacity can be improved following different kinds of training. Specially, I reviewed the reasons why the cognitive construct of WM and WM training itself is of special interest for older demographic groups. Finally, I have discussed several methodological limitations that could be driving the inconsistency between the results reported across the literature. The methodological design of the present project builds upon these limitations and takes them into account.

### 3 Knowledge gap

Throughout the introduction and the depiction of the current state-of-the-art research in the previous chapters, several questions arose that have yet to be addressed. First, there is no systematic overview of the neural correlates of vvWM, specifically, since the two relevant meta-analyses described in section 1.7 do not differentiate between auditory and visual verbal WM studies (Owen et al., 2005; Rottschy et al., 2012). Moreover, these meta-analyses do not provide accurate analyses of publication bias or heterogeneity. This could prove to be a major limitation when interpreting the reported results. In addition, as described in section 1.7.1 there are several factors that can be assumed to critically influence vvWM performance and associated brain activation patterns. It remains to be clarified, however, which of these are essential and should be taken into consideration in future vvWM studies.

Second, the literature on the neural effects of vvWM training in older adults is sparse (although see Dahlin et al. (2008b); Brehmer et al. (2011); Heinzl et al. (2016)). A decrease in brain activity following training has repeatedly been reported, however the results are far from conclusive which might be due to methodological differences between the reported studies and other general limitations. Moreover, there are no studies focusing on the behavioral and neural effects of vvWM training in a more finely defined older demographic group. Within this age cohort, the group of middle-aged adults is presumably of special interest, given that they are more likely to benefit from WM training as compared to old subjects.

## 4 Thesis Objectives

Taking into consideration the presented knowledge gap, the research presented herein aims to achieve two main goals.

First, in chapter 5, we will identify the neural correlates of vvWM using a state-of-the-art meta-analysis approach. As discussed above and to the best of my knowledge, this is the first meta-analysis focusing on this specific topic. Moreover, the meta-analysis is designed to overcome some of the common limitations described above by taking into consideration the aspects of publication bias and between-study heterogeneity. Possible factors influencing the neural correlates of vvWM were investigated (namely, age, sex, type of task, task difficulty, mean RT, and statistical threshold). Thus, this meta-analysis provides an updated and extended illustration of the neural correlates of vvWM in healthy humans using a coordinate-based approach.

Second, chapter 6 is aimed at investigating the behavioral and neural effects of an intensive, standardized vvWM training in a group of healthy middle-aged participants. We took into consideration a number of limitations found in the previous literature by carefully choosing the study design (i.e., active control group, adaptive online training, performance feedback after each session to increase motivation, regular check-ups on training progress). We specifically included participants between 50 and 65 years of age to minimize the influence of relevant age-related changes and to maximize the benefits of training. To the best of our knowledge, this is the first study investigating vvWM training effects in healthy middle-aged participants.

## **PART II: RESEARCH ARTICLES**



## 5 Neural correlates of visual verbal WM

This chapter includes the research article entitled “Neural Correlates of Verbal Working Memory: An fMRI Meta-Analysis”. The article discusses the results of a coordinate-based meta-analysis concerning the neural correlates of vvWM in healthy participants as well as the possible influential factors. The article was published in *Frontiers in Human Neuroscience* in 2019.

Contributions:

*Authors: Mónica Emch, Claudia Christina von Bastian, and Kathrin Koch*

The author of the thesis is the first author of this research article. M.E., C.C.B, and K.K. contributed to the conception and design of the study. M.E. selected the analyzed studies, performed the statistical analysis, and wrote the first draft of the manuscript. C.C.B and K.K. wrote sections of the manuscript. All authors contributed to manuscript revision, read and agreed on the submitted version.







# Neural Correlates of Verbal Working Memory: An fMRI Meta-Analysis

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Verbal Working memory (vWM) capacity measures the ability to maintain and manipulate verbal information for a short period of time. The specific neural correlates of this construct are still a matter of debate. The aim of this study was to conduct a coordinate-based meta-analysis of 42 fMRI studies on visual vWM in healthy subjects ( $n = 795$ , males = 459, females = 325, unknown = 11; age range: 18–75). The studies were obtained after an exhaustive literature search on PubMed, Scopus, Web of Science, and Brainmap database. We analyzed regional activation differences during fMRI tasks with the anisotropic effect-size version of seed-based d mapping software (ES-SDM). The results were further validated by performing jackknife sensitivity analyses and heterogeneity analyses. We investigated the effect of numerous relevant influencing factors by fitting corresponding linear regression models. We isolated consistent activation in a network containing fronto-parietal areas, right cerebellum, and basal ganglia structures. Regarding lateralization, the results pointed toward a bilateral frontal activation, a left-lateralization of parietal regions and a right-lateralization of the cerebellum, indicating that the left-hemisphere concept of vWM should be reconsidered. We also isolated activation in regions important for response inhibition, emphasizing the role of attentional control in vWM. Moreover, we found a significant influence of mean reaction time, load, and age on activation associated with vWM. Activation in left medial frontal gyrus, left precentral gyrus, and left precentral gyrus turned out to be positively associated with mean reaction time whereas load was associated with activation across the PFC, fusiform gyrus, parietal cortex, and parts of the cerebellum. In the latter case activation was mainly detectable in both hemispheres whereas the influence of age became manifest predominantly in the left hemisphere. This led us to conclude that future vWM studies should take these factors into consideration.

**Keywords:** verbal working memory, meta-analysis, neuroimaging, fMRI, subcortical areas, fronto-parietal activation, right cerebellum

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## INTRODUCTION

Working memory (WM) is a cognitive system that holds information available that is needed for complex cognition in the present moment (Baddeley, 2010; Oberauer and Hein, 2012). It has been shown that WM capacity is a strong predictor of a wide range of complex cognitive tasks such as analytic problem solving, language acquisition, and reading comprehension

(Daneman and Carpenter, 1980; Engle et al., 1999; Wiley and Jarosz, 2012). There have been several attempts to understand the organization of human WM. The arguably most influential model is the multiple-component model proposed by Baddeley and Hitch (1974). The authors hypothesized the existence of a “central executive” component, which controls the incoming information and passes the information to two subsystems: the “phonological loop” and the “visuospatial sketchpad.” Within the phonological loop, due to the interplay of its two components—the phonological store and the articulatory loop—the verbal material representation can be kept in an active state. Verbal information is processed in perceptual systems before it enters the phonological loop in which it is temporarily stored in the phonological store and maintained through the articulatory loop using subvocal rehearsal of the information. In addition to subvocal rehearsal, the articulatory loop is also thought to be involved whenever verbal information is presented visually: whereas auditory verbal information (e.g., spoken words) can directly enter the phonological store, visually presented verbal information (e.g., written words) must first be recoded into phonological information. In other words, subvocalization is necessary in order to reroute visually derived verbal material into the phonological store (Buchsbaum and D’Esposito, 2008). The visuospatial sketchpad is responsible for integrating visual and spatial information. Later, the “episodic buffer” was added (Baddeley, 2000). It binds the information from the different subsystems into integrated episodes. Alternative models proposed that WM holds any type of information in a state of heightened availability (Oberauer, 2010; Cowan et al., 2012) whereas others models have emphasized on the role of attentional control in WM (e.g., Kane and Engle, 2003; Unsworth and Engle, 2007). These different theoretical conceptualizations of WM are not necessarily mutually exclusive (Cowan et al., 2012), with common features including a variety of processes such as encoding, maintaining and retrieving information of various domains (e.g., letters, geometric forms, or words), and some attentional control mechanism that supports dealing with interference from irrelevant or distracting information. Thus, the neural correlates of WM may vary depending on the processes, the type of information, and the modality of stimulation (auditory or visual). Given the variety across studies with regard to WM domain and the lack of process differentiation in most studies, the present meta-analysis focused exclusively on visually presented verbal working memory (vWM) across all processes involved in WM.

### Visual Verbal Working Memory

Several fMRI studies over the past years have specifically investigated the brain areas involved in vWM (Honey et al., 2000; Veltman et al., 2003; Chen and Desmond, 2005; Narayanan et al., 2005; Wolf et al., 2006). They basically corroborated the general notion that a variety of brain networks are activated during vWM mainly including areas in the prefrontal cortex (PFC) and the parietal cortex as well as cerebellar and basal ganglia regions (Paulesu et al., 1993; Petrides et al., 1993; Desmond et al., 1997; Crosson et al., 1999; Lewis et al., 2004; Chang et al., 2007; Buchsbaum et al., 2011; Thürling et al., 2012; Moore et al.,

2013; Chai et al., 2018). Previous meta-analyses have indicated that the left PFC might be predominantly involved in vWM processes whereas the right PFC seems to be more strongly involved in spatial WM, leading to a lateralization of this region due to different input (Wager and Smith, 2003; Owen et al., 2005). However, there is no general consensus on the functional organization of the PFC (Eriksson et al., 2015). Functional neuroimaging studies suggested that the articulatory loop is associated with the left inferior frontal cortex—where Broca’s area is located –, left supplementary motor area (SMA), left premotor cortex (BA6), and left insula. The phonological store has been shown to be associated with the left BA 40, corresponding to the left supramarginal gyrus located in the left inferior parietal lobule. Thus, these regions are essential for any kind of vWM task (Paulesu et al., 1993; Smith and Jonides, 1998; Henson et al., 2000; Buchsbaum and D’Esposito, 2008). Moreover, parietal activation has been interpreted as a buffer for modality-specific information. Whereas, the relevance of prefrontal and parietal regions for vWM has long been recognized, the cerebellum came into focus only some years ago. Originally regarded mainly as a structure involved in motor control and coordination, its involvement in higher-order cognitive processes, such as vWM, is no longer called into question (Ravizza et al., 2006; Hayter et al., 2007; Cooper et al., 2012; Thürling et al., 2012; Tomlinson et al., 2014). More specifically, it has been suggested that the cerebellum plays a relevant role in subvocal rehearsal, but the specific contribution of the cerebellum to the various processes involved in vWM is still a matter of debate (Desmond et al., 2003; Pleger and Timmann, 2018). Like the cerebellum, the basal ganglia (BG) are critical structures for motor control by enhancing desired motor behaviors and suppressing undesired ones (Alexander et al., 1986; Mink, 1996). In addition, the BG are involved in various cognitive processes, such as language production and working memory (McNab et al., 2008). Again, for many years, fMRI studies on vWM tended to focus on cortical structures such as parietal and frontal regions, underestimating the relevance of BG structures such as caudate, putamen and globus pallidus. Finally, limbic areas, such as cingulate, are known to be involved in vWM, but its contribution has likewise long been underestimated (Moore et al., 2013).

### Influencing Factors in the Neural Correlates of vWM

Activation in these brain regions can be influenced by several factors, such as age, gender, and type and difficulty (i.e., WM load) of the fMRI task. Moreover, the activation can be assumed to depend on individual performance (e.g., response velocity/speed as assessed by mean response times) and the statistical threshold which analyses are based on.

#### Age

Older adults compared to younger adults have been found to show a more bilateral pattern of prefrontal cortex activity under comparable task demands, a finding which constituted the basis of the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model (Cabeza, 2002; Cabeza et al., 2004). One hypothesis is that bilateral activity in older adults

could reflect a functional compensatory mechanism, in which age-related asymmetry reductions compensate neurocognitive decline leading to a less lateralized brain activity. This is known as the compensation view. A second hypothesis is the so-called dedifferentiation view which assumes a less specific recruitment of neural networks due to gradual changes occurring with age. In a PET study, Reuter-Lorenz et al. (2000) showed that PFC activity in younger adults was left lateralized for verbal and right lateralized for spatial stimuli, whereas older adults presented a bilateral PFC activation for verbal and visual tasks. This model is not only supported by functional neuroimaging results but also by behavioral results from a letter matching task (Reuter-Lorenz et al., 1999). Apart from these models, a number of other theories related to age differences in brain activation have been proposed, such as the Posterior-Anterior Shift in Aging (PASA). This theory assumes both frontal over-activation and posterior midline cortex under-activation in older adults compared to younger ones (Davis et al., 2009). The Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) proposes that people will activate more cortical regions if task difficulty increases (Reuter-Lorenz and Cappell, 2008). Finally, the Scaffolding Theory of Aging and Cognition (STAC and STAC-r) suggests that the increased frontal activation with age is a marker of the adaptive human brain indicating a compensation for the structural and functional decline going along with aging (Park and Reuter-Lorenz, 2009). This theory takes a holistic view by considering compensation a normal process involved in our daily lives in order to be able to achieve our goals.

## Gender

The influence of gender in the context of WM and, more specifically, vWM, is still rather controversial, with some studies reporting no gender effects (Bell et al., 2006; Schmidt et al., 2009) and others reporting significant differences between male and female participants (Lejbak et al., 2011; Zilles et al., 2016). The controversial results might be due to the potential influence of sex hormones, which have been shown to influence several cognitive functions including vWM (Mordecai et al., 2008; Joseph et al., 2012). Sex hormones are known to fluctuate with, for instance, menstrual cycle or hormonal contraception. However, most studies did not provide any information on these aspects which may explain the result heterogeneity to some degree.

## Additional Factors (Tasks, Load, Mean, Reaction Time)

A previous meta-analysis showed differences in brain activity due to WM task type (Rottschy et al., 2012). They found that n-back and Sternberg tasks, which are typical fMRI WM tasks, not only showed differences in mental processes but also in brain activation. Moreover, tasks can vary in their difficulty through modulating the WM load (i.e., the number of items that need to be remembered). Load effects reflect the neural activation related to the increasing memory demands of information (Cowan et al., 2012; Cowan, 2017). Rottschy et al. (2012) found that load effects were mainly associated with activation in the bilateral inferior frontal gyrus. Finally, Honey et al. (2000) demonstrated

that prolonged mean reaction times (RT) in response to a vWM task could influence activation in WM related brain regions. Therefore, these findings suggest that all the previously mentioned potential factors should be taken into consideration.

## Aim of the Study

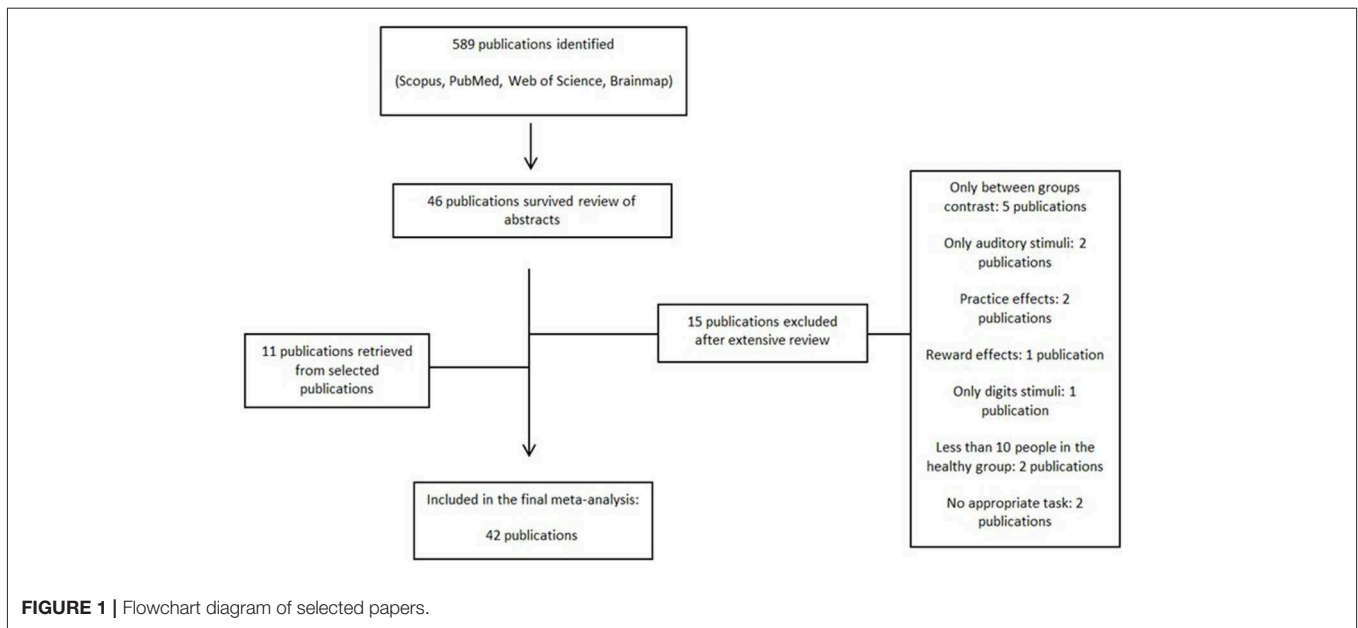
Against this background, the first aim of the present study was to provide an updated and extended meta-analysis of the neural correlates of vWM in healthy humans using a coordinate-based meta-analysis. The second aim was to find out more about the role of the potential moderators (age, gender, type and difficulty of the fMRI task, mean RT, and statistical threshold). Although task performance which is related to the difficulty level could be another potential factor, it was not taken into consideration due to the heterogeneous assessment in the selected studies (i.e., absolute correct values, percentage of correct values, accuracy) as pointed also by Meule (2017). To our knowledge this is the first meta-analysis to study these factors in vWM. A better knowledge about their influence on the neural correlates of vWM will increase understanding of the general mechanisms of vWM as well as help to improve methods and analyses of future vWM studies.

## MATERIALS AND METHODS

### Literature Search and Inclusion of Studies

An exhaustive literature search was conducted on whole-brain fMRI studies on vWM from January 2000 to December 2017. We searched the databases PubMed, Scopus and Web of Science for English-language studies with the combination of the following key words: “n-back,” “DMTS,” “Sternberg,” “delayed matched to sample,” “delayed match to sample,” plus “verbal working memory,” “fMRI,” “healthy.” The Brainmap database was also searched with their respective search criteria (Subjects Size is more than 10, Experiments Paradigm Class is Delayed Match to Sample/n-back, Experiments Imaging Modality is fMRI, Conditions Stimulus is Visual Letters, and Subjects Handedness is Right). Further studies (11 publications) were identified through chasing citations from the selected studies (see **Figure 1** for flowchart diagram). The “Meta-analysis of Observational Studies in Epidemiology” (MOOSE) guidelines Stroup et al. (2000) were used for the literature search and selection of studies. All articles were identified, selected and coded by a single investigator (M.E.). The same investigator double-checked the manually extracted peak coordinates and effect size values from the selected studies.

The criteria for inclusion were whole-brain analyses with reported results in a standard reference space (Talairach or MNI), inclusion of more than 10 healthy subjects and studies with clear boundaries between inclusion and exclusion criteria. Studies were excluded if they only included region-of-interests (ROI) analyses, did not report peak coordinates, investigated between- or within-group effects of pharmacological treatment, disease, living conditions, or used reward trials or emotional retrieval. We also excluded studies that re-analyzed previously reported data to avoid overestimating the effects. Positron emission tomography (PET) experiments were also not included in this meta-analysis due to methodological differences (e.g.,



differences in temporal resolution between PET and MRI) and differences in the underlying physiology (i.e., BOLD contrast vs. glucose mechanism).

## Comprehensive Meta-Analysis

We first conducted a meta-analysis of all the vWM studies. The demographic and study characteristics are shown in **Table 1**. The vast majority of the selected studies used the SPM software (<https://www.fil.ion.ucl.ac.uk/spm/software/>) to perform their fMRI analyses (83.3% of studies) indicating a clear bias toward this software package. Coordinates and *t*-values included in the analysis are shown in **Supplementary Table 1**. When only *p*- or *z*-values were reported, they were transformed into *t*-values taking into account the sample size per study. The influence of gender (% female), mean age, type of fMRI task (DMTS including the Sternberg task or n-back), mean RT, and the type of threshold used in the study (uncorrected vs. corrected) were studied with meta-regressions. The majority of studies corrected for multiple comparisons by controlling the false-discovery rate (FDR), except for one study that used the family-wise error rate (FWE) and another one that used Bonferroni correction. Those studies presenting results with peak coordinates at  $p < 0.005$  or  $p < 0.001$  uncorrected (33.3%) controlled for the cluster-size with different thresholds (5, 8, 10, 17, or 25 contiguous voxels). On a side note—although IQ and years of education have been shown to be associated with WM performance (Fukuda et al., 2010; Boller et al., 2017), we could not assess these factors here because the majority of studies did not provide any information on IQ or years of education.

There are several established fMRI vWM paradigms: n-back, Sternberg, and delayed matching to sample (DMTS) tasks (Kirchner, 1958; Sternberg, 1966; Paule et al., 1998). N-back tasks include a sequential presentation of stimuli. Subjects have to decide whether the current stimulus is the same as the one *n*

positions before (e.g., the previous one in a 1-back condition or the one two positions back in a 2-back condition). In Sternberg tasks, a set of stimuli is presented simultaneously that need to be maintained over a certain period which is followed by a single probe stimulus for which participants need to decide whether it was part of the set or not. In DMTS tasks, a single stimulus is presented. After the maintenance period, a set of multiple probes is presented from which participants need to recognize the single stimulus they had to memorize. While n-back tasks are normally presented in the form of a block-design, DMTS and Sternberg tasks are presented in an event-related design.

## Load-Effect Meta-Analysis

To assess the neural correlates of increasing vWM load (i.e., the difficulty of the fMRI task), we performed a load-effect meta-analysis. We only included studies in which there was a contrast between higher and lower vWM loads, such as 3-back vs. 1-back or 3-back vs. 2-back. The selected studies are shown in **Supplementary Table 2**.

## Meta-Analytical Approach: ES-SDM

We used the anisotropic effect-size version of seed-based *d'* mapping software (<http://www.sdmproject.com>) to conduct coordinate-based meta-analyses. The software uses a voxel-based meta-analytic approach. First, a strict selection of the reported peak coordinates of gray matter differences was applied by only including the studies containing whole-brain analyses. This is essential in order to avoid biased results from some neuroimaging studies, in which more liberal statistical thresholds were used for some ROIs relative to the rest of the brain. Peak coordinates in MNI or Talairach and effect size values were manually extracted from each contrast of interest in each study. All *p*- or *z*-values were transformed into *t*-values using SDM web utilities. Second, a map for the activation in gray matter was created for each

**TABLE 1** | Characteristics of the 42 fMRI studies included in the meta-analysis.

References	Demographic data			% Fem	fMRI task		Phases	Mean RT (ms)	Mean accuracy (%)
	N	Mean age (age range)	SD age		Task	Contrast			
Altamura et al., 2007	18	27.4 (NA)	NA	38.9	Sternberg	Modulated by load and delay <sup>†</sup> , load alone <sup>†</sup>	Block design	999.2	87.83
Bunge et al., 2001	16	27.0 (18–40)	NA	18.8	Sternberg	Load 6 > load 4	E,M,R	NA	93
Cabeza et al., 2002	20	22.6 (NA)	3.7	35	DMTS	WM > baseline	E,M,R	1486	91.6
Cairo et al., 2004	18	27.5 (NA)	NA	55.6	Sternberg	Average across loads <sup>†</sup> , Linear regression with load <sup>†</sup>	E,M,R	NA	NA
Caseras et al., 2006	12	33.5 (24–45)	7.1	66.7	n-back	Modulated by load		635.8	89.83
Chen and Desmond, 2005a	17	28.6 (NA)	7.4	52.9	Sternberg	High load > low load (6 letters > 1 letter)	E,M,R	NA	84.6
Chen and Desmond, 2005b	15	22.5 (18–28)	2.7	46.7	Sternberg	High load > low load (6 letters > 2 letters) <sup>†</sup>	E,M,R	NA	88.5
Deckersbach et al., 2008	17	25.6 (NA)	5.9	100	n-back	2 > baseline		787.6	94.43
Desmond et al., 2003	13	55.6 (NA)	11.3	0	Sternberg	High load > low load (6 letters > 1 letter)	E,M,R	NA	NA
Dima et al., 2014	40	31.5 (NA)	10.4	50	n-back	1 > control, 2 > control, 3 > control <sup>†</sup>		1: 596 2: 659 3: 748	1: 100 2: 91.2 3: 72.8
Garrett et al., 2011	19	34.9 (NA)	12.5	31.6	n-back	1 > control, 2 > control <sup>†</sup>		558.2	97.26
Gruber et al., 2010	18	33.9 (NA)	11.5	61.1	DMTS	Task > control	E,M,R	NA	91.9
Honey et al., 2000	20	39.3 (NA)	13.6	0	n-back	2 > control		560	96
Johnson et al., 2006	18	37.4 (NA)	11.5	16.7	Sternberg	Modulated by load <sup>†</sup>	E,R	995	92.45
Karlsgodt et al., 2005	13	24.1 (NA)	3.5	53.8	DMTS	WM > baseline	E,M,R	843.3	95.2
Kirschen et al., 2010	16	21.7 (NA)	6.0	31.3	Sternberg	High load > low load (6 letters > 2 letters)	E,M,R	NA	NA
Knops et al., 2006	16	27.0 (NA)	7.7	0	n-back	2 > 1		983.5	NA
Lim et al., 2008	12	68.6 (NA)	6.2	58.3	n-back	1 > baseline		650	96.9
Lythe et al., 2012	20	26.7 (NA)	6.7	0	n-back	Activation with increasing load		722	88.1
Marquand et al., 2008	20	43,7 (NA)	8.3	65	n-back	2 > control		NA	NA
Marvel and Desmond, 2010	16	23.7 (19–28)	NA	62.5	Sternberg	Task > baseline	E,M,R	NA	NA
McMillan et al., 2007	14	25.6 (NA)	3.6	64.3	n-back	2 > control: identification, 2 > control: color <sup>†</sup>		1562.5	78
McNab et al., 2008	11	24 (22–34)	4.0	63.6	Sternberg	Task > control	E,M,R	1460	91.3
Meisenzahl et al., 2006	12	33.6 (22–48)	9.27	8.3	n-back	2 > control		752	NA
Monks et al., 2004	12	45.6 (NA)	3.5	0	Sternberg	All levels	E,M,R	1080	90

(Continued)

TABLE 1 | Continued

References	Demographic data			% Fem	fMRI task		Phases	Mean RT (ms)	Mean accuracy (%)
	N	Mean age (age range)	SD age		Task	Contrast			
Monks et al., 2004	12	45.6 (NA)	3.5	0	n-back	2 > control		NA	99.31
Mu et al., 2005	33	28.6 (18–45)	6.6	0	Sternberg	Task > control	E,M,R	621	NA
Narayanan et al., 2005	12	20.6 (19–26)	NA	41.7	Sternberg	WM > baseline	E,M,R	NA	NA
Norbury et al., 2014	15	38.3 (21–61)	NA	33.3	n-back	Tasks > control		932.6	NA
Ragland et al., 2002	11	32.2 (21–53)	NA	54.5	n-back	1 > control, 2 > control <sup>†</sup> , 2 > 1 <sup>‡</sup>		NA	NA
Ravizza et al., 2004	10	24.8 (NA)	4.5	50	n-back	3 > control		NA	NA
Ravizza et al., 2004	11	NA (NA)	NA	NA	n-back	3 > control		NA	NA
Scheuerecker et al., 2008	23	32.6 (NA)	9.9	17.4	n-back	2 > control		751	NA
Schlösser et al., 2008	41	29.2 (NA)	8.9	34.1	Sternberg	Alphabetize > forward	E,M,R	1700.4	88.3
Schmidt et al., 2009	25	34.4 (18–58)	13.2	0	n-back	Task > control		670	83.84
Schmidt et al., 2009	21	33.1 (18–58)	12.3	100	n-back	Task > control		673.3	88.92
Seo et al., 2012	22	38.3 (NA)	8.5	100	n-back	2 > control		966.5	95.5
Valera et al., 2005	20	33.0 (18–55)	10.6	40	n-back	2 > control		843	90.2
Veltman et al., 2003	21	22.7 (NA)	3.6	66.7	Sternberg	Modulated by load	E,M,R	790	94.7
Veltman et al., 2003	21	22.7 (NA)	3.6	66.7	n-back	Modulated by load		715	97.7
Walter et al., 2003	13	27.1 (NA)	4.7	61.5	n-back	2 > control: identification, 2 > control: color <sup>†</sup>		NA	NA
Walter et al., 2007	17	30.9 (NA)	8.8	47.1	Sternberg	L1 > control, L2 > control, L3 > control <sup>†</sup>	E,M,R	L1: 760 L2: 873 L3: 1020	L1: 93.2 L2: 90.9 L3: 87.1
Wishart et al., 2006	22	68.5 (25–75)	13.3	50	n-back	2 > control		NA	75.0
Wolf et al., 2006	15	28.1 (NA)	4.2	46.7	Sternberg	L2 > L1, L3 > L2 <sup>†</sup>	E,M,R	L1: 770.8 L2: 882.0 L3: 1034.5	L1: 95.5 L2: 92.6 L3: 93.0
Yan et al., 2011	28	20.9 (NA)	1.5	57.1	n-back	2 > control		617.4	95.9
Yoo et al., 2004	12	26.3 (20–36)	NA	33.3	n-back	2 > 1		NA	96.2

*n*, sample size; *SD*, standard deviation; *NA*, not announced; % *Fem*, percentage of female participants; *L*, level; *E*, encoding; *M*, maintenance; *R*, recall; *RT*, reaction time.

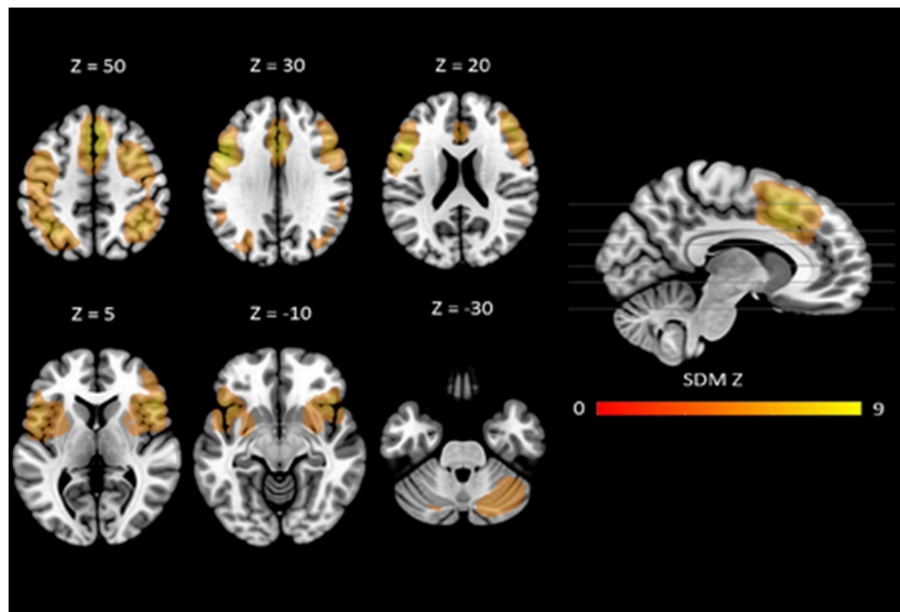
<sup>†</sup>Combination of several contrasts into the final study contrast.

<sup>‡</sup>Contrast selected for the load-effect meta-analysis.

study using the Automated Anatomical Labeling (AAL) atlas partitioned into 116 brain regions (Tzourio-Mazoyer et al., 2002). If a study included more than one contrast of interest, we adjusted for multiple contrasts by combining the created images of each contrast into one image for the final analyses. The ES-SDM software re-creates the maps from the studies by converting the *t*-value of each peak to Hedge's *g* (Alegría et al., 2016). Third, an anisotropic non-normalized Gaussian kernel was applied by

assigning different values to the different neighboring voxels based on the spatial correlation between them (Radua et al., 2014). At the end, we obtained a mean map by a voxelwise calculation of the mean of the study maps, weighted by the square root of the sample size, so that studies with larger sample sizes contributed more strongly (Radua and Mataix-Cols, 2009).

To assess the robustness of the main findings, we performed a whole-brain Jackknife analysis. Jackknife analysis consists of



**FIGURE 2** | Neural correlates of vWM estimated by meta-analysis. Results are displayed at  $p < 0.005$  (cluster size  $\geq 10$ ) projected on the MNI 151 T1 template.

repeating the statistical analyses several times by discarding one study each time thus demonstrating the stability of the results (Müller et al., 2018). Heterogeneity of effect sizes and publication bias were assessed with the  $I^2$  index and Egger's test (Egger et al., 1997; Müller et al., 2018). The  $I^2$  index provides the proportion of variability across studies that is due to true heterogeneity relative to that from sampling error (Higgins and Thompson, 2002). Egger's tests were used to test for asymmetry of funnel plots, serving as an indicator of publication bias (see **Supplementary Figure 1** for examples).

Statistical significance was determined with random-effects models. We used the default threshold for the calculated mean (voxel-level  $p < 0.005$  uncorrected, peak height threshold 1, minimum cluster extent 10 contiguous voxels) (Radua and Mataix-Cols, 2009). To control for multiple testing in the several meta-regressions we used a more conservative threshold, Bonferroni-corrected threshold of  $p < 0.001$ .

## RESULTS

### Comprehensive Meta-Analysis (42 Studies)

The mean map of brain regions of the whole-brain meta-analysis for vWM is shown in **Figure 2**. The majority of studies reported only task-positive activation. We observed extended activation patterns in the frontal lobe including left superior frontal gyrus (SFG), medial frontal gyrus, right middle frontal gyrus (MFG), right inferior frontal gyrus (IFG), triangular, orbital and opercular part of the right IFG, orbital and opercular part of the left IFG, bilateral SMA, bilateral precentral gyrus, and left rolandic operculum. There was also activation in parietal areas including left post-central gyrus, right angular gyrus, and left inferior parietal gyri (IPG). Moreover, there was activation

in the bilateral median cingulate, the left insula, the right lenticular nucleus (i.e., putamen and pallidum) and in bilateral cerebellum (crus I).

Robustness analyses showed that these results were preserved in all studies. Egger's tests indicated that there were some regions for which there was evidence of heterogeneity: left SFG, left SMA, left precentral gyrus, left post-central gyrus, right angular gyrus, left IPG, right median cingulate, left insula, and right cerebellum (crus I) (see **Table 2**).

Meta-regression analyses confirmed that mean age and mean RT moderated activation in some brain regions. Mean age was associated with decreased activation in the left rolandic operculum, left insula, left superior temporal gyrus (STG), left IFG (opercular part), left heschl gyrus, left post-central gyrus, left lenticular nucleus (putamen), and the right MFG. Mean RT was positively associated with activation in the left precentral gyrus and the left MFG (see **Figure 3** and **Table 3**). None of the other meta-regression analyses yielded any significant results.

### Load-Effect Meta-Analysis (16 Studies)

We found activation in several frontal areas: right SFG (dorsolateral and medial part), left SFG (medial part), right MFG, right IFG (triangular part), left IFG (triangular and opercular part), right SMA, bilateral precentral gyrus, bilateral rolandic operculum. Moreover, there was activation in several parietal areas (left post-central gyrus, left angular gyrus, left SPG, and bilateral IPG) as well as in the left anterior cingulate gyri, bilateral median cingulate gyri, left fusiform gyrus, and right cerebellum (crus I and hemispheric lobule VI) (see **Table 4**).

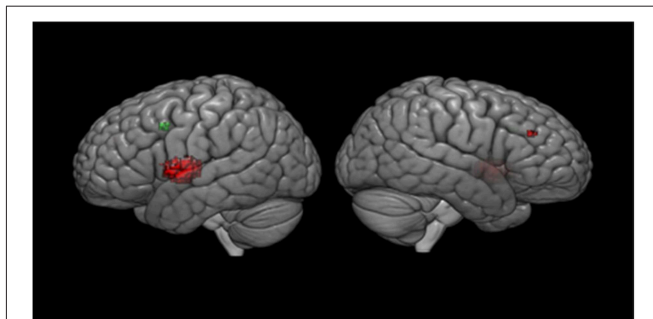
Jackknife analyses showed that the findings were preserved across studies, except for the right rolandic operculum and left fusiform gyrus, which were no longer detectable after discarding



**TABLE 2** | Comprehensive meta-analysis results.

MNI coordinates	SDM-Z	p-value	Region	Voxels	I <sup>2</sup>	JK	Egger test (p-value)
-50,12,28	8.985	<0.00005	L. inferior frontal gyrus, opercular part	758	51.98	45/45	0.374
-46,8,36	8.831	<0.00005	L. precentral gyrus	1807	58.65	45/45	0.001
4,18,44	8.534	<0.00005	R. median cingulate / paracingulate gyri	631	59.46	45/45	0.015
4,24,46	8.483	<0.00005	R. supplementary motor area	784	55.79	45/45	0.051
0,18,40	8.359	<0.00005	L. superior frontal gyrus, medial	772	55.76	45/45	0.027
-2,8,36	8.322	<0.00005	L. median cingulate / paracingulate gyri	510	4.06	45/45	0.314
-2,22,46	8.214	<0.00005	L. supplementary motor area	1166	62.59	45/45	0.020
50,26,2	7.580	<0.00005	R. inferior frontal gyrus, triangular part	1246	0.00	45/45	0.732
50,18,8	7.397	<0.00005	R. inferior frontal gyrus, opercular part	888	3.29	45/45	0.168
40,-58,44	7.259	<0.00005	R. angular gyrus	873	23.80	45/45	0.001
46,24,-6	7.237	<0.00005	R. inferior frontal gyrus, orbital part	401	2.47	45/45	0.561
-36,-54,48	7.055	<0.00005	L. inferior parietal gyri	1804	45.38	45/45	0.000
40,6,50	6.917	<0.00005	R. precentral gyrus	1297	0.00	45/45	0.656
-44,0,16	6.293	<0.00005	L. rolandic operculum	428	10.86	45/45	0.386
26,6,50	5.911	<0.00005	R. middle frontal gyrus	1604	0.00	45/45	0.083
-42,18,-6	5.724	<0.00005	L. inferior frontal gyrus, orbital part	446	54.76	45/45	0.000
-48,-22,46	5.496	<0.00005	L. post-central gyrus	1582	45.32	45/45	0.002
-36,8,0	5.006	<0.00005	L. insula	939	8.50	45/45	0.019
22,-76,-30	4.683	0.000005	R. cerebellum, crus I	1186	45.55	45/45	0.009
32,0,-10	4.249	0.000107	R. lenticular nucleus, putamen	577	0.77	45/45	0.086
24,0,-6	4.167	0.000177	R. lenticular nucleus, pallidum	32			
-20,-78,-30	3.641	0.002827	L. cerebellum, crus I	36			

Only one local peak per gray matter regions is displayed. Robustness analyses displayed for clusters > 100 voxels (as in Fullana et al., 2018). MNI, Montreal Neurological Institute; SDM, signed differential mapping; I<sup>2</sup>, percentage of variance attributable to study heterogeneity; JK, jackknife sensitivity test; L., left; R., right.



**FIGURE 3** | Meta-regression results. Results are displayed at  $p < 0.001$  on MNI 152 2009. Red color, age regressor results; Green color, RT regressor results.

two papers. We only observed heterogeneity in the right inferior parietal gyrus (see **Table 4**).

## DISCUSSION

The present comprehensive meta-analysis across 42 whole-brain vWM fMRI tasks showed vWM processing to be based on a fronto-parieto-cerebellar network and to involve also subcortical regions such as the cingulate, left insula and right lenticular nucleus. Thus, the present

results corroborate previously discussed networks, but also provide evidence for the involvement of additional regions that have been neglected in the past in the discussion of vWM processing.

## Dual-Selection Model

A tentative explanation of the results is provided by the dual-selection model. Nee et al. (2013) proposed this model based on a meta-analysis of 36 event-related fMRI studies aimed at understanding the executive processes of WM. According to this model the caudal superior frontal sulcus (SFS) is associated with a spatial selection while the mid-lateral PFC is especially sensitive to non-spatial content, matching the “where” and “what” based selections, respectively. This proposal was further corroborated by a previous meta-analysis of 24 experiments based on an n-back task (Owen et al., 2005). The results of the present meta-analysis lend further support to the dual-selection model given that we also found activation of the mid-lateral PFC (bilateral IFG, right MFG, and medial part of the left SFG). The left SFG appeared to be a heterogeneous region. The fact that we found a noticeable bilateral prefrontal activation in this meta-analysis suggests that the assumption of a strongly left-lateralized verbal WM activation in PFC should be reconsidered. However, it needs to be clarified that we did not include studies systematically comparing spatial vs. non-spatial WM. Therefore, these conclusions need to be drawn with caution because the mere fact that

**TABLE 3** | Meta-regression analysis.

Mean_age	Clusters showing a negative correlation with age			Maximum		Cluster	
	MNI Coordinates	SDM value	p-value	Voxels	Description	Breakdown	Voxels
	-48,-4,8	-2.387	< 0.00005	1204	L. rolandic operculum	L. rolandic operculum	415
						L. insula	332
						L. superior temporal gyrus	175
						L. inferior frontal gyrus, opercular part	115
						L. heschl gyrus	47
						L. post-central gyrus	34
						L. temporal pole, superior temporal gyrus	16
						L. lenticular nucleus, putamen	13
						L. precentral gyrus (undefined)	56
						R. middle frontal gyrus	10
						R. inferior frontal gyrus, triangular part	6
						48,38,24	-1.736
Mean_RT	Clusters showing a positive correlation with RT		Maximum		Cluster		
	MNI Coordinates	SDM value	p value	Voxels	Description	Breakdown	Voxels
	-46,10,42	3.949	0.00028	29	L. precentral gyrus	L. middle frontal gyrus	17
						L. precentral gyrus	12

MNI, Montreal Neurological Institute; SDM, signed differential mapping, R., right; L., left.

we found the same activation does not fully support the dual-selection model.

## Phonological Loop

We did not find activation of the left supramarginal gyrus, which is known to be important for the phonological store, but instead in the region where the supramarginal gyrus is located, the left inferior parietal cortex. The activation of this region was found to be heterogeneous, which tends to be in line with the hypothesis of Buchsbaum and D'Esposito (2008). They argue that the phonological store does not precisely correspond to a single specific functional brain region, but rather is associated with several brain regions that underlie neural processes from perception and production of speech. Surprisingly, the present meta-analysis did not reveal any activation in the Wernicke area although this is an essential area for the comprehension and/or production of verbal material (Binder, 2015). This area is assumed to comprise mainly the posterior part of the superior temporal gyrus as well as the occipito-parieto-temporal junction including the angular gyrus. However, the exact location of the Wernicke area is still a matter of debate also due to its comprehensive and partly heterogeneous functionality in the context of verbal processing. Moreover, the fact that we used the AAL atlas, which comprises relatively large brain regions, might also explain why we were not able to isolate activation

of this specific and somewhat ill-defined region. The fact that we did not find any activation in the right parietal cortex was also expected, since this region is assumed to serve spatial rehearsal. Hence, as opposed to the bilateral activation in the prefrontal cortex, activation in the parietal cortex turned out to be strongly left-lateralized, presumably due to modality. As predicted, we also found activation in the left IFG containing the Broca's area, as well as in the left SMA, which are components central to the articulatory loop. The fact that we did not find any activation in the premotor cortex could also be due to the atlas used. The AAL atlas does not contain this region because the labeled SMA embeds both the premotor cortex and the pre-SMA. Therefore, we cannot exclude that there was specific activation of the premotor cortex. In addition, there was activation in the left rolandic operculum, which is caudally adjacent to Broca's area. It has been demonstrated that this brain area is involved in speech production (Koelsch et al., 2009) and speech prosody processing (Wu et al., 2017). To the best of our knowledge, this is the first WM meta-analysis isolating activation specifically in this area. This finding may indicate that the majority of the participants used an overt rehearsal strategy during the vWM tasks. Further studies testing the impact of the opportunity for rehearsal during vWM tasks on brain activation are however needed to confirm this hypothesis.

**TABLE 4** | Load-effect meta-analysis results.

MNI coordinates	SDM-Z	p-value	Region	Voxels	I <sup>2</sup>	JK	Egger test (p-value)
-46,8,38	5.617	< 0.0000001	L. precentral gyrus	1315	52.15	15/15	0.152
46,34,18	5.502	< 0.0000001	R. middle frontal gyrus	1378	31.70	15/15	0.339
8,32,48	5.442	< 0.0000001	R. superior frontal gyrus, medial	387	5.78	15/15	0.828
-48,14,26	5.395	< 0.0000001	L. inferior frontal gyrus, triangular part	1211	55.42	15/15	0.107
-50,16,22	5.356	< 0.0000001	L. inferior frontal gyrus, opercular part	757	47.91	15/15	0.170
8,24,48	5.231	< 0.0000001	R. supplementary motor area	452	29.95	15/15	0.741
0,28,50	5.201	< 0.0000001	L. superior frontal gyrus, medial	892	38.10	15/15	0.864
-2,6,36	4.902	< 0.0000001	L. median cingulate / paracingulate gyri	429	7.39	15/15	0.746
4,6,38	4.879	< 0.0000001	R. median cingulate / paracingulate gyri	587	0.00	15/15	0.831
-40,-58,46	4.793	< 0.0000001	L. angular gyrus	120	0.00	15/15	0.415
-2,8,30	4.686	< 0.0000001	L. anterior cingulate / paracingulate gyri	633	4.28	15/15	0.687
50,30,4	4.646	< 0.0000001	R. inferior frontal gyrus, triangular part	1228	0.59	15/15	0.534
-38,-48,44	4.563	0.00000001	L. inferior parietal gyri	961	39.39	15/15	0.487
22,-80,-30	4.248	0.00000101	R. cerebellum, crus I	1443	8.61	15/15	0.883
40,-46,48	4.143	0.00000179	R. inferior parietal gyri	682	62.41	15/15	0.001
22,14,56	3.676	0.00002283	R. superior frontal gyrus, dorsolateral	94			
-50,-16,42	3.640	0.00002819	L. post-central gyrus	688	1.97	15/15	0.790
52,10,-2	3.434	0.00009483	R. rolandic operculum	144	11.73	14/15	0.700
30,-50,-34	3.401	0.00011838	R. cerebellum, hemispheric lobule VI	704	7.75	15/15	0.974
-50,-6,14	3.354	0.00015760	L. rolandic operculum	347	0.20	15/15	0.827
-26,-60,54	3.242	0.00029481	L. superior parietal gyrus	255	0.00	15/15	0.343
46,-10,46	3.160	0.00046253	R. precentral gyrus	348	0.00	15/15	0.624
-32,-76,-16	2.933	0.00154328	L. fusiform gyrus	320	0.55	14/15	0.725

Only one local peak per gray matter regions is displayed. Robustness analyses displayed for clusters > 100 voxels (as in Fullana et al., 2018). MNI, Montreal Neurological Institute; SDM, signed differential mapping; I<sup>2</sup>, percentage of variance attributable to study heterogeneity; JK, jackknife sensitivity test; R., right; L., left.

## Attentional Control

Many conceptualizations of WM include an attentional control mechanism that supports dealing with interferences such as from other items in memory. The right IFG has been proposed to be an important region for attentional control (Aron et al., 2003; Forstmann et al., 2008). Specifically, Aron et al.'s (2003) data strongly suggest that response inhibition is uniquely located in the right IFG, in particular in its triangular part. The data were acquired by studying patients with lesions of the right frontal lobe during a go/no-go task. Forstmann et al. (2008) found a direct linkage between structural and functional properties of the right IFG, and its role in response inhibition. Another fMRI study (Aron and Poldrack, 2006) found that the IFG targets the subthalamic nucleus (STN) and regions in its vicinity. The STN sends excitatory projections to the globus pallidus externus, which, in turn, suppresses the thalamo-cortical output; this is assumed to lead to an inhibition of the initiated response. Finally, a strongly right-lateralized network comprising the right IFG, the STN, and also the pre-SMA, is recruited during response suppression (Aron, 2007). It remains unclear, however, whether the right IFG triggers the STN directly or via the pre-SMA (Aron et al., 2014). We found a strong activation of the right IFG, especially in the triangular part, the right SMA—which also includes the pre-SMA in this atlas—and the right pallidum, giving support to the idea that these areas constitute a network subserving response inhibition in the context of vWM

processing. Indeed, a substantial body of behavioral research has found that attentional control as employed in response inhibition tasks is related to WM capacity (Kane and Engle, 2003; Unsworth and Engle, 2007, but see Rey-Mermet et al., 2019). Notably, heterogeneity analyses confirmed the stability of these networks indicating that activation in these regions is not likely due to a possible publication bias. However, it is important to mention that the selected studies did not manipulate attention. The fact that we found activation in the same areas that mediate response inhibition in other experimental contexts does not completely mean that they do so in the context of vWM.

In addition to the IFG, the angular gyrus has been found to be activated in the context of response inhibition (Wager et al., 2005). The angular gyrus is located in the posterior part of the inferior parietal lobule and has been found to be activated in a variety of tasks (Seghier, 2013). Some anatomical studies (Makris et al., 2005, 2009; Uddin et al., 2010) define the angular gyrus as an important seed point, given its strong interaction with temporo-frontal subsystems as well as regions such as hippocampus, caudate, and precuneus. It is a key component of the default-mode network and shows activation in most tasks demanding information retrieval (Spaniol et al., 2009; Kim, 2010). The role of this region in memory retrieval is plausible given its strong connectivity with the hippocampus. To the best of our knowledge, this is the first time that the right angular gyrus appears in a vWM meta-analysis. Considering that this region

has been reported to be important for inhibition and retrieval we conclude that the activation of the angular gyrus in the present meta-analysis may predominantly reflect the employment of attentional control during information retrieval. Although we cannot exclude the possibility of this region's activity being found due to presence of publication bias in the selected literature. Further studies allowing for a separate analysis of the retrieval process are however needed to further explore this assumption.

## Cerebellar and Subcortical Activations

It has been shown that cerebellum is connected not only to motor areas, but also to prefrontal cortical areas (Schmahmann, 1996); this suggests an involvement of the cerebellum in higher-order cognitive processes. A distinct cross-cerebro-cerebellar circuitry for vWM has been proposed with predominant involvement of right cerebellum, especially the lobule VI (Ng et al., 2016). In accordance with this proposal, earlier studies already pointed at the relevance of the right cerebellum in the context of vWM. Using inhibitory continuous theta burst stimulation (cTBS) Tomlinson et al. (2014) found that participants were less accurate during a verbal version of the Sternberg task if a trial was preceded by a stimulation of the right cerebellar hemisphere. Moreover, patients with right-sided cerebellar lesions have been found to be impaired in verbal memory, whereas patients with left cerebellar lesions turned out to be slower in a visuospatial task (Hokkanen et al., 2006). All these findings suggest a lateralized function of the cerebellum with its right hemisphere contributing mainly to verbal and its left hemisphere to visuospatial processing. Moreover, a meta-analysis (Stoodley and Schmahmann, 2009) analyzing cerebellum neuroimaging studies found that regions involved in vWM studies overlap with those involved in language tasks which is in agreement with domain-specific storage modules as in Baddeley's model. It corroborates the idea that vWM is more right-lateralized with a strong activation occurring mostly at the junction lobule VI/Crus I. Our results showing a significantly stronger activation in the right cerebellum (crus I) support this hypothesis. A case study of a right cerebellar hemispherectomy in an 18-years-old patient reported that the patient suffered from a disproportionate impairment of the rehearsal system, while the phonological store was preserved (Silveri et al., 1998). This could be due to anatomical connections between Broca's area, left SMA, right lobule VI and crus I of the cerebellum (Schmahmann, 1991). However, in the present meta-analysis, we did not differentiate between those processes and, thus, we cannot further investigate whether the right cerebellum is mainly involved in rehearsal. Still, our analysis provides clear evidence for the relevance of the right cerebellum, especially crus I, in the context of vWM processing. Further studies disentangling the different vWM processes are warranted to elucidate the specific function of the right cerebellum in vWM.

Apart from the cerebellum, a number of additional subcortical areas are assumed to be relevant for vWM. Thus, basal ganglia regions, especially the caudate and the lenticular nucleus, have been found to be activated during encoding and maintenance phases during vWM tasks (Lewis et al., 2004; Chang et al., 2007; Moore et al., 2013). Although in the present meta-analysis

basal ganglia activation was restricted to the right lenticular nucleus, it remains unclear whether the activation is ascribable to these processes. Again, we were unable to distinguish between the different vWM processes given the available data. Caudate, putamen and capsular regions are known to receive afferents from the left pre-SMA region, which is involved in vWM (Inase et al., 1999). Crosson et al. (2003) found that basal ganglia activity was accompanied by activation of the left pre-SMA during a word production task. They hypothesized that the increase of right basal ganglia activation serves to suppress the non-dominant right frontal cortex, whereas the increase of the left basal ganglia activation serves to enhance the language processing of the left dominant hemisphere. Against the background of these findings, the basal ganglia can be assumed to interact closely with the frontal cortex and to serve as a selective gating mechanism for the prefrontal cortex (Frank et al., 2001). From this perspective, the findings showing the basal ganglia to be active only during encoding and maintenance phases seem plausible, because selective gating plays a major role for these processes. However, as we did not study the phases separately, we cannot rule out that these activations also reflect attentional processes in addition to pure vWM processes. Moreover, six publications compared activation conditions with a simple baseline (e.g., fixation of a cross hair). Hence, we cannot rule out that some parts of the subcortical activation were due to motor activity (i.e., button press in the activation conditions vs. no button press in the baseline condition). In the present meta-analysis we also found left pre-SMA activation, but a conclusion about their influence on basal ganglia is unwarranted without any connectivity data. In addition to the pre-SMA activation, our meta-analysis demonstrated significant activation in the anterior cingulate which has been found to be activated during vWM tasks before (Bedwell et al., 2005; Narayanan et al., 2005). It should be noted that in the AAL atlas the significant cluster was labeled as median cingulate, which is part of the anterior cingulate. It is striking, however, that a majority of vWM did not find an involvement of the anterior cingulate. Hence, future studies should make an attempt to clarify the specific contribution of the different parts of the cingulate to vWM.

## Age, Load, and Mean RT as Influencing Factors

Age-related changes in vWM are not fully understood because of a lack of longitudinal data. A recent longitudinal study found the activation of left prefrontal cortex (i.e., MFG and parts of the IFG) to be reduced during a vWM manipulation task in older people (Rieckmann et al., 2017). Somewhat in accordance with this finding, the present meta-analysis demonstrated a negative association between activation in the left and right IFG—including Broca's area—and age. In addition, we found a negative association between activation in the right MFG and age. It is known that cortical thickness, surface area, and volume of this region decrease with age (Lemaitre et al., 2012) which may, to some degree, explain this finding. Moreover, the right MFG plays a central role in reorienting attention from exogenous to endogenous attentional control (Japee et al., 2015).

Our results are in agreement with the ontogenetic model of brain development according to which those brain regions that are the last to mature are the first to be affected by aging (Raz et al., 2005). Of note, all the other regions exhibiting a negative association between activation and age were localized in the left hemisphere. We found this negative association in the left insula, which—as stated above—plays a relevant role in the context of rehearsal, in the left putamen, which is involved in the active filtering of irrelevant material allowing us to focus on relevant material (Moore et al., 2013) in the left rolandic operculum, important for overt rehearsal, and in the left superior temporal gyrus, parts of which are critically involved in phonological storage. The fact that these regions important for different vWM processes showed a negative association with age might explain why older people tend to exhibit worse vWM performance, although it should be kept in mind that we did not take into account any longitudinal data or individual subject performance. Since these associations were detectable mainly in the left hemisphere and age-related changes were not restricted to the right PFC, our results seem to speak against the HAROLD model (Cabeza et al., 2002). Overall, the present results do not provide any evidence for a decrease of this lateralization with age, as claimed in other studies (Reuter-Lorenz et al., 2000; Cabeza et al., 2002, 2004). The fact that we found a decreased frontal activation with increasing age could either mean that the brain is not as adaptive as proposed by the earlier discussed STAC model or indicate that task demands were too high for elderly people leading to a “breakdown” of frontal activation instead of a compensatory increase. In order to draw any further conclusion it would be helpful to study the activation of these regions in elderly people taking also into account their individual task performance (e.g., accuracy). However, only three studies selected for the meta-analysis specifically included older populations; thus, the age-range was clearly undersampled in the current meta-analysis and the power to reliably assess the influence of age was too low. This might also explain why our results do not seem to be in line with the HAROLD model. Therefore, more empirical data comparing older and younger populations are necessary in order to find out more about specific age differences in activation during vWM. A better understanding of these age-related differences would pave the way for creating more sophisticated methods to preserve or enhance cognitive function in elderly populations.

Höller-Wallscheid et al. (2017) hypothesized the decreased lateralization across the PFC to be independent of age, but to depend on the subjective difficulty of WM tasks. In line with this hypothesis we found a bilateral activation across the PFC in the load effect meta-analysis. Our results are also in accordance with the load effect meta-analysis performed by Rottschy et al. (2012). The CRUNCH model states that the extent of cortical activation depends on the task load. Our results support this model, since we found a positive correlation between activation in several cortical regions (e.g., frontal areas) and task load. Apart from PFC areas we also found activation in the parietal cortex (IPG and left SPG) to be influenced by load, as reported in a previous study by Braver et al. (1997). Likewise, activation of the right lobule VI and crus I of the cerebellum turned out to depend on the difficulty of the vWM tasks. This is in accordance with

a previous study which showed these parts of the cerebellum to respond to changes in vWM load (Kirschen et al., 2005). As stated before, there are anatomical connections between these parts of the cerebellum and frontal areas. Hence, the increased input from frontal regions involved in the articulatory system during a load manipulation could also reflect the increased activation of the right cerebellum. In addition, we found an association between load and activation in the fusiform gyrus. Tsapkini and Rapp (2010) pointed out that lesions of the left fusiform gyrus were significantly associated with reading and spelling deficits. In light of this finding, the positive correlation between load and activation in the left fusiform gyrus in the present study might indicate that a majority of people may have used overt rehearsal as a strategy to cope with increasing task difficulty.

It has long been recognized that RT is sensitive to manipulations of any kind of WM load (Just and Carpenter, 1992). Therefore, RT can also be viewed as a measure of load. A previous study found a significant positive correlation between RT and fMRI signal in nine subjects in the MFG and the left IFG (Braver et al., 1997). The present meta-analysis partially corroborates these findings showing both the left MFG and the left precentral gyrus to be positively associated with RT. However, our results seem to contradict a study by Honey et al. (2000), which reported that posterior parietal cortical activation was predicted by a prolonged RT in a vWM task. Importantly though, as states earlier, activation in the parietal cortex is influenced by load, which—in turn is related to RT. Moreover, the present meta-analysis revealed a positive association between left precentral gyrus activation and RT. This finding is plausible considering that the left precentral gyrus constitutes a major part of the primary motor area and its activation is contralateral to the side of the hand movement. Hence, increased activation in the primary motor cortex might facilitate faster responding. It should be emphasized that RT information was not available for all studies. Moreover, RT depends on many other factors such as number of responses alternatives, type of discrimination or delay time. Therefore, results of this factor should be treated with caution.

Although we performed a meta-analysis in which only fMRI studies were included, there has been a previous meta-analysis in which they selected both fMRI and PET studies to isolate the neural correlates of human working memory (Wager and Smith, 2003). Although they found some support for left frontal cortex dominance in vWM tasks, this was only for tasks with low executive demand. These results support our finding regarding the lateralization, i.e., the higher the difficulty on the task, the less lateralization of PFC activation is to be expected.

Finally, we expected the type of fMRI paradigm to be a significant moderator as demonstrated in a previous meta-analysis (Rottschy et al., 2012). This expectation was not met by the data. This could be due to a strong overlap in task activation, with potentially existing subtle quantity differences being too weak to be significant. We also found that gender did not affect activation associated with vWM tasks. However, we cannot exclude that gender differences would emerge when controlling for effects of sex hormones. Hence, future studies are required that carefully consider these potentially confounding factors.

## Limitations

In the present meta-analysis we discussed a number of relevant networks based on fMRI activity, such as the attentional system, but we did not take into account brain connectivity. However, the localization of brain areas is just the first step toward a more comprehensive understanding of the neural correlates of vWM. Analyses based on temporal dynamics, such as EEG or single-unit recordings, are essential to build a more integrative view. Another limitation regards our cerebellum findings. There is strong reason to assume that we did not find any inferior cerebellum activation because some of the scans included in the present meta-analysis did not cover the whole cerebellum due to methodological limitations (e.g., trade-off between brain coverage and repetition time).

## CONCLUSIONS

We used a coordinate-based meta-analysis to integrate the current literature on vWM in healthy humans. We found activation of the established fronto-parietal network and the right cerebellum, especially crus I, and lobule VI. Our results support the dual-selection model, according to which a mid-lateral PFC activation occurs due to verbal input. Moreover, our results illustrate that we should not underestimate the activation of subcortical regions that play an important role for response inhibition. Age, mean RT, and load moderate vWM task activation and, thus, should be taken into consideration in future research. Especially the influencing factor of age should be further analyzed since the sample included in the present meta-analysis consists of primarily young people. Mean reaction time, moreover, could be influenced by many other

factors. Further, more fine-grained studies are needed to gain a better understanding of the neural correlates underlying processes involved in vWM including encoding, maintenance, and retrieval.

## AUTHOR CONTRIBUTIONS

ME, CB, and KK contributed to the conception and design of the study. ME selected the analyzed studies, performed the statistical analysis, and wrote the first draft of the manuscript. CB and KK wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnhum.2019.00180/full#supplementary-material>

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## 6 Effects of visual verbal WM training in middle-aged healthy adults

This chapter contains a published paper entitled “Neural and Behavioral Effects of an Adaptive Online Verbal Working Memory Training in Healthy Middle-Aged Adults”. The article presents the neural and behavioral effects of verbal adaptive  $n$ -back training in healthy participants aged between 50 and 65 years. The article was published in *Frontiers in Aging Neuroscience* in 2019.

Contributions:

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The author of the present thesis is the first author of this research article. M.E., I.Y., and K.K. contributed to the conception and design of the study. M.E. designed the stimuli and online training, programmed the tasks, analyzed the neuroimaging data and training data, and wrote the first draft of the manuscript. M.E. and I.R. recruited, scanned, and tested the participants. I.R. analyzed part of the task-fMRI behavioral data and revisited all different versions of the manuscript. Q.W. analyzed the cognitive tests. K.K. wrote sections of the manuscript. All authors contributed to the manuscript revision and approved the submitted version.





# Neural and Behavioral Effects of an Adaptive Online Verbal Working Memory Training in Healthy Middle-Aged Adults

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Neural correlates of working memory (WM) training remain a matter of debate, especially in older adults. We used functional magnetic resonance imaging (fMRI) together with an n-back task to measure brain plasticity in healthy middle-aged adults following an 8-week adaptive online verbal WM training. Participants performed 32 sessions of this training on their personal computers. In addition, we assessed direct effects of the training by applying a verbal WM task before and after the training. Participants (mean age  $55.85 \pm 4.24$  years) were pseudo-randomly assigned to the experimental group ( $n = 30$ ) or an active control group ( $n = 27$ ). Training resulted in an activity decrease in regions known to be involved in verbal WM (i.e., fronto-parieto-cerebellar circuitry and subcortical regions), indicating that the brain became potentially more efficient after the training. These activation decreases were associated with a significant performance improvement in the n-back task inside the scanner reflecting considerable practice effects. In addition, there were training-associated direct effects in the additional, external verbal WM task (i.e., HAWIE-R digit span forward task), and indicating that the training generally improved performance in this cognitive domain. These results led us to conclude that even at advanced age cognitive training can improve WM capacity and increase neural efficiency in specific regions or networks.

**Keywords:** task-fMRI, working memory training, active control group, verbal working memory, middle-aged adults, fronto-parietal activation, supramarginal gyrus, n-back task

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## INTRODUCTION

Working memory (WM) is a capacity-limited cognitive system which is responsible for not only temporally storing information but also manipulating it (Baddeley, 2010). Research on WM is well motivated by the fact that WM exhibits correlations with cognitive abilities such as fluid intelligence (Chooi, 2012), reading comprehension (Daneman and Carpenter, 1980), or mathematical problem solving (Wiley and Jarosz, 2012). Therefore, during the past decade there has been mounting interest in training designs aimed at improving our WM capacity. The most prominent target population of such cognitive interventions is the older demographic group, as it has been shown that WM capacity decreases with age (Park and Reuter-Lorenz, 2009; Pliatsikas et al., 2018).

The present paper focuses on the investigation of verbal working memory (vWM) and its training-associated changes, since vWM has been less investigated as compared to visuo-spatial WM, and has a tremendous importance for the daily life. There have been some attempts to study the neural correlates of vWM. In a recently published paper we performed a systematic fMRI meta-analysis to explore the neural correlates of vWM (Emch et al., 2019). We found vWM was associated with brain activity within a fronto-parieto-cerebellar network as well as subcortical regions, such as parts of the basal ganglia.

There have been studies since 2002 aiming at investigating the effects of WM training, showing that WM can be improved when adequate training procedures are used (Klingberg et al., 2002; see von Bastian and Oberauer, 2014 for a review). A meta-analysis from last year demonstrated functional brain changes following WM training within different networks such as the dorsal attention and salience network, sensory areas, and striatum (Salmi et al., 2018). Moreover, a number of studies suggested that younger adults benefit more from training than older participants (Dahlin et al., 2008; Li et al., 2008), but behavioral plasticity effects have also been reported at advanced age (Borella et al., 2010), and even more advanced age (Buschkuhl et al., 2008). However, the lifelong potential for plasticity is far from being fully understood. Apart from these unresolved questions results of previous studies investigating the effects of WM training on brain activation are still quite heterogeneous, both with regard to location as well as direction (i.e., increases vs. decreases) of reported activation changes (Salmi et al., 2018). One important reason could be the methodological heterogeneity of the studies: Thus, the studies or study samples differed with regard to (1) age neglecting the fact that older populations present differences not only in brain function but also in behavioral performance compared to younger populations; (2) training tasks as well as intensity and duration of the trainings (Salmi et al., 2018) which can lead to less or stronger WM training effects (Jaeggi et al., 2008); thus, as summarized in a systematic review on the effects of WM training (von Bastian and Oberauer, 2014), increasing the total duration of the training seems to increase the probability that training effects carry over to cognitive processes not directly practiced by the training; (3) training conditions, i.e., in some studies participants performed the training sessions in the vicinity of the investigators in order to control whether the participants were doing the training (Jansma et al., 2001; Miró-Padilla et al., 2018), thus neglecting the observer's paradox which could go along with a decrease in WM training effects. Given the decline in WM capacities with increasing age the decrease caused by the observer's paradox might be even more pronounced in older populations; (4) participants' motivation which had sometimes not been taken into account despite evidence of its impact on training gains especially in older populations (Carretti et al., 2011); and (5) the type of control condition (i.e., waiting control group without contact to the investigator vs. passive control group vs. active control group). Whereas the implementation of a "no contact" or "passive" control group allows retesting the effects arising from pre- and post-designs, an active control group additionally controls for expectancy effects and generic

intervention effects, such as consequences of using a computer or having a regular training schedule (von Bastian and Oberauer, 2014). All these issues mentioned above should be considered when investigating the effects of a WM intervention program. Hence, taking the following aspects into consideration might counteract further result heterogeneity: The training should ideally be administered in the form of an online training unobserved by the investigator thus minimizing the negative impact of observation on performance while allowing to monitor participants and safeguarding regular participation (Kulikowski and Potasz-Kulikowska, 2016). As stated before, participants' motivation should be taken into account since it has been shown to impact training gains (Linares et al., 2019). In order to motivate participants to continuously improve their WM capacity and complete the task, in the present study mean reaction time, and accuracy was reported at the end of each block. We are highly confident that this boosted participants' motivation to improve from one session to the next.

We investigated a group of healthy middle-aged volunteers within a limited age range (i.e., 50–65 years). The inclusion of this age group should minimize the influence of relevant age-related changes, such as atrophy or amyloid plaques, while maximizing the usefulness of the training with regard to training gains. We also avoided the inclusion of subjects with cognitive impairment and cognitive complaints, which are preclinical cognitive declines associated with dementia (Knopman, 2012). The selected participants performed an adaptive online WM training task (i.e., n-back task with each session level adapted to the participant's performance) in order to keep task demands and motivation on a high level. Regarding training extent little is known about the ideal training duration. The number and duration of training sessions varies strongly amongst the published studies up to now. Most trainings contain about 20 training sessions each lasting about 30 min, but only little systematic research investigated the optimal intensity and duration of WM training interventions. Given findings by Jaeggi et al. (2008) who reported dose-dependent training effects (i.e., the longer the training, the larger the effects) we decided for an above-average training extent comprising 32 sessions with a total duration of 8 weeks which should be sufficient to cause significant training-related effects. We employed an active control training demanding a low-level vWM training task for the verbal task (i.e., 1-back level), to make sure that training conditions were the same for both groups to control for the Hawthorne effect which describes an improvement in the participant's performance in response to the increased attention to their behavior (Landsberger, 1958). Finally, to assess potential direct effects of the training, a vWM task was employed before and after the training (i.e., HAWIE-R digit span forward and backward), which is an established test to investigate this cognitive construct.

The aim of this study was to investigate the behavioral and neural changes following an adaptive online verbal WM training in healthy middle-aged participants between 50 and 65 years old. We expected to provide evidence for neural plasticity and/or improvement in behavioral performance in healthy adults within this specific age range.

## MATERIALS AND METHODS

### Participants

Sixty-three subjects participated in the study. Six participants had to be excluded due to different reasons: one subject dropped out after the first session, two participants had clinically relevant alterations in brain structure, one volunteer moved more than 3 mm during the task-fMRI, one subject's scanning data was not completely saved, and one participant was a training outlier. Therefore, the final sample contained fifty-seven healthy right-handed volunteers (28 male, 29 female) ranging between 50 and 65 years (mean age =  $55.85 \pm 4.24$ ; mean years of education =  $16.56 \pm 3.14$ ). Subjects were recruited via advertisements in the internet or newspaper. First, a telephone interview was conducted to assess the basic inclusion criteria: right handed, no mental disorder and presence of metal in the body. Afterward, the following diagnostic checklists were performed: the short form of the geriatric depression scale (GDS) (Yesavage et al., 1983), the mini-mental-status-test (MMST) (Folstein et al., 1975), the clock drawing test (Berit and Ove, 1998), and the M.I.N.I. International Neuropsychiatric Interview (Sheehan et al., 1998). Based on these screening, left-handed subjects, subjects with depression or other types of psychiatric disorders, and subjects with cognitive impairments were excluded from the study (see **Figure 1** for study design).

Written informed consent was provided by each subject before the first session. Study participation was remunerated. Assignment of participants to one of the two groups (experimental or control group) occurred pseudo-randomly taking into account gender, age and years of education (YOE). The experimental group included 30 participants (mean age =  $55.8 \pm 4.3$ , 15 female, mean YOE =  $16.96 \pm 3.18$ ), the control group consisted of 27 participants (mean age =  $55.92 \pm 4.25$ , 14 female, mean YOE =  $16.11 \pm 3.11$ ). There were no significant differences between both groups regarding age, sex or YOE ( $p = 0.91$ ,  $p = 0.89$ ,  $p = 0.31$ , respectively). The study was approved by the Ethical Committee of the Klinikum Rechts der Isar and the Federal Office for Radiation Protection.

### Experimental Paradigm

#### Adaptive Online WM Training Task

We used the n-back task as WM training paradigm, in which letters are presented sequentially and the subject is asked to press a key whenever the current letter is identical to the one that appeared n-back positions earlier in the sequence. The active control group performed a low-level vWM training (i.e., stable level of verbal 1-back task). The vWM training of the experimental group was based on an adaptive online n-back paradigm comprising 9 blocks per session adapted from Jaeggi et al. (2010). In each block 6 targets were presented, meaning that the total number of possible hits was 54 per session. Both groups completed 32 training sessions with four sessions per week (i.e., 8 weeks in total) on their personal computers. Participants had the restriction of only performing one training session per day. In order to be able to analyze the training data we used

the Inquisit software [Inquisit 5 (2016) retrieved from: <https://www.millisecond.com>], which is a precision software for online psychological experiments allowing the investigator to check for training participation and performance directly after each session. Each vWM training session started with a 1-back level and the level increased/decreased or stayed the same depending on the subject's performance. Given a percentage of at least 90% correct answers, the n-back level increased by one in the next block. Given an accuracy level below 80%, the n-back level decreased by one. Otherwise, the n-back level remained the same. The maximum n-back level a participant could reach was 9. Both groups received a feedback at the end of each block (with regard to mean RT and percentage of correct answers). Both groups performed two different WM training modalities: verbal and visual n-back task. Given that the regions involved in verbal and visual WM processes are known to differ and considering that the visual n-back training differed significantly from the verbal training (i.e., the presented stimuli consisted of yellow abstract random shapes with low association value; the starting level was lower because of the unfamiliarity of the random shapes; and the active control group performed an attentional, i.e., X-back, visual online training) results of the visual training are reported elsewhere.

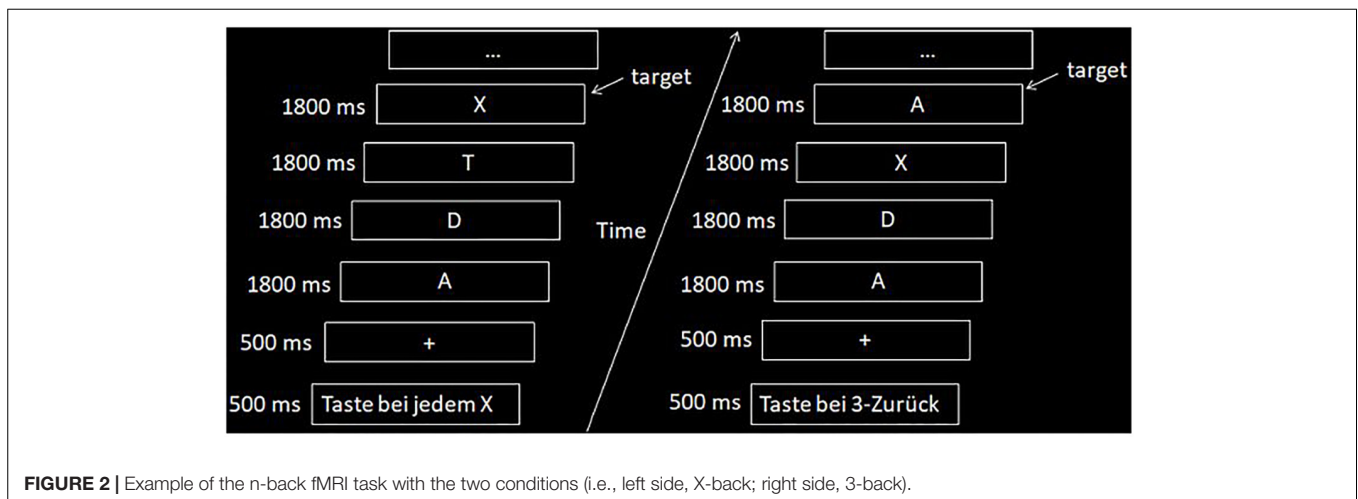
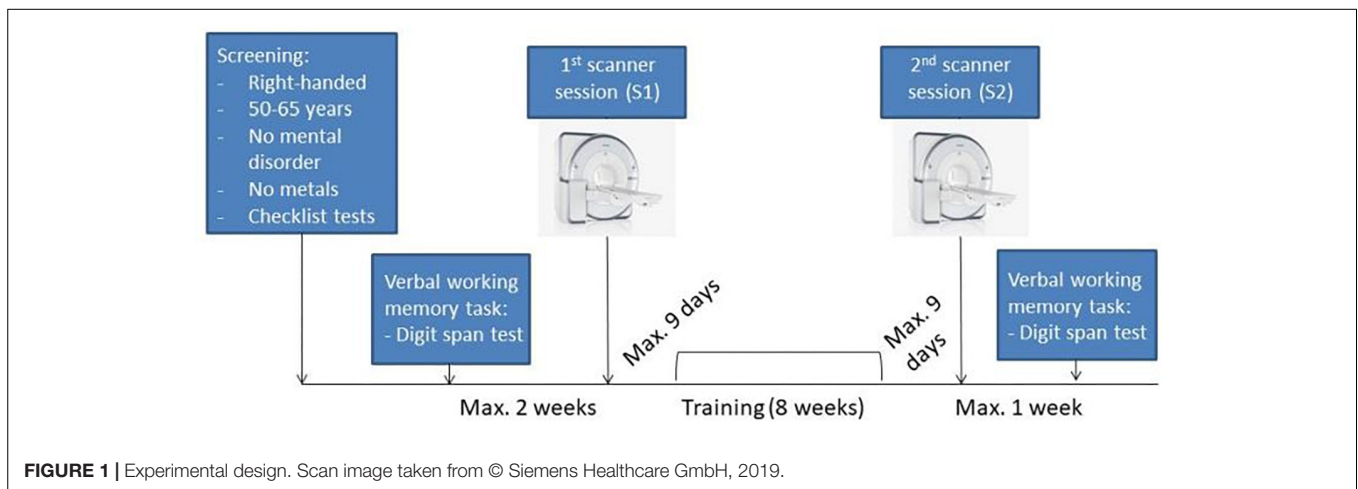
#### Task-fMRI Paradigm

In the scanner, subjects likewise performed a visual and a verbal n-back task. As already mentioned, visual WM results will be reported elsewhere. The WM paradigm was explained to the subjects before entering the scanner. In addition, subjects were asked to perform a short training version of the task to familiarize themselves with the stimulus presentation. Participants were allowed to repeat the practice task until they reported that they fully understood the task. The vWM task comprised the presentation of 26 capital white letters from the alphabet on a black background in the form of a block design. The whole task consisted of seven blocks of control condition (i.e., X-back task) and seven blocks of active task condition (i.e., 3-back task) presented in random order. Each condition lasted 45 s and consisted of 5 s of an instruction display indicating the following condition in German (3-back or X-back/0-back), 5 s of a fixation cross presentation, and 35 s of presentation of the letters (see **Figure 2**). Each block contained three possible hits giving a maximum of 21 possible hits per session and per condition. In the 3-back task any letter could be a target, in the X-back condition only the capital letter "X" was a target. The order of presentation with regard to verbal and visual n-back task was counterbalanced between the first and the second session. They did not receive a performance feedback after each block as in comparison for the training sessions.

#### Direct Effects

In order to investigate potential direct effects of the vWM training we asked participants to perform the HAWIE-R digit span subtest (forward and backward version) (Molz et al., 2010) before and after the 32 training sessions. This test requires the subject to repeat up to nine numbers in the same order as read aloud by the examiner (forward version), and afterward in reverse





serial order (backward version). Every item on the digit span test consists of two trials, each of which is scored with either 0 (incorrect) or 1 (correct). In case of at least one correct response, the examiner proceeds to read aloud the next-larger sequence of numbers. The task was explained beforehand and all participants practiced one short version of the task in order to familiarize themselves with the task. Performance assessment was based on the values of each subtest from the HAWIE-R and the test was orally presented with a rate of one number per second. The whole procedure lasted no more than 8 min. We hypothesized that if the participants successfully trained a specific process (i.e., vWM), they should demonstrate a significantly improved performance also in another test investigating the same process (i.e., HAWIE-R digit span).

## Behavioral Analysis

We used JASP<sup>1</sup> and IBM SPSS Statistics software (Version 25 Armonk, New York, NY, United States) to analyze the fMRI behavioral data and the HAWIE-R test data. Two different statistical programs were employed to double-check the

correctness of our results. Python version 3 was used to analyze the training data and *scipy.stats* was the package used for the statistical analyses. For the fMRI behavioral data we conducted two repeated-measures analyses of variance (ANOVAs) with Group (experimental group vs. control group) as between-subjects factor, Session (S1 vs. S2) as within-subject factor, and mean reaction time or  $d'$  values during each condition (3-back or X-back) as dependent variable. We selected  $d'$  instead of accuracy values [hits – false alarms (FA)] because this parameter takes the range for both components into account by calculating the relative proportion of hits minus FA (Haatveit et al., 2010; Meule, 2017). Higher values of  $d'$  means better performance whereas lower values of  $d'$  values means worse performance. We also performed a two-sample *t*-test between the active control and the experimental group at S1 (for the 3-back and X-back  $d'$  values as well as mean reaction time) to test whether there were any baseline differences between the groups. For the HAWIE-R subtest we likewise conducted repeated-measures ANOVAs with Group (experimental group vs. control group) as between-subjects factor and Session (S1 vs. S2) as within-subject factor.

For the training data, we analyzed the mean n-back level achieved in each session as well as the  $d'$  values. As data

<sup>1</sup><https://jasp-stats.org/>

from the last three sessions of one subject in the experimental group were lost, we interpolated the missing data with her own previous training data with a forward linear method. *T*-tests comparing the first four and the last four sessions were performed to investigate whether there was a significant improvement in training performance in both groups.

## fMRI Acquisition

There were two scanner sessions: one immediately (i.e., no longer than 9 days) before the 8 weeks online training (S1) and another one immediately (i.e., no longer than 9 days) after the training (S2). The WM paradigm was presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, United States)<sup>2</sup>. The participants were able to see the task through a mirror fixed to the head coil which reflected the MRI-compatible screen. Participants were positioned supinely in the scanner. Their responses were collected via fORP 932 subject response package (Cambridge Research Systems). Participants held the button-box in their right hand and the emergency button in their left hand.

Images were acquired on a 3 T Biograph MR-PET Siemens scanner (Siemens, Erlangen, Germany), equipped with a 16-channel head coil at the Klinikum rechts der Isar, Munich, Germany. Specific cushions were used to prevent head movement. The imaging protocol included the following sequences: T1 MPRAGE, T2, FLAIR, DTI, echo-planar imaging (EPI) resting state, task-fMRI, and FDG-PET. Scan sessions lasted approximately 1 h. Results of the other sequences (i.e., DTI, resting-state fMRI, and FDG-PET) will be reported elsewhere. A high-resolution MPRAGE anatomical sequence was acquired with the following parameters: 160 slices; TR = 2300 ms; TE = 2.98 ms; flip angle = 9°; voxel size = 1.0 × 1.0 × 1.0; slice thickness = 1 mm; no gap; FOV = 256 mm; interleaved acquisition. Functional data were obtained using a gradient-echo T2\*-weighted EPI sequence with the following parameters: 237 slices; TR = 2700 ms; TE = 30 ms; flip angle = 90°; voxel size = 3.0 × 3.0 × 3.0; slice thickness = 3 mm; 0.6 mm gap; FOV = 192 mm; interleaved acquisition. The same sequences were used in S1 and S2.

## Image Preprocessing

Preprocessing as well as statistical analysis of fMRI data were conducted with SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom)<sup>3</sup> in MATLAB v2018b. First, we performed head motion correction. Here the functional images were realigned and resliced to fit the mean functional image and then co-registered to the MPRAGE image using normalized mutual information. Movement was visually checked for each participant and participants moving more than 3 mm maximum displacement were not included in the final dataset. For the final dataset ( $n = 57$ ) we calculated the root mean squared head position change (RMS movement) and converted the rotation parameters from degree to mm by calculating displacement on the surface of radius 50 mm to get the frame

<sup>2</sup>www.neurobs.com

<sup>3</sup>http://www.fil.ion.ucl.ac.uk/spm

**TABLE 1** | Head motion parameters.

		Experimental group	Control group	Group differences <i>p</i> -value
fMRI (S1)	Translation (mm)	0.109 ± 0.052	0.098 ± 0.063	0.505
	Rotation (rad)	0.045 ± 0.023	0.041 ± 0.027	0.512
fMRI (S2)	Translation (mm)	0.104 ± 0.051	0.09 ± 0.044	0.252
	Rotation (rad)	0.043 ± 0.022	0.036 ± 0.018	0.203

Mean translation in mm ± SD and mean rotation in radius ± SD are presented for both groups and time points. *T*-tests were performed between groups at both time points.

wise displacement (FD), as reported by Power et al. (2012, 2014). The FD is defined as the sum of absolute derivatives of these six parameters with the three rotational parameters converted to distance. There were no significant differences in both head motion parameters between both groups in S1 or S2 (see **Table 1** for head movement parameters). Because subject motion not only degrades resting but also task-fMRI data, we censored some images to improve quality of task fMRI, as suggested in Siegel et al. (2014). We used a strict threshold of FD > 0.5 mm to censor the data since our study is based on a healthy cohort. We created a motion regressor taking into account the censored images. Then, we applied the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) pipeline (Ashburner, 2007) to obtain a group specific structural template. We used it for segmentation and normalization to MNI space. Finally, data were smoothed using a 6 mm × 6 mm × 6 mm FWHM Gaussian Kernel.

## Image Analyses

A general linear model at the single subject level was conducted to obtain the task activation contrasts of interest. The task design function was convolved with a canonical haemodynamic response function (HRF) and its time derivative, allowing for a slight temporal shift. Six motion realignment parameters and motion censor regressor (i.e., FD > 0.5 mm) were included as covariates of no interest. We used a high-pass filter of 220 s to the functional data to eliminate low-frequency components because the default filter (128 s) was not adequate for our design (i.e., a filter of 128 s would have removed parts of the task-related activation).

For the second level analysis we conducted a one-sample *t*-test to obtain areas activated during the n-back task (3-back > X-back level) in general. We also performed a two-sample *t*-test to examine whether there were differences at S1 between the experimental and the active control group. The longitudinal analyses were performed by assessing the interaction effects between Session (S1 vs. S2) and Group (experimental group vs. control group) using the factorial design in SPM. The statistical criterion was set at  $p < 0.05$  false-discovery rate (FDR) corrected. In addition, the number of expected voxels per cluster was used as an extent threshold.

## RESULTS

### Behavioral Results

#### Cognitive Training

As is illustrated in **Figure 3**, the experimental group showed a significant improvement in both n-back level and  $d'$  values (both  $p < 0.001$ ) when comparing performance between the first and the last four training sessions. In the control group, only  $d'$  values were analyzed, since the n-back level (i.e., 1-back level) stayed the same during all training sessions. Expectedly,  $d'$  values of the control group did not significantly differ between the first and last four training sessions ( $p = 0.184$ ).

#### Direct Effects

The average HAWIE-R forward subtest values for the control group were 7.37 ( $SD = 0.41$ ) at S1 and 6.89 ( $SD = 0.33$ ) at S2. Those for the experimental group were 7.77 ( $SD = 0.39$ ) at S1 and 8.83 ( $SD = 0.32$ ) at S2. The repeated measures ANOVA on the HAWIE-R forward subtest showed a non-significant effect of Session [ $F_{(1,55)} = 2.46, p = 0.122$ ] but a significant main effect for Group [ $F_{(1,55)} = 5.94, p = 0.018$ ]. The interaction between Session and Group was significant [ $F_{(1,55)} = 17.248, p < 0.001$ , **Figure 4**]. *Post hoc* analyses revealed a performance decrease in the control group ( $p = 0.045$ ) and a highly significant improvement in the experimental group ( $p < 0.001$ ).

The average HAWIE-R backward subtest values for the control group were 6.85 ( $SD = 0.33$ ) at S1 and 7.48 ( $SD = 0.43$ ) at S2. Those for the experimental group were 6.73 ( $SD = 0.31$ ) at S1 and 7.5 ( $SD = 0.41$ ) at S2. The repeated measures ANOVA on the HAWIE-R backward subtest showed an effect of Session [ $F_{(1,55)} = 5.78, p = 0.02$ ] and no effect of Group [ $F_{(1,55)} = 0.013, p = 0.91$ ]. The interaction between Group and Session yielded no significant results [ $F_{(1,55)} = 0.056, p = 0.814$ ].

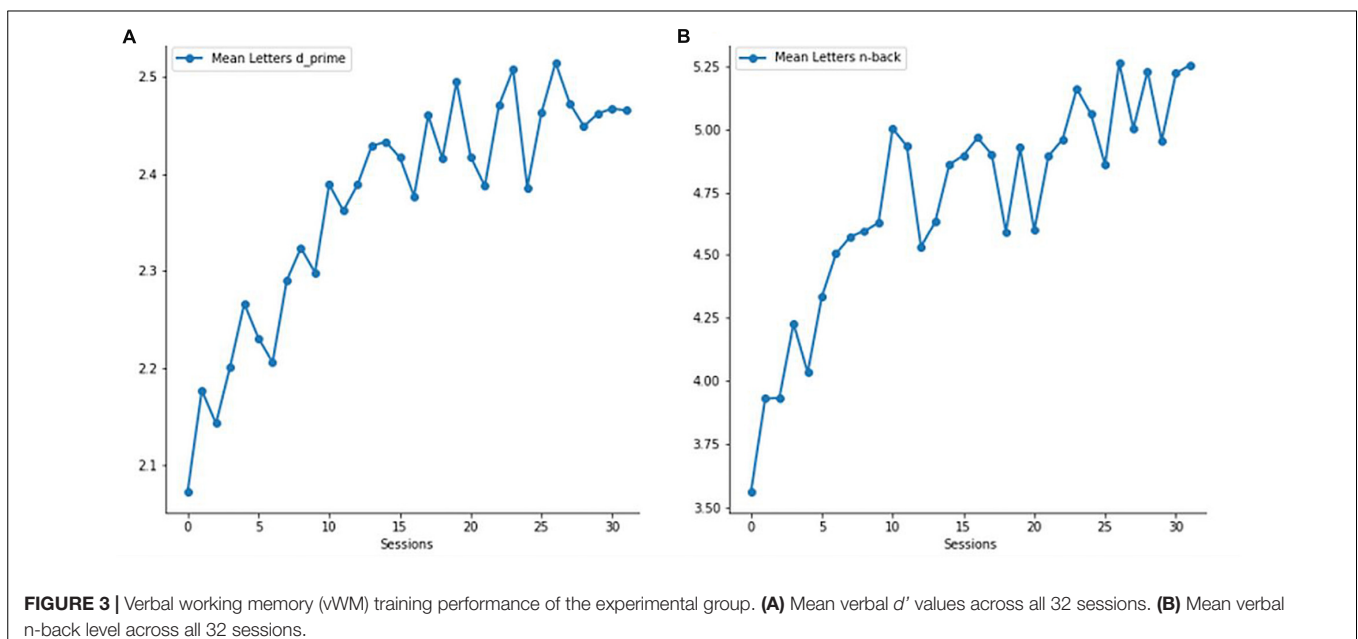
#### Task-fMRI ( $d'$ )

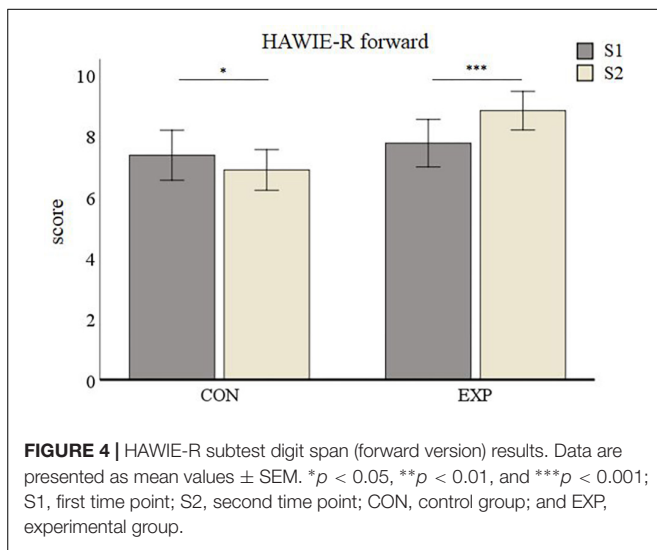
The comparison between experimental and active control group yielded no significant differences at baseline (S1) in any condition for  $d'$  values (i.e., 3-back:  $p = 0.864$  and X-back:  $p = 0.124$ ). The average 3-back  $d'$  values for the control group were 2.73 ( $SD = 0.53$ ) at S1 and 2.96 ( $SD = 0.61$ ) at S2. Those for the experimental group were 2.74 ( $SD = 0.51$ ) at S1 and 3.69 ( $SD = 0.78$ ) at S2 (see **Figure 5A**). The repeated measures ANOVA on the 3-back  $d'$  values showed a main effect for Session [ $F_{(1,55)} = 47.03, p < 0.001$ ] and for Group [ $F_{(1,55)} = 10.33, p = 0.002$ ] and, accordingly, the interaction between Session and Group was significant [ $F_{(1,55)} = 18.07, p < 0.001$ ]. *Post hoc* analyses revealed no significant improvement in the control group ( $p = 0.06$ ), but a highly significant improvement in the experimental group ( $p < 0.001$ ).

For the X-back condition the control group had mean  $d'$  values of 4.18 ( $SD = 0.13$ ) and 4.08 ( $SD = 0.19$ ) at S1 and S2, respectively, whereas the experimental group had a mean of 4.10 ( $SD = 0.29$ ) and 4.13 ( $SD = 0.21$ ) at S1 and S2, respectively (see **Figure 5B**). The repeated measures ANOVAs for the X-back condition yielded no significant main effect for Session [ $F_{(1,55)} = 0.93, p = 0.34$ ] or Group [ $F_{(1,55)} = 0.331, p = 0.567$ ]. The interaction was also not significant [ $F_{(1,55)} = 2.74, p = 0.103$ ] indicating no performance improvement for the X-back condition in any group after the training.

#### Task-fMRI (Mean Reaction Time)

The comparison between experimental and active control group yielded no significant differences at baseline (S1) in any condition for mean reaction time (i.e., 3-back:  $p = 0.646$  and X-back:  $p = 0.531$ ). Mean reaction time (RT) 3-back for the control group was 782.7 ms ( $SD = 183.75$ ) at S1 and 713.04 ms ( $SD = 172.31$ ) at S2, whereas the experimental group had a mean RT of 805.71 ms ( $SD = 191.67$ ) at S1 and 567.35 ms ( $SD = 155.75$ ) at





S2 (see **Figure 6A**). The repeated measures ANOVA conducted for 3-back mean reaction time showed a main effect of Session [ $F_{(1,55)} = 42.1$ ,  $p < 0.001$ ], no effect of Group [ $F_{(1,55)} = 2.3$ ,  $p = 0.134$ ], and a significant interaction between both factors [ $F_{(1,55)} = 12.63$ ,  $p < 0.001$ ]. *Post hoc* analyses revealed a significant improvement from S1 to S2 in the control group ( $p = 0.0017$ ) as well as in the experimental group ( $p < 0.001$ , see **Figure 6A**).

In the X-back condition, the control group had a mean RT of 446.93 ms ( $SD = 72.95$ ) at S1 and a mean RT of 403.21 ms ( $SD = 72.32$ ) at S2, whereas mean RT in the experimental group was 458.62 ms ( $SD = 66.3$ ) at S1 and 428.06 ( $SD = 60.53$ ) at S2 (see **Figure 6B**). The repeated measures ANOVA for X-back showed a main effect of Session [ $F_{(1,55)} = 22.51$ ,  $p < 0.001$ ] but no significant effect for Group [ $F_{(1,55)} = 1.27$ ,  $p = 0.265$ ]. There was also no significant Session by Group interaction [ $F_{(1,55)} = 0.706$ ,  $p = 0.404$ ]. This means that both groups improved after the second session. *Post hoc* analyses revealed that both the control

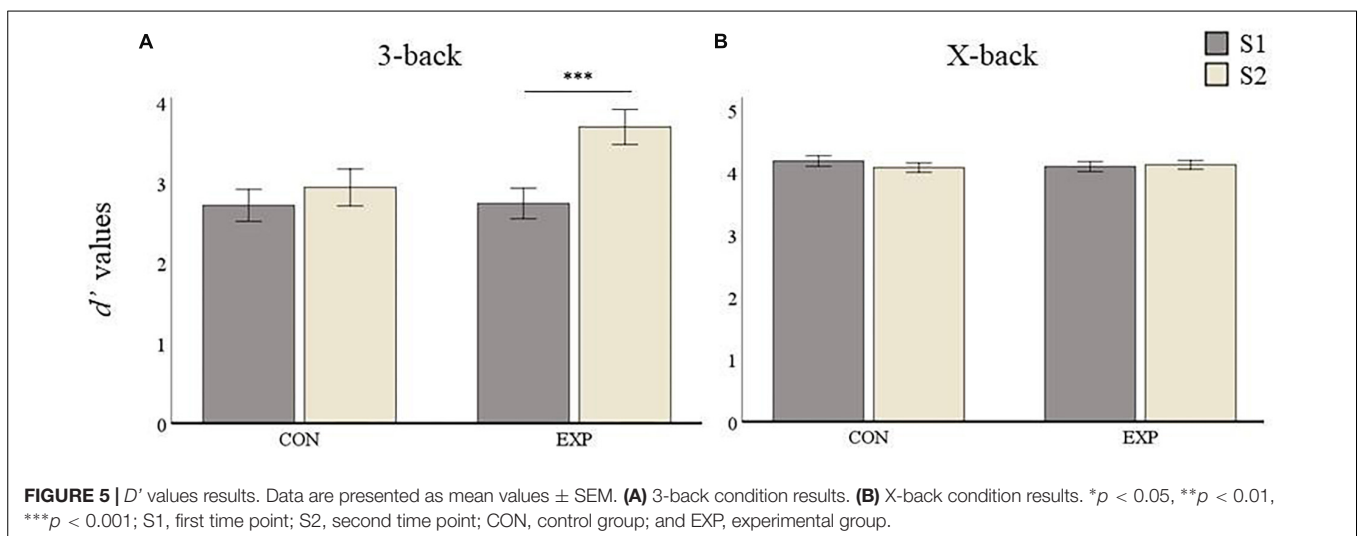
group ( $p = 0.002$ ) as well as the experimental group ( $p = 0.002$ ) improved from S1 to S2.

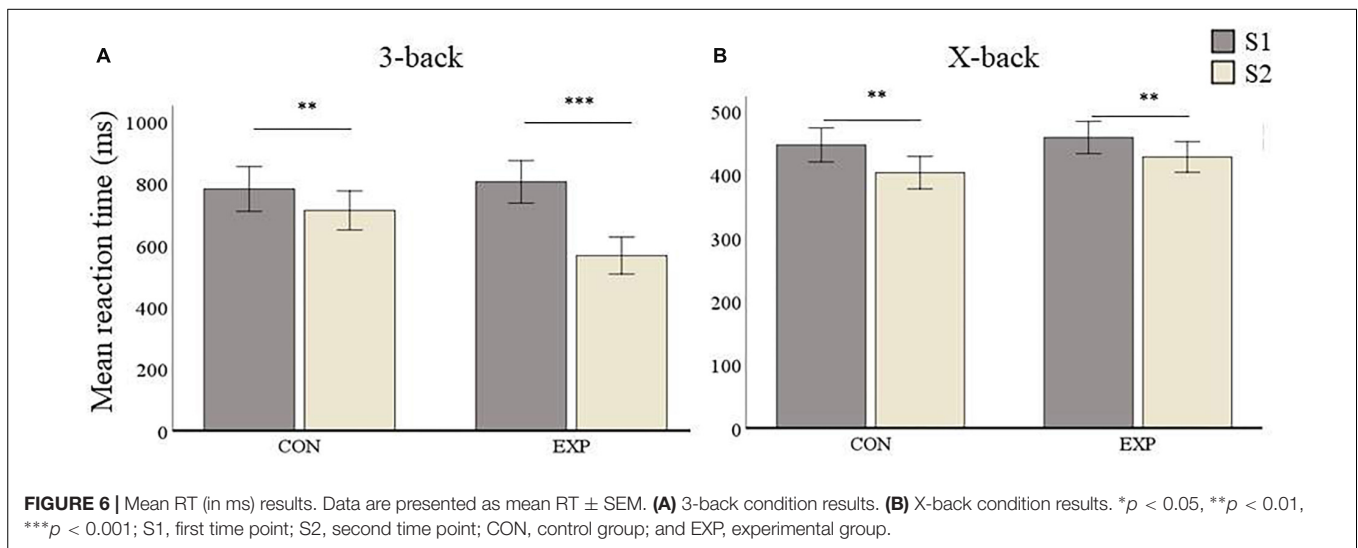
## Neuroimaging Results

The whole-brain one-sample  $t$  test to investigate the brain regions activated in the n-back task (3-back > X-back) independent from training revealed wide-spread cortical as well as subcortical activity (**Figure 7**). We found activity mainly in bilateral precuneus, superior parietal lobule, inferior parietal lobule, superior frontal gyrus, sub-gyral frontal lobe, medial frontal gyrus, cingulate gyrus, and different parts of the cerebellum. There was also activity in the thalamus, specifically in the medial dorsal nucleus and in subcortical regions such as insula and caudate. These results were  $p < 0.05$  FDR corrected with a cluster extension of  $k = 53$  voxels.

We also performed a two-sample  $t$  test at S1 to investigate whether there were any baseline differences between the experimental and the active control group in the n-back task (3-back > X-back). The analysis yielded no significant differences. This means that we can interpret the differences between the groups at S2 as differences arising from the training. All results were  $p < 0.05$  FDR corrected.

The factorial repeated-measures ANOVAs with Group (experimental group vs. control group) as between-subjects factor and Session (S1 vs. S2) as within-subject factor investigating the effects of the cognitive training in both groups for 3-back vs. X-back showed significant results for the interaction *Experimental Group (S1 > S2) > Control Group (S1 > S2)* in mainly superior frontal and parietal regions (see **Table 2**). The reverse contrast did not yield any significant results. In addition, the comparison *Experimental Group S1 > Experimental Group S2* yielded significant activation in mainly cerebellum and parietal regions (supramarginal gyrus) (see **Table 3** and **Figure 8**). The reverse contrast did not yield any significant results indicating that there was a reduction of activity in specific brain regions in the experimental group after the training. The *Control Group S1 > Control Group S2* as well as the *Control Group S1 < Control*





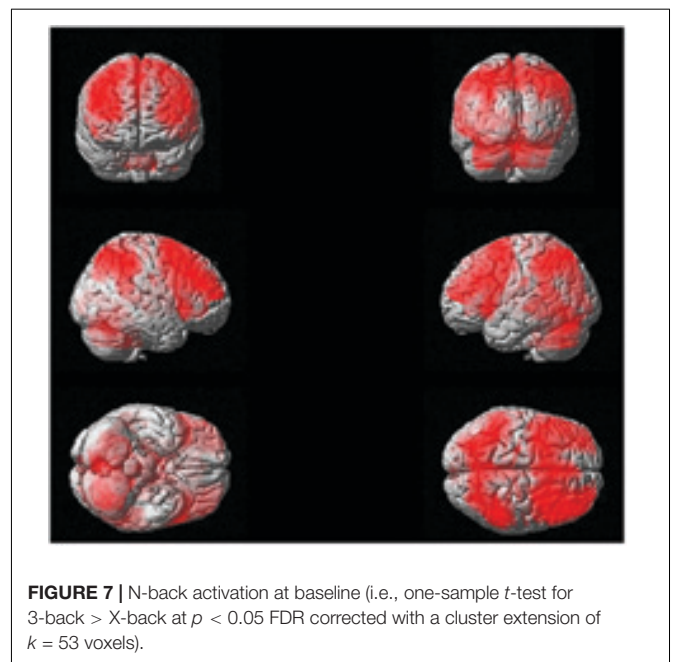
Group S2 contrast did not show any significant results. All results were  $p < 0.05$  FDR corrected.

## DISCUSSION

In the present study, we applied task-fMRI to investigate neural and behavioral effects of an 8-week adaptive online vWM training in middle-aged healthy subjects. We found no differences in brain activity during the n-back task between the experimental and active control group at baseline. Comparing both time points the results showed no activation differences in the control group, but a significantly decreased activation in vWM characteristic regions in the experimental group after the training. These activation decreases, most probably reflecting training-associated gains in cerebral efficiency, were accompanied by significant vWM performance improvements in the experimental group.

### Pre-training Activation

The general (i.e., training-independent) activation in a predominantly fronto-parieto-cerebellar network that we found by analyzing activation of the whole group at the first timepoint is largely in line with previous studies investigating vWM (Owen et al., 2005; Rottschy et al., 2012; Emch et al., 2019). However, one aspect which seems to distinguish the present results from previous findings especially in, on average, younger populations is the rather bilateral prefrontal activation in the present study (Cabeza, 2002; Cabeza et al., 2004). This weakly lateralized activity in predominantly frontal areas speaks in favor of the hemispheric asymmetry reduction in older adults (HAROLD) model (Cabeza, 2002) stating that lateralization/specialization in brain activity decreases with increasing age. There are different hypotheses regarding the underlying mechanism. One hypothesis assumes a compensatory mechanism underlying this activity expansion, whereas another assumption suggests a less specific recruitment of neural networks due to gradual changes that happen with age. Even though the present findings do not allow drawing any conclusions on the mechanism explaining this



phenomenon, they nevertheless provide additional support in favor of this model.

### Training-Related Changes in Activation

Adaptive online vWM training resulted in reduced brain activity in several parietal areas, first and foremost in the left supramarginal gyrus (SMG), which has been found to be important for the phonological store component, although the exact neural basis of this WM component is still under debate (Buchsbaum and D'Esposito, 2008; Aboitiz et al., 2010). We also found reduced activation in the right homologous region. The right SMG has also been reported to be engaged during vWM in a study by Deschamps et al. (2014). When inhibiting activation of the SMG by applying TMS on both

**TABLE 2 |** List of higher brain activation in the experimental group at S1 compared to S2 [i.e., experimental group (S1) > experimental group (S2) at  $p < 0.05$  FDR corrected with a cluster extension of  $k = 10$  voxels].

Name	BA	Cluster extent	MNI space			Z-value
			x	y	z	
L. Cerebellum (Tuber)	–	25	–42	–76	–30	5.11
R. Substantia nigra	–	48	20	–20	–6	4.99
R. Supramarginal gyrus	40	294	60	–48	26	4.9
L. Supramarginal gyrus	40	533	–50	–50	38	4.81
L. Cerebellum (Uvula)	–	240	–22	–72	–26	4.79
L. Middle temporal gyrus	20	66	–56	–36	–8	4.65
R. Cingulate gyrus	31	40	22	–52	24	4.3
R. Cuneus	7	441	16	–72	38	4.27
R. Posterior cingulate	23	22	4	–30	26	4.22
R. Middle occipital gyrus	19	24	42	–78	16	4.21
L. Lentiform nucleus	–	24	–12	4	–2	4.18
L. Cerebellum (Uvula)	–	116	22	–84	–26	4.13
L. Cerebellum (Tonsil)	–	105	–28	–58	–48	4.12
L. Lingual gyrus	19	50	–18	–66	6	4.12
R. Cerebellum (Declive of Vermis)	–	58	0	–70	–22	4.11
R. Middle frontal gyrus	9	35	32	26	30	4.09
L. Cerebellum (Culmen)	–	27	–22	–50	–24	4.09
R. Cerebellum (Tonsil)	–	33	8	–64	–42	4.01
R. Paracentral lobule	5	57	20	–30	54	3.97
L. Cerebellum (Declive)	–	26	–40	–78	–16	3.93
R. Middle frontal gyrus	6	12	36	20	40	3.80
L. Posterior cingulate	29	40	–2	–48	12	3.78
R. Precentral gyrus	4	29	34	–20	58	3.78
L. Middle frontal gyrus	10	12	–32	44	10	3.78
R. Superior frontal gyrus	9	28	28	56	24	3.75
R. Superior parietal lobe	7	31	26	–66	52	3.73
L. Superior occipital gyrus	19	20	–34	–74	36	3.72
L. Inferior occipital gyrus	18	11	–34	–88	–2	3.69
R. Cuneus	18	19	12	–80	26	3.65
R. Cerebellum (Culmen)	–	13	6	–38	0	3.65
R. Inferior parietal lobule	40	23	52	–30	36	3.65
R. Thalamus	–	17	4	–2	6	3.62
R. Middle occipital gyrus	18	10	32	–86	12	3.6
L. Middle temporal gyrus	37	12	–38	–60	12	3.59
L. Middle temporal gyrus	39	10	–48	–72	22	3.59
R. Thalamus	–	14	6	–12	12	3.55
R. Cerebellum (Culmen)	–	18	36	–52	–28	3.52
L. Superior frontal gyrus	8	21	–4	46	42	3.52
L. Parahippocampal gyrus	30	12	–12	–42	4	3.51

L, left; R, right; BA, brodmann area.

sides participants had a slower performance in the verbal 2-back task – an indicator for the involvement of the bilateral SMG in vWM. We also found decreased activation in a number of additional frontal, parietal and cerebellar regions, and thus in regions known to closely interplay in any kind of WM task (Owen et al., 2005; Rottschy et al., 2012; Emch et al., 2019). Surprisingly, there was also a decreased activation in the right substantia nigra, which supports the previously discussed hypothesis that this region is not only crucial for motor functions but also involved in learning and memory functions (Packard and Knowlton, 2002). Moreover, decreased activation in the

experimental group after the training was detectable in the middle temporal gyrus. In a study with chronically intractable epilepsy patients this region has been found to represent stimuli held in WM (Kornblith et al., 2017). While up to the publication of this study the role of the middle temporal gyrus in WM processes was controversial, it is assumed to play a central role in the temporary maintenance of stimuli in WM. In addition, there was a reduced activity in the bilateral posterior cingulate gyrus, which is robustly activated during vWM tasks as demonstrated in our recently published meta-analysis (Emch et al., 2019), as well as in the bilateral cuneus, which has been

**TABLE 3** | List of brain activations for the interaction [i.e., experimental group (S1 > S2) > control group (S1 > S2)] at  $p < 0.05$  FDR corrected with a cluster extension of  $k = 6$  voxels].

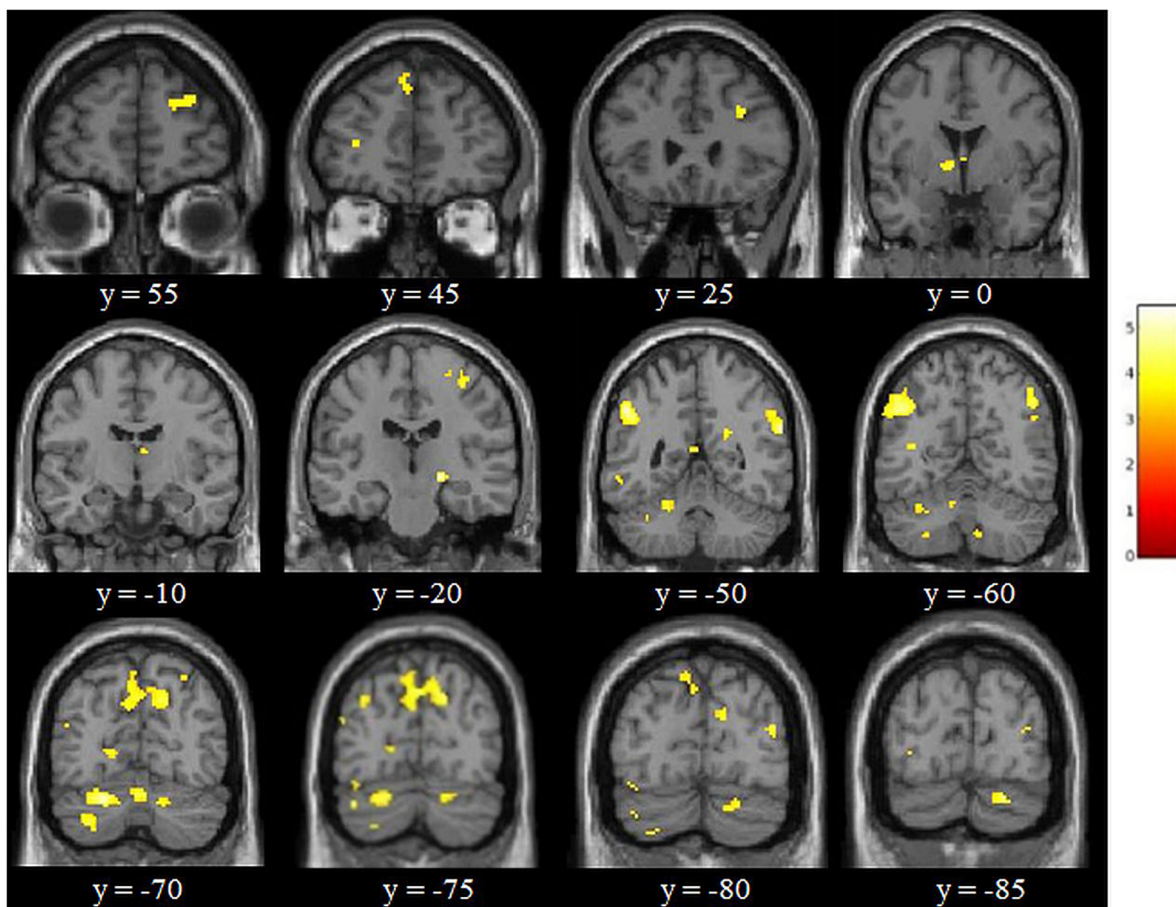
Name	BA	Cluster extent	MNI space			Z-value
			x	y	z	
R. Cerebellum posterior lobe (declive)	–	29	0	–68	–22	5.07
L. Cerebellum posterior lobe (crus I)	–	14	–42	–76	–30	4.79
R. Substantia nigra	–	28	18	–22	–6	4.66
L. Middle temporal gyrus	20	8	–58	–38	–8	4.65
R. Cerebellum posterior lobe (tonsil)	–	10	16	–66	–34	4.44
L. Cerebellum posterior lobe (inferior semi-lunar)	–	87	–22	–76	–36	4.43
R. Middle occipital gyrus	19	9	40	–80	18	4.33
R. Angular gyrus	39	16	46	–58	40	4.33
L. Middle temporal gyrus	39	25	–52	–70	26	4.23
R. Superior frontal gyrus	9	11	18	50	28	4.23
R. Middle frontal gyrus	9	11	32	28	30	4.13
R. Superior frontal gyrus	9	7	18	56	24	4.09
L. Supramarginal gyrus	40	19	–50	–50	38	4.08
L. Parahippocampal gyrus	30	7	–12	–42	6	4.03
R. Supramarginal gyrus	40	15	60	–46	24	4.02
L. Middle temporal gyrus	39	27	–48	–62	38	4.00
R. Posterior cingulate	29	7	4	–44	10	3.97
R. Anterior cingulate	32	7	6	46	4	3.93
L. Cuneus	7	6	–2	–72	40	3.91
R. Occipital lobe (cuneus)	18	7	12	–80	24	3.9

L, left; R, right; BA, brodmann area.

reported to be activated with increasing memory load in vWM (Habeck et al., 2012).

These results are consistent with previous neuroimaging studies that show decreased activation in regions involved in WM processing following cognitive training (Schneiders et al., 2012; Schweizer et al., 2013; Miró-Padilla et al., 2018). Critically, none of these studies included an active control group. Hence, although the findings of these studies are relevant, it remains somewhat unknown whether the reported training effects were specific to WM or to the training itself, regardless of the type of training. Conversely, a study by Thompson et al. (2016) studied WM training effects with an active control group. Their experimental group performed WM training with a dual n-back task, the active control group performed a similarly intensive visuospatial training task demanding multiple objects tracking whereas the passive control group did not participate in any training but merely performed the same n-back task as the other groups before, and after the WM training time interval. They found that the experimental group compared to the active control group exhibited significantly reduced brain activity at 2-back and 3-back conditions in WM characteristic fronto-parietal networks. Vartanian et al. (2013) performed a study to investigate the effects of a verbal n-back training on a classical test of divergent thinking. Participants in the active control group completed a 4-choice RT task. The experimental group showed activity reductions in specific regions of the prefrontal cortex. Brehmer et al. (2011) examined the neural activity following 5 weeks of intensive WM training in healthy older adults. Similar to our design, in this study the experimental group received

an adaptive training whereas the active control group did a fixed low-level practice. They did not find specific training-related changes in WM but the experimental group showed a larger decrease in cortical brain regions compared to the active control group in a high load WM task. As mentioned before, given methodological differences between studies, results on WM training effects are still heterogeneous with some studies also reporting training-associated increases in activation (Salmi et al., 2018). Nevertheless, our findings and the results of methodologically similar studies led us to conclude that the decreased activation in WM areas after training can be interpreted as an indicator of a training-associated increase in neural efficiency (i.e., less neural energy needs to be invested in order to attain the same or an even better performance level after training). In other terms, practice-related activation decreases are the result of a more efficient use of specific neuronal circuits (Poldrack, 2000; Kelly and Garavan, 2005). This assumption is supported by a couple of additional aspects. First, studies demonstrating a negative association between WM activation and performance -i.e., with better performing subjects showing less activation in WM-characteristic networks (Bokde et al., 2010; Zilles et al., 2016)- reinforce this hypothesis. Second, the above mentioned HAROLD model is based on this assumption. According to this model younger people, usually characterized by higher cognitive capacities, tend to demonstrate less (i.e., more restricted, more lateralized) activation in relevant networks compared to elderly people. Third, findings showing a linear relationship between vWM demands and activation in WM-relevant regions clearly illustrate an association between the



**FIGURE 8 |** Results of the adaptive online n-back training [i.e., experimental group (S1 > S2) > control group (S1 > S2)] for 3-back > X-back at  $p < 0.05$  FDR corrected with a cluster extension of  $k = 6$  voxels). Coordinates are in MNI space and the color bar expresses the  $t$ -score.

level of cognitive demand and the strength and extent of neural activation (Champos and Petrides, 2010). Also, our results are somewhat consistent with the CRUNCH theory, which stands for the “compensation-related utilization of neural circuit’s hypothesis” (Reuter-Lorenz and Cappell, 2008). It suggests that older adults engage more neural activity than younger adults to meet task demands. The brain activity reduction after training in the experimental group may be explained by this theory, since after the training this group activated less brain regions in order to perform the vWM task successfully. We could hypothesize that after training the brain activity of older adults during the task is more similar to a “younger brain,” potentially as a result of neural plasticity. Thus, we assume that the decreased activation after training in association with decreasing WM demands (i.e., in our study as a result of intensive WM training) reflects a higher neuro-cognitive efficiency brought about by the vWM training.

### Behavioral Changes and Direct Effects

As expected, the training-associated changes in neural activation were accompanied by a significant enhancement in vWM performance in the fMRI task. Thus, we observed a significant improvement in the experimental group in terms of  $d'$  values

for the vWM condition (i.e., 3-back condition) whereas there was no such improvement in the low-level X-back condition demanding merely attentional processes. Considering that the training was an adaptive WM training this result is according to expectation. Interestingly, mean reaction times in the 3-back condition decreased in both groups, with the experimental group, however, improving to a considerably larger extent. Taking into account that motor response was practiced in both trainings, this result is likewise in line with our expectations. The performance improvement in the vWM condition from the fMRI task (i.e., 3-back level) in the experimental group was backed up by a significant training performance improvement of this group. This means that the improvement manifested itself both in the n-back task performed on the home-computer as well as in a different environment (i.e., in the fMRI scanner) with a stable n-back level - a clear indication of practice effects. Moreover, the experimental group improved their HAWIE-R digit span forward (i.e., vWM) performance compared to the control group thus demonstrating direct effects on a similar vWM task. Hence, the training had the expected effects on vWM performance. These results imply that the training was an effective and adequate method to improve WM-relevant processes (i.e., the encoding, maintenance, and



retrieval of verbal stimulus material). The finding that there were no significant improvements in the digit span backward test could be due to the fact that this subtest is significantly more complex than the forward version. Considering that the vWM training did not possess this level of complexity the lacking significance in the backward version is in line with recent results suggesting that the effects of WM training tend to be restricted to the cognitive demands provided by the training (Holmes et al., 2019; Linares et al., 2019).

Findings from previous studies seem to largely corroborate the effectiveness of WM trainings. Thus, Dahlin et al. (2008) examined the effects of a 5-week computer-based training demanding information updating in WM in a group of young and older adults. They observed significant training gains in both groups with the younger adults, however, recalling more four-letter sequences compared to the older trainees. Another study by Li et al. (2008) examined the effects of a 45-day non-adaptive spatial n-back training both in younger and older adults. Both groups improved in a spatial and a numerical 3-back task as well as in additional WM tasks. Similar results were reported by Buschkuehl et al. (2008). In a senior cohort they investigated the effects of a WM training which consisted of three tasks: one simple and two complex WM span tasks. As opposed to Dahlin et al. (2008) and Li et al. (2008), they investigated an active control group participating in light physical training. They also reported significant improvements on the training tasks in the experimental group compared to the active control group. In a study by Brehmer et al. (2012) two groups of participants (a younger and an older cohort) were investigated. Half of them performed an adaptive training, the other half performed a low-level task difficulty training (i.e., active condition). Their results indicated that the adaptive training led to larger training gains compared to the low-level practice, even in the older cohort. The results by Brehmer et al. (2012) are moreover in line with another recent study demonstrating an increase in WM performance in older individuals as a consequence of an adaptive computerized WM training (Tusch et al., 2016). Taken together, these findings and the results from our study suggest that there is room for cognitive improvement also at advanced age.

## Limitations

This study has some limitations. First, the control group performed a fixed n-back level during the 32 sessions not allowing them to improve. The training was too easy for them and we see a ceiling effect because most active control participants achieved the highest possible scores in a short period of time. This means that there is little or no variance between the participants – a fact which complicated result interpretation. Second, we did not control for lure items in the adaptive online n-back training. Lure items in the n-back task are non-target items that match an item earlier in the sequence but not at the current critical target position (Oberauer, 2005). Participants could potentially have responded to the item not because of the specific location but because of familiarity, leading to this interference. This problem is particularly pronounced among older adults suggesting that the contribution of familiarity items to WM performance increases with age (Schmiedek et al., 2009). Future studies should take these

limitations into account. Nevertheless, we think that this paper helps us to understand how WM training can lead to an improved neural efficiency in middle-aged adults.

## CONCLUSION

The present vWM training study which was carefully designed by taking into account methodologically relevant influencing factors (i.e., active control group, performance adapted training design, feedback during the training to motivate the participants, and advanced-age participants with a limited age range) led to significant activation decreases in WM-relevant regions and considerable improvements in vWM performance. In correspondence with the concept of “lifelong learning” present results clearly indicate that neural plasticity and behavioral improvement following vWM training is possible not only at younger age, but also in middle-aged adults.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Klinikum Rechts der Isar. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

ME, IY, and KK contributed to the conception and design of the study. ME designed the stimuli and online training, programmed the tasks, analyzed the neuroimaging data and training data, and wrote the first draft of the manuscript. ME and IR recruited, scanned, and tested the participants. IR analyzed part of the task-fMRI behavioral data and revisited all different versions of the manuscript. QW analyzed the cognitive tests. KK wrote sections of the manuscript. All authors contributed to the manuscript revision and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## **PART III: DISCUSSION**



## 7 Overall key results

The first study (chapter 5) investigated the neural correlates of vvWM through a comprehensive meta-analysis across 42 task-fMRI studies. The results showed that a fronto-parieto-cerebellar network and subcortical areas are involved in vvWM processing. Hence, the presented results corroborate the involvement of the previously discussed regions and provide evidence for the involvement of additional regions that have been underestimated in the literature up to now (namely, the cerebellum, the right lenticular nucleus, the left pre-SMA, and the bilateral median cingulate). Moreover, the first study investigated the effects of other factors possibly influencing the neural correlates of this cognitive construct. Meta-regression analyses suggested that age and mean RT contributed to the observed effects. It was found that age was negatively associated with activation in the bilateral IFC, right medial frontal gyrus, left insula, left putamen, left rolandic operculum, and the left superior temporal gyrus. It should be emphasized, however, that the meta-analysis included only three studies with older populations. For this reason, the results of the meta-analysis do not allow drawing any conclusions on the specific influence of age on the neural correlates of vvWM. Regarding mean RT, we found a positive association between this factor and left medial frontal gyrus and left precentral gyrus activation. It should be mentioned, however, that the information of mean RT was not available for all studies and that this factor is influenced by multiple other variables (e.g., delay time, type of discrimination, number of response alternatives in the task, among others). Therefore, we should be careful when drawing conclusions from these results. It is striking, however, that activation closely associated with mean RT turned out to be located in regions critically involved in motor performance. Nevertheless, further research trying to control for these additional influencing factors is certainly needed. Finally, we performed an additional meta-analysis on those studies that assessed the neural correlates of increasing vvWM load (i.e., difficulty of the task). This analysis revealed activation in several frontal and parietal areas as well as in the left anterior cingulate gyri, bilateral median cingulate gyri, and right cerebellum, thus delineating a specific network relevant for increasing vvWM task demands.

The second study (chapter 6) investigated the effects of an adaptive online vvWM training in healthy middle-aged adults. The experimental group performed an adaptive  $n$ -back training whereas the active control group performed a stable fixed-level  $n$ -back training. Results showed that mean training performance in the experimental group improved significantly across the training period (i.e., both regarding the achieved  $n$ -back level as well as with regard to performance accuracy). In addition, the experimental group showed a significant improvement in the task-fMRI task (i.e., performance in the 3-back condition) compared to the active control group as well as in the external vvWM task (i.e., the forward digit-span task). Thus, the experimental group showed a significantly improved performance not only in the training itself, but also in the  $n$ -back task within the fMRI scanner as well as the external WM task which was not detectable in the control group. This clearly indicates that the training successfully improved WM performance. However, there was no significant improvement in the backward digit-span task in the experimental group compared to the control group. Nevertheless, the behavioral improvements in the experimental group were accompanied by relative activity decreases in regions that are assumed to be essential for vvWM. In sum, these results clearly demonstrate that the standardized, intensive WM training caused a significant WM performance improvement accompanied by an increase in neural efficiency in our cohort of middle-aged training participants.

## 8 Integrating Results into the WM literature

The contribution of the presented publications can be summarized in two main points:

First, there is a set of core regions that are essentially involved in vvWM performance. These are the fronto-parieto-cerebellar network and several subcortical areas. Moreover, the activation of these areas is modulated by specific influencing factors.

Second, these specific brain activations decrease with a training-related improvement in vvWM performance in healthy middle-aged adults. Hence, present results suggest that prolonged online WM training in middle-aged participants leads to a more automatized performance and a more efficient neural processing. Thus, these findings clearly support the concept of life-long learning.

In the following section I will discuss the relevant regions in more detail and compare them with the WM literature.

### 8.1 Training-related brain changes in activation

As mentioned before, fronto-parietal activity has been commonly observed during vvWM tasks (see meta-analyses by Owen et al. (2005); Rottschy et al. (2012)). Our first study (chapter 5) seems to specifically corroborate the dual-selection model proposed by Nee et al. (2013) regarding the frontal organization. Moreover, our study also shows that there was a left-lateralization of parietal areas during vvWM tasks.

The adaptive online vvWM training resulted in reduced brain activity in several regions,



believed to be essential for vvWM processing. Interestingly, there was a considerable overlap between the regions showing training-related changes (chapter 6) and those regions identified in the meta-analysis (chapter 5) (i.e., the left SMG, cerebellum, cingulate gyrus, right angular gyrus, and right middle frontal gyrus (MFG)). As there is good reason to assume that these regions are of particular importance for vvWM they will be specifically discussed in the following section.

### 8.1.1 Left SMG

The left SMG, located in the left inferior parietal lobule, is also known as Brodmann area (BA) 40. It has been proposed as the location of the *phonological store* (Paulesu et al., 1993). Buchsbaum and D’Esposito (2008) discussed how the exact location of the *phonological store* has been reported in different parts of the brain by several studies. Therefore, the precise brain location of the *phonological store* is still under debate, -assuming there is only one- (Buchsbaum and D’Esposito, 2008; Aboitiz et al., 2010). The results from chapters 5 and 6 reflect this issue as well. In the meta-analysis, we found activity in the left inferior parietal lobule, which, however, turned out to be a heterogeneous result in the heterogeneity analyses, whereas in the second study we found activity decreases specifically in the left SMG. Our results, as well as the literature, converge on one point: there is no single specific brain area that perfectly contains the *phonological store*. Accordingly, we have good reason to assume that the *phonological store* is simply not restricted to a single region. Nevertheless, although the precise role of the left inferior parietal lobe—and, specifically, the left SMG—remains controversial, there is anatomical evidence supporting the area’s participation in auditory-vocal processing (Aboitiz et al., 2010). Oberhuber et al. (2016), on the other hand, studied the function of the left SMG in healthy participants and found four “functionally-distinct” brain areas within the left SMG. This finding further questions the idea of a functional unity of the area and suggests that this region does not have one single, specific function.

### 8.1.2 Cerebellum

The cerebellum is mainly considered important for motor control (Holmes, 1939; Glickstein, 1992). It is comprised of ten lobules, grouped as follows: the anterior lobe (lobules I to V), the posterior lobe (lobules VI to IX), and the flocculonodular lobe (lobule X) (Voogd and Glickstein, 1998). In the past decade, the involvement of the cerebellum has also been implied in some higher cognitive functions, such as attention and WM (Ravizza et al., 2006, see O'Halloran et al. (2012) for a review). The results from our presented meta-analysis provide further support in favor of the cerebellum's importance for cognitive abilities—more specifically, the involvement of the right cerebellum (specifically, Crus I) in vvWM. However, the published meta-analysis does not discuss the heterogeneity analysis which fails to confirm the stability of this region. Thus, the activation of this specific region could indicate a possible publication bias. However, the fact that the right Crus I is connected to prefrontal cortical areas (Schmahmann, 1996) and the cerebellum has been found to be lateralized in clinical studies (Silveri et al., 1998; Hokkanen et al., 2006; Tomlinson et al., 2014) speaks in favor of this area contributing to vvWM. The specific role of this area for vvWM is still unknown. Nevertheless, Desmond et al. (1997) proposed that the superior lobule VI/Crus I is linked to Broca's area, which is involved in articulatory rehearsal. In line with the latter, Silveri et al. (1998) report a case study of a patient with an impairment of the rehearsal processing after a right cerebellar hemispherectomy but a preserved function of the *phonological store*. This result points to a connection between the right cerebellum and subvocal rehearsal (*articulatory loop*).

In the second study, we found activation in the posterior lobe of the cerebellum. The fact that we did not find any activity in the anterior lobe of the cerebellum was expected since its function is related to overt speech, which was not required the fMRI task (Marvel and Desmond, 2010). Previous studies proposed that the posterior cerebellum plays a key role in higher-order functions (Allen et al., 1997; Gottwald et al., 2004). Moreover, cognitive impairments have been reported in patients with posterior lobe lesions affecting lobules VI and

VII, including Crus I and Crus II (Stoodley and Schmahmann, 2010). Therefore, observing a decrease in activity following WM training in lobules VI and VII and crus I and II is in line with the literature given our assumption that the training-related decrease reflects an increase in cerebral efficiency. To our surprise, however, we also found decreased activity in the left posterior cerebellum following WM training, showing no lateralization of the cerebellum when the verbal  $n$ -back task was presented. However, this is in agreement with a number of studies that specifically report bilateral cerebellar posterior activation during the  $n$ -back task (Labar et al., 1999; Honey et al., 2002; Tomasi et al., 2005; Valera et al., 2005; Miró-Padilla et al., 2019). One ad hoc speculation is that there are different WM-related brain regions depending on the verbal WM task used. The fact that we did not find brain activity differences between the different tasks in our meta-analysis could be due to the existing task differences being too weak to be significant. It is important to mention that studies using  $n$ -back and Sternberg/DMTS tasks were included in the meta-analysis, whereas no study using complex span task has been analyzed, which has been found to correlate poorly with the  $n$ -back task (Redick and Lindsey, 2013). Therefore, there are strong grounds for believing that we would have detected brain activity differences between  $n$ -back and complex span tasks. In accordance with our findings, the meta-analysis by Rottschy et al. (2012) did likewise not find any difference in cerebellum activity depending on the task. Taken together, our findings provide additional support for the assumption of  $n$ -back task-specific activity in the posterior cerebellum (i.e., bilateral activity).

### 8.1.3 Cingulate

Apart from the cerebellum and the SMG the cingulate turned out as a region relevant for vvWM in our studies. The cingulate cortex is located in the medial aspect of the cerebral cortex and it is considered to be part of the limbic lobe (Jumah and Dossani, 2019). Evidence points to a functional differentiation between a dorsal (cognitive) and ventral (emotional) subdivision (Bush et al., 2000). Accordingly, we detected activity of the dorsal cingulate in the meta-analysis (see Fig. 2 of chapter 5) as well as in additional parts of the cingulate in

the second paper. Regarding WM specific processes, there is evidence of the anterior and posterior cingulate being involved in encoding and retrieval (or recall) (Rypma and D'Esposito, 1999). On the other hand, Bedwell et al. (2005) reported bilateral middle cingulate activity during encoding and maintenance and anterior cingulate activity during retrieval. These conflicting results could in part be explained by the fact that there is still no clearly agreed upon anatomical separation between the different parts of the cingulate. It is essential to stress the high degree to which the results reported in the meta-analysis depend on the anatomical atlas used. The Automated Anatomical Labelling (AAL) atlas labeled the activity of the cingulate to the median part, but the cingulate cortex has been classically separated into anterior and posterior cingulate as well as ventral and dorsal cortices (however, see Jumah and Dossani (2019)). Therefore, a clearer sub-division of the cingulate would be essential in order to elucidate the role of its different parts in vvWM.

#### 8.1.4 Right angular gyrus

The angular gyrus is a brain region in the posterior part of the inferior parietal lobe corresponding to BA 39. It lies immediately posterior to the SMG and has been found to be active during several tasks (e.g., attention, memory, and language) (Seghier, 2013). The function of this region relevant to memory could be explained by its connection to the hippocampus (Makris et al., 2005, 2009; Uddin et al., 2010). Moreover, it has been specifically associated with vvWM, especially during the retrieval of verbal material (Jonides et al., 1998). This region has also been found to be activated in the context of response inhibition (Wager et al., 2005). To the best of my knowledge, the activity of this region has not been reported in any previous vvWM meta-analyses. The heterogeneity analyses of the meta-analysis moreover labeled the angular gyrus finding as heterogeneous. Therefore, even if we found activity of this region in the reported meta-analyses and there was a training-associated decrease in this region in the second study, further analyses are necessary to establish its role in vvWM processing.

### 8.1.5 Right MFG

The right MFG, as the name indicates, is part of the frontal lobule and corresponds to BA 9. The right MFG constitutes a major part of the DLPFC which is a functional structure that has connections to several parts of the brain, such as the orbitofrontal cortex and basal ganglia. The DLPFC is involved in WM as well as in planning (Barbey et al., 2013). There has been an ongoing debate in cognitive neuroscience about the specific function of this area in relation to WM (Miró-Padilla, 2018). On the one hand, there are studies suggesting domain-general functions, specifically monitoring and the manipulation of information (D’Esposito et al., 1998; Petrides, 2000; Curtis and D’Esposito, 2003), whereas on the other hand, domain-specific models suggest a role of the DLFC in the preparation of visuo-spatial information processing and in re-directing attention from external objects to internal representations of sensory stimuli and motor plans (Barbey et al., 2013; Japee et al., 2015). Strong evidence for the domain-general functions of this area comes from studies with nonhuman primates in which it was shown that lesions of this area disrupt performance in typical WM tasks. Additional support comes from a number of studies with human participants (Petrides, 2005; Balconi, 2013; Barbey et al., 2013). Considering that in our studies we were not able to differentiate between the different WM sub-processes, present findings cannot really corroborate any of the models.

Last but not last, it has been observed that the magnitude of age-related decreases in cortical surface is the greatest in this area (Lemaitre et al., 2012). The fact that we found a negative correlation between right MFG activation and age in the meta-analysis (chapter 5) provides support to the ontogenetic model of Raz et al. (2005), which states that those brain regions that are the last to mature are the first to be affected by age.

## 8.2 Neural efficiency and the effectiveness of WM training

As described in chapter 6 we found that the standardized, intensive WM training was associated with significant activation decreased in multiple regions. As mentioned in the discussion of the results reported in chapter 6, decreased activation in training-related WM areas could be an indicator of increased neural efficiency. This means that less brain activity is needed in order to successfully perform the given cognitive task. A number of studies corroborate this hypothesis by demonstrating a negative association between WM activation and performance, i.e. with better performing subjects showing less activation in WM-characteristic networks (Bokde et al., 2010; Zilles et al., 2016). Likewise, findings showing a linear relationship between vWM demands and activation in WM-relevant regions are in line with this hypothesis (Champod and Petrides, 2010). Moreover, one could also conclude that the training did not only go along with a higher performance after the training, but also with brain activation patterns more similar to those of younger people. This observation is based on two closely related theories: the HAROLD model and the CRUNCH theory. First, the HAROLD model assumes that younger people need less brain activity compared to elderly people to show the same performance. Second, the CRUNCH theory, which stands for the “compensation-related utilization of neural circuit’s hypothesis” (Reuter-Lorenz and Cappell, 2008), suggests that a compensatory increase in brain activity is employed in older people compared to younger adults to meet task demands. In accordance with the HAROLD model and CRUNCH theory, we conclude that the decrease in activity in association with an increase in performance following WM training in our middle-aged cohort reflects an increased neural efficiency or, in other terms, a cerebral rejuvenation brought about by the training.

Regarding behavioral changes going along with the (experimental) training, we found training effects (i.e., significant improvements in training performance), practice effects (i.e., improvements on the trained task) and direct-/near- transfer effects for only one task (namely, the forward digit span task). The forward digit span task is based on digits (and therefore

different from the training task). The fact that we did not find transfer to the other version of the task (i.e., backward version of the digit span task) partially supports the view that vvWM training does not transfer to other WM task categories. This is in clear agreement with the results reported in a recently published meta-analysis on the effects of WM training in older adults (Sala et al., 2019), in which an effect of the intervention on the trained tasks and only modest near-transfer effects were found. Far-transfer effects of WM training are beyond the scope of this thesis, as they were not addressed directly by the current studies.

In sum, we can only conclude that the WM training intervention presented in this thesis increases WM capacity, however, improvements in this cognitive construct did not yield changes in the processes involved in other WM tasks (i.e. backward digit span task).

## 9 Thesis achievements, limitations and future work

The present papers add to the knowledge of the neural correlates of vvWM and its training-related brain changes in middle-aged populations. In the following lines, several achievements as well as limitations and potential future work will be addressed.

First, the coordinate-based meta-analysis on the neural correlates of vvWM provides insight into the implicated brain regions and elucidates the role of several potential influential factors. To the best of our knowledge, it is the first time that a meta-analysis has investigated these potential influential factors. Considering, however, that the vast majority of the selected studies (i.e., all but three) was based on healthy younger populations the results of the age factor need to be considered with caution. Moreover, we have chosen a coordinate-based meta-analysis over an image-based meta-analysis for practical reasons (most of the neuroimaging papers do not include their imaging data). This might be considered a limitation given that Salimi-Khorshidi et al. (2009) argue that image-based meta-analyses should be preferred over coordinate-based meta-analyses. In order to facilitate this kind of meta-analysis, the neuroimaging community should provide an effective mechanism to share imaging data within the scientific community. Regarding more methodological future directions, it is also advisable to disentangle the neural correlates of the specific vvWM periods that can be specifically studied using Sternberg or DMTS tasks (i.e., encoding, maintenance, and retrieval).

Second, we have investigated the behavioral and neural effects of vvWM training in a healthy middle-aged population. To the best of our knowledge, this is the first time in the literature that a study investigates these effects in this specific age range (namely, 50 to 65 years old). Moreover, we have taken the previous limitations of the WM training literature into account and tried to overcome them with a well-defined study design. Nevertheless, some limitations should be mentioned. There was no control for lures, that is, non-target



items that match an item earlier in the presented item's sequence but not at the current target position (Oberauer, 2005). This might have led to an interference problem, meaning that participants could have responded to the item because of familiarity (allowing for a strategy requiring participants to only remember the presented items but not the order of presentation). Moreover, the participants did not train only one specific WM modality (e.g., verbal) but rather two (verbal as well as visual WM, with abstract shapes as stimuli). This could have led to interference problems in the results. Another issue that needs to be discussed is that the active control group did not improve inbetween the first and last sessions due to a ceiling effect. In this case, the ceiling effect is observed because the independent variable (i.e. training) no longer has an effect on the measured dependent variable (i.e. performance). However, to the best of my knowledge there is no gold-standard control training in the WM training literature (von Bastian and Oberauer, 2014). Therefore, fixed  $n$ -back training might be the best possible active control task, since participants are training the same cognitive construct as the experimental group but to a lower extent and at a considerably lower level of difficulty. I also believe that this specific training has less expectation differences between both groups (i.e., there is a similar level of expectation of improvement), since both groups are training WM (Oken, 2008). Regarding future work, I would like to investigate near- and far-transfer effects of this training as well as its long-term effects by performing a task-fMRI and cognitive test battery after nine months of training. Moreover, there are only three studies on the neural effects of WM training in a near-transfer effect task (Dahlin et al., 2008a; Beatty et al., 2015; Heinzl et al., 2016) and one study in a far-transfer effect task (Clark et al., 2017). It would be interesting to see whether the transfer effects are also reflected on a neural level.

## 10 Conclusion

Working memory is one of the essential psychological constructs and strongly correlated with several higher-order cognitive functions. Thus, WM training has been a persistent and central research issue in the psychological and neurocognitive literature for the past 20 years. Today, this kind of training constitutes a multimillion dollar industry, primarily targeted toward the aging and elderly (Costandi, 2016). Currently, however, there is little evidence that WM training leads to transfer effects. Nevertheless, there are strong reasons to believe that the brain is still flexible at middle-age. We are only just beginning to understand the way in which the brain can adapt to environmental demands. Technological advances will provide us with better tools to image the brain in more detail, and in turn allow us to deepen our knowledge about the changes in the brain structure and function following WM trainings.



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## List of publications

Alves-Pinto, A., Emch, M., & Lampe, R. (2020). A case study of piano training effects in unilateral cerebral palsy using probabilistic and deterministic tractography. [Journal article] *Brain and Behavior*. (submitted)

Bunk, S., Emch, M., Koch, K., Lautenbacher, S., Zuidema, S., & Kunz, M. (2020). Pain processing in older adults and its association with prefrontal characteristics. [Journal article] *Journal of Pain Research*. (submitted)

Emch, M., von Bastian, C. C., & Koch, K. (2019). Neural Correlates of Verbal Working Memory: An fMRI Meta-Analysis. *Frontiers in Human Neuroscience*, 13: 1–17. <https://doi.org/10.3389/fnhum.2019.00180>

Emch, M., Ripp, I., Wu, Q., Yakushev, I., & Koch, K. (2019). Neural and Behavioral Effects of an Adaptive Online Verbal Working Memory Training in Healthy Middle-Aged Adults. *Frontiers in Aging Neuroscience*, 11: 1–14. <https://doi.org/10.3389/fnagi.2019.00300>

Emch, M. (2015). Ventro-striatal/Nucleus accumbens alterations in adult ADHD: effects of pharmacological treatment: a neuroimaging region of interest study. Bachelor thesis, Universitat Pompeu Fabra.



## **Eidesstattliche Versicherung/Affidavit**

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation "Exploring visual verbal working memory - Neural correlates & the effect of an adaptive online training on brain activity and cognitive performance" selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation "Exploring visual verbal working memory - Neural correlates & the effect of an adaptive online training on brain activity and cognitive performance" is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 21.02.2020

Munich, 21.02.2020

Mónica Emch Franco

