Aus dem Institut für Medizinische Psychologie der

Ludwig-Maximilians-Universität München

Morphometric reorganization induced by working memory training: perspective from vertex and network levels

Dissertation

zum Erwerb des Doktorgrades der Humanbiologie

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

vorgelegt von

Qiong Wu

aus

Jiangsu, China

Jahr

2023

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

Erster Gutachter:	Prof. Dr. Dr. h.c. mult. Ernst Pöppel
Zweiter Gutachter:	Prof. Dr. Kathrin Koch
Dritter Gutachter:	Prof. Dr. Thomas Liebig
Dekan:	Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 11.01.2023

Table of content

Table of content

Zusammenfassung

Der sich beschleunigende globale Alterungsprozess und die Tatsache, dass sich die kognitiven Fähigkeiten mit dem Alter verschlechtern, was sich erheblich auf die Lebensqualität älterer Erwachsener auswirkt, insbesondere bei altersbedingten Störungen (z. B. kognitiver Beeinträchtigung, Demenz), weisen auf einen dringenden Bedarf an Ansätzen zum Schutz und zur Verbesserung der kognitiven Fähigkeiten sowie an Untersuchungen der neuronalen Substrate altersbedingter Veränderungen und der Neuroplastizität hin. Da man davon ausgeht, dass das Arbeitsgedächtnis (WM) die grundlegende Ursache für altersbedingte kognitive Beeinträchtigungen bei einer Vielzahl von kognitiven Fähigkeiten darstellt, ist das Arbeitsgedächtnistraining (WMT) zu einem aktuellen Thema und einem beliebten Ansatz geworden. Frühere Studien haben gezeigt, dass das Arbeitsgedächtnistraining (WMT) die kognitive Leistung verbessert. Die spezifischen Auswirkungen sowie die zugrunde liegenden neurobiologischen Mechanismen sind jedoch nach wie vor umstritten.

Ziel dieser Arbeit ist es, die durch das WMT induzierte neuronale strukturelle Plastizität auf mehreren Ebenen sowie die Verhaltenseffekte des WMT zu untersuchen. In der ersten Studie untersuchten wir die topographischen Veränderungen der Morphologie der grauen Substanz durch WMT, indem wir vier strukturelle Metriken (d.h. die kortikale Dicke, das kortikale Volumen, die kortikale Oberfläche und den lokalen Gyrifikationsindex, LGI) sowie die subkortikalen Volumina explorierten. Konkret wurden 59 gesunde Probanden mittleren Alters nach dem Zufallsprinzip entweder einem adaptiven WMT oder einer nicht-adaptiven Intervention zugewiesen. Alle Teilnehmer unterzogen sich vor und nach der 8-wöchigen WMT-Phase einer Neurobildgebung sowie kognitiven Tests. Vor und nach dem WMT wurden vier kortikale Metriken auf Scheitelpunktniveau und sieben subkortikale Volumina sowie die globale mittlere kortikale Dicke berechnet. Das wichtigste Ergebnis war, dass die WMT-Gruppe im Vergleich zur aktiven Kontrollgruppe eine größere Zunahme der kortikalen Faltung in den bilateralen parietalen Regionen zeigte. Die Ergebnisse deuten darauf hin, dass strukturelle Veränderungen durch WMT in WM-bezogenen Regionen, insbesondere in parietalen Regionen, die Verarbeitung einer höheren WM-Belastung erleichtern können. Darüber hinaus könnte die kortikale Faltung das relevanteste und plastischste Merkmal von WM und Lernen sein und WMT-Effekte stärker widerspiegeln als andere Metriken.

Basierend auf den Ergebnissen der ersten Studie haben wir darüber hinaus untersucht, ob die trainingsinduzierten Effekte des WMT in der kortikalen Faltung auf Vertex-Ebene von topologischen Veränderungen begleitet werden. Zu diesem Zweck untersuchten wir in Studie zwei die durch WMT verursachte Plastizität auf Netzwerkebene mit Hilfe eines strukturellen Kovarianzansatzes (SC), der auf denselben Stichproben basiert. Es wurden gyrifikationsbasierte SC-Matrizen für jede Gruppe vor und nach dem Training sowie longitudinale gyrifikationsbasierte SC-Matrizen erstellt. Innerhalb jeder Gruppe ergab die LGI-basierte SC-Analyse keine Hinweise auf WMT-induzierte Veränderungen der kortiko-kortikalen Verbindungen, weder in der WMT- noch in der aktiven Kontrollgruppe. Die Ergebnisse der longitudinalen SC-Analyse (unkorrigiert $p < 0,005$) zeigten, dass die trainingsinduzierten Veränderungen der kortikalen Faltungsintensität signifikante Unterschiede zwischen Paaren von parietalen Regionen sowie Paaren von frontalen Regionen aufwiesen.

Insgesamt deuten die kombinierten Ergebnisse dieser beiden Studien darauf hin, dass erstens WMT neuronale strukturelle Plastizität hervorrufen kann; zweitens die kortikale Faltung das relevanteste und plastischste Merkmal von WM und Lernen sein könnte, das die Auswirkungen von WMT besser widerspiegelt als andere Indikatoren auf Vertex-Ebene; und drittens die trainingsinduzierten lokalisierten Veränderungen der kortikalen Faltung von einem ähnlichen Muster vergleichbarer struktureller Veränderungen zwischen ROIs innerhalb der Regionen begleitet wurden. In Zukunft sind weitere Forschungen erforderlich, um diese Ergebnisse zu wiederholen und zu validieren sowie um trainingsinduzierte topologische und topografische Veränderungen anhand einer breiteren Palette von Metriken und Eigenschaften zu untersuchen.

Abstract

The accelerating global aging process and the fact that cognitive abilities deteriorate with age, which has a significant impact on the quality of life of older adults, particularly those with age-related disorders (e.g., cognitive impairment, dementia), all point to an urgent need for approaches to protect and enhance cognitive abilities, as well as studies of the neural substrates of aging-related changes and neuroplasticity. Since working memory (WM) has been assumed to be the fundamental source of age-related cognitive impairments in a variety of cognitive abilities, working memory training (WMT) has become a hot topic as well as a popular approach. Previous studies have established that working memory training (WMT) improves cognitive performance. However, the specific effects, as well as the underlying neurobiological mechanisms, remain a matter of controversy.

The purpose of this thesis is to investigate WMT-induced neural structural plasticity at multiple levels together with the behavioral effects of WMT. In study one, we investigated the topographic changes of grey matter morphology due to WMT by combining four structural metrics (i.e., cortical thickness (CT), cortical volume (CV), cortical surface area (CSA), and local gyrification index (LGI)) as well as subcortical volumes. Specifically, 59 healthy volunteers between the ages of 50 and 65 were randomly assigned to either an adaptive or a non-adaptive intervention. All participants underwent neuroimaging as well as cognitive testing before and after the 8-week intervention. Four cortical metrics at vertex level and seven subcortical volumes, as well as global mean cortical thickness, were calculated before and after the intervention. The most important finding was that the adaptive WMT group showed greater increases in cortical folding in bilateral parietal regions in comparison to the active control group who performed the non-adaptive intervention. The results indicate that structural changes due to adaptive WMT in WM related regions, particularly parietal regions, may facilitate the processing of a higher WM load. In addition, the cortical folding might be the most relevant and plastic feature of WM and learning, reflecting WMT effects more than other metrics.

Based on the findings of study one, we further asked whether the training-induced effects of WMT in cortical folding at vertex-level are accompanied by topological changes. To this end, study two investigated network-level plasticity due to WMT by using the structural covariance (SC) approach based on the same samples. Gyrification based SC matrices for each group before and after training, together with longitudinal gyrification SC

matrices, were constructed. Within each group, the LGI-based SC analysis revealed no evidence of WMT-induced changes in cortical-cortical connections, either in the WMT or the active control groups. The results of the longitudinal SC analysis (uncorrected $p < 0.005$) revealed that the training induced changes of cortical folding intensity showed significant difference between pairs of parietal regions as well as pairs of frontal regions.

Overall, the combined findings of these two studies indicate that: firstly, WMT can produce neural structural plasticity; secondly, cortical folding might be the most relevant and plastic feature of WM and learning, better reflecting the effects of WMT than other vertex-level indicators; and thirdly, the training induced localized changes in cortical folding were accompanied by the pattern of similar structural changes between ROIs within the regions. In the future, more research is required to replicate and validate these findings, as well as to investigate training-induced topological and topographic changes using a broader set of metrics and properties.

List of figures

List of tables

List of abbreviations

AD	Alzheimer’s disease
ANOVA	Analysis of variance
CDT	Clock Drawing Test
CSF	Cerebrospinal fluid
CSV	Cortical surface area
CT	Cortical thickness
CV	Cortical volume
EHI	Edinburgh Handedness Inventor
LGI	local gyrification index
LME	Linear mixed effects
LTM	Long-term memory
M.I.N.I	Mini-International Neuropsychiatric Interview
MANOVA	Multivariate analysis of variance
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
PMC	Primary motor cortex
ROI	Region of interest
SBA	Surface-based analysis
SBM	Surface-based Morphometry
SC	Structural covariance
sMRI	Structural magnetic resonance imaging
SPC	Symmetrized percent change
VBM	Voxel-based Morphometry
WM	Working memory
WMT	Working memory training

1. Introduction

1.1 Working memory

What is working memory (WM)? This term actually evolved from the concept of short-term memory, which refers to the capacity for temporally holding information but not manipulating it. In contrast, WM, as the term itself implies, includes two key parts: "memory" and "working", which represent a combination of temporal storage of information and manipulation. Namely, it is required to hold information and perform mental operations on that information at the same time. WM is defined as a cognitive system that is capable of retaining a limited amount of temporal accessible information and manipulating and using that information in the course of ongoing cognitive processing (A. Baddeley, 2010; A. D. Baddeley & Hitch, 1974). The amount of information that can be accessed is limited by the capacity of the WM, which is varying among individuals (Cowan, 2005).

Several theoretical models of WM have been proposed for how WM functions (e.g., multi-store model, embedded-processes model, multiple component model et al.) (Atkinson & Shiffrin, 1968a; A. D. Baddeley & Hitch, 1974; Cowan, 1999). Here I will focus mainly on the model proposed by Baddeley – the multicomponent WM model, which is the most influential and accepted model for explaining WM (A. Baddeley, 2010; A. D. Baddeley & Hitch, 1974).

An initial three-component model was proposed by Baddeley and Hitch (1974), including three critical components: an attentional system that is aided by two short-term storage systems. The role of the attentional system (i.e., the central executive) is to guide executive attention to the most relevant aspects of information in a time period and to manage the WM capacity. Two additional short-term storage systems (i.e., the visuospatial sketchpad and the phonological loop) are in charge of verbal acoustic information and visual information, respectively. Over the years, the model has been refined and improved; today, the term "multicomponent WM model" refers to the revised version, which includes a fourth component called the episodic buffer (A. Baddeley, 2010). The episodic buffer is a temporal storage system with a limited capacity that allows for the interaction

and combination of visual and verbal information as well as other types of information (e.g., smell and taste) are allowed to be interacted with and combined (A. Baddeley, 2012). Namely, the episodic buffer serves as a mental workspace in which it is capable of holding, manipulating, and integrating various sensory inputs. Apart from serving as a buffer for information exchange between the components of WM, the episodic buffer is also linked to perception and long-term memory (LTM). Thus, WM is not only for current cognitive processing (short-term use), but also for further cognitive processing. By bridging perception, LTM and action, WM aids the brain in organizing new information for long-term storage (A. Baddeley, 2000). The brain may store information in a messy and disorganized manner, which has an impact on LTM, if there are deficits in WM. LTM refers to the storage of large quantities of information over a prolonged period of time. The duration as well as the capacity of LTM is potentially unlimited (Atkinson & Shiffrin, 1968b).

For a schematic overview of the multicomponent WM model, please see Figure 1 (A. Baddeley, 2010).

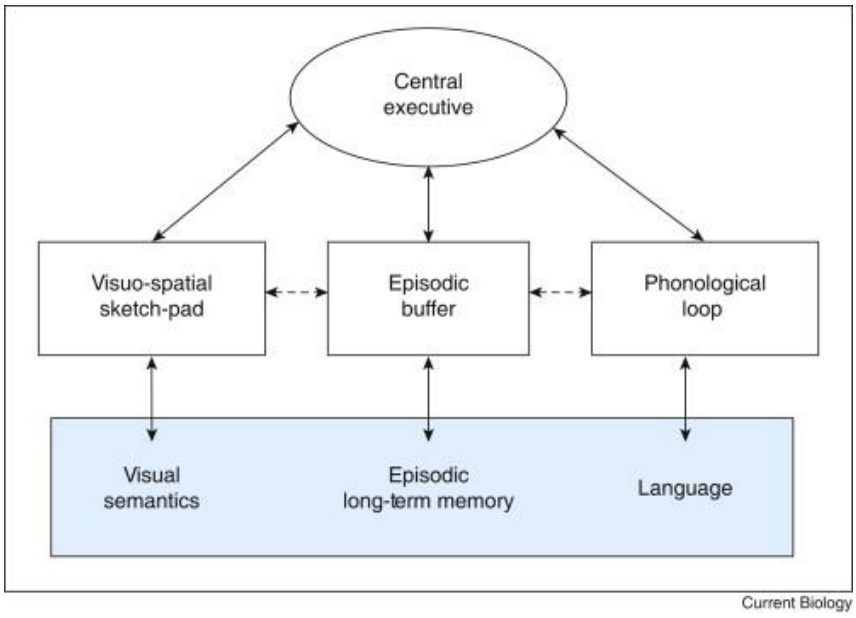


Figure 1: A schematic overview of the multicomponent model of working memory (A. Baddeley, 2010).

Neuroimaging techniques have enabled numerous neuroimaging studies aimed at decoding WM from a neuroscientific perspective. Previous neuroimaging studies have demonstrated that the degree to which different brain areas contribute to WM varies significantly

across the lifespan. During early development, WM is primarily dependent on subcortical structures (e.g., hippocampus, thalamus, striatum, and insula), with gradual extension to cortical structures in late childhood/early adolescence, and then WM is primarily dependent on a cortical network of frontoparietal regions (Froudist-Walsh et al., 2018). Due to the fact that the frontoparietal network is the primary network associated with WM (e.g., greater involvement in WM), it is also referred to as the WM neural network. This network is composed primarily of brain areas including the anterior cingulate cortex (ACC), the parietal cortex, as well as the dorsolateral prefrontal cortex (DLPFC)(Kim et al., 2015; Osaka et al., 2003). WM is involved in multiple brain regions, meaning that WM relies on not only the functional specialization of isolated brain regions, but also the functional integration of relevant brain areas (A. D. Baddeley, 2000). Please see Figure 2 that depicts the neural representation of the multicomponent WM model (Chai et al., 2018).

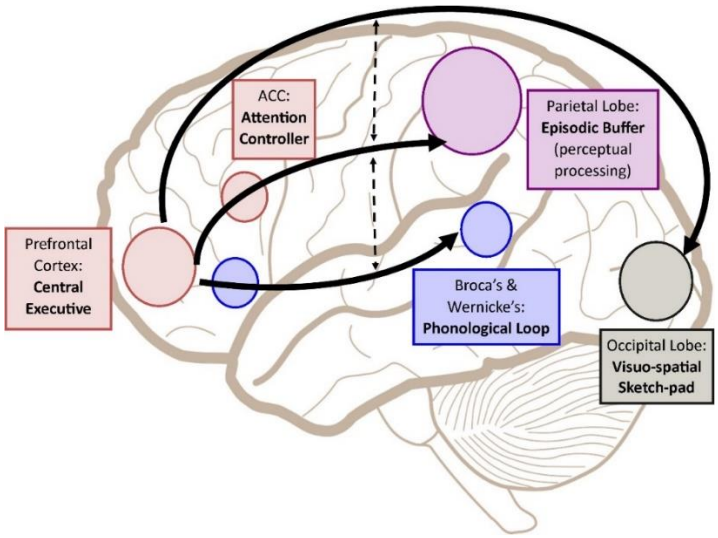


Figure 2: Neuroanatomical depiction of multicomponent WM model (Chai et al., 2018). *With permission from Chai et al. (2018)*

1.2 Aging, working memory, and brain structure

With the development of society, economy and medical care, people worldwide are living longer. In 21st century, the life span of the population has changed unprecedentedly, and one of the most significant population trending is aging (Izekenova et al., 2015). According the results of the 2019 version of World Population Prospects, the world's population aged 65 years and older was 702.9 million in 2019, which was over 9% of the world's population (https://population.un.org/wpp/). According to the United Nations Population Fund (UNPFA), the number of people aged 65 years and older is expected to reach 1548.9

million by 2050. The global population over the age of 65 is projected to hit 16% in 2050 (see Figure 3). Aging is a global phenomenon and the pace of population aging worldwide is increasing dramatically. Global aging has a significant impact on society and brings all countries the challenge – how to enable people experience healthy aging, in other words, how to develop and maintain the functional ability in order for people to enjoy a relatively good quality of life in their later years (Sciubba, 2020).

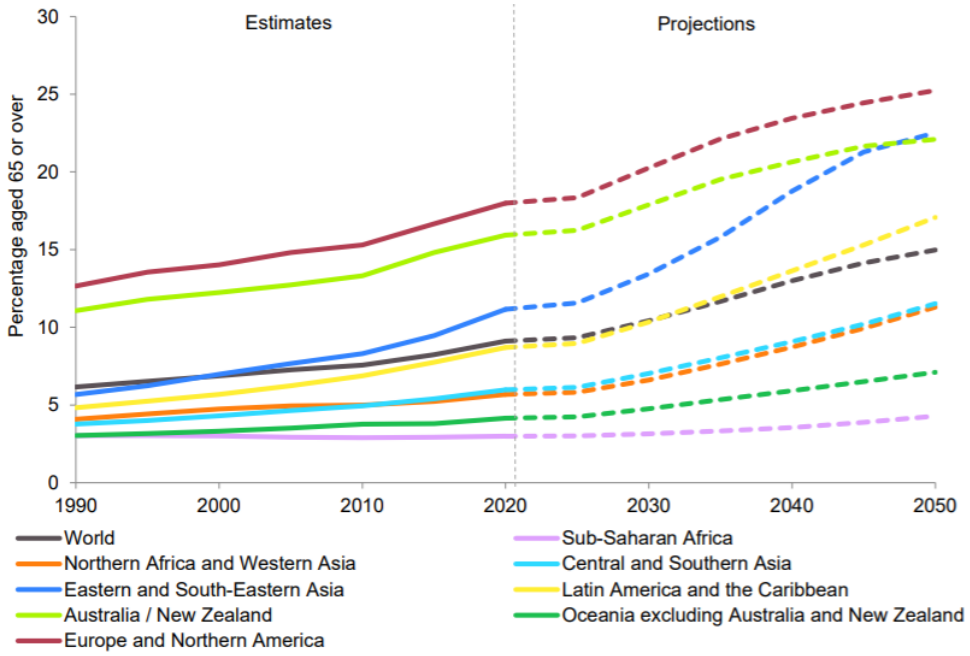


Figure 3: Proportion of the population aged 65 or older.

Source: United Nations Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019.

Human aging is related to the accumulated changes of physical, psychological, behavioral, and social changes in a human being over time (Shock, 2020). As people age, they may grow wiser as the effects of experience and learned knowledge. However, they also experience some decreases in cognitive abilities, which are referred to as fluid intelligence. Previous studies of cognitive function across the life span revealed that performances on measures of fluid intelligence including short-term memory, working memory, speed of processing, as well as long-term memory decline with age (Glisky, 2007; Park et al., 2002) (see Figure 4). Specifically, WM has been hypothesized to be the primary cause of age-related deficits in a variety of cognitive abilities (e.g., long-term memory, language, decision making, and problem solving) (Glisky, 2007). WM has been hypothesized as the fundamental source for the reason that WM is associated with higher-order cognitive

processes (e.g., reasoning, problem solving, planning, etc.) That appears to be critical for a variety of cognitive tasks and engaging processing strategies. (Diamond, 2013; Kane et al., 2007). Namely, WM is associated with higher-order cognitive functions which are crucial in daily life.

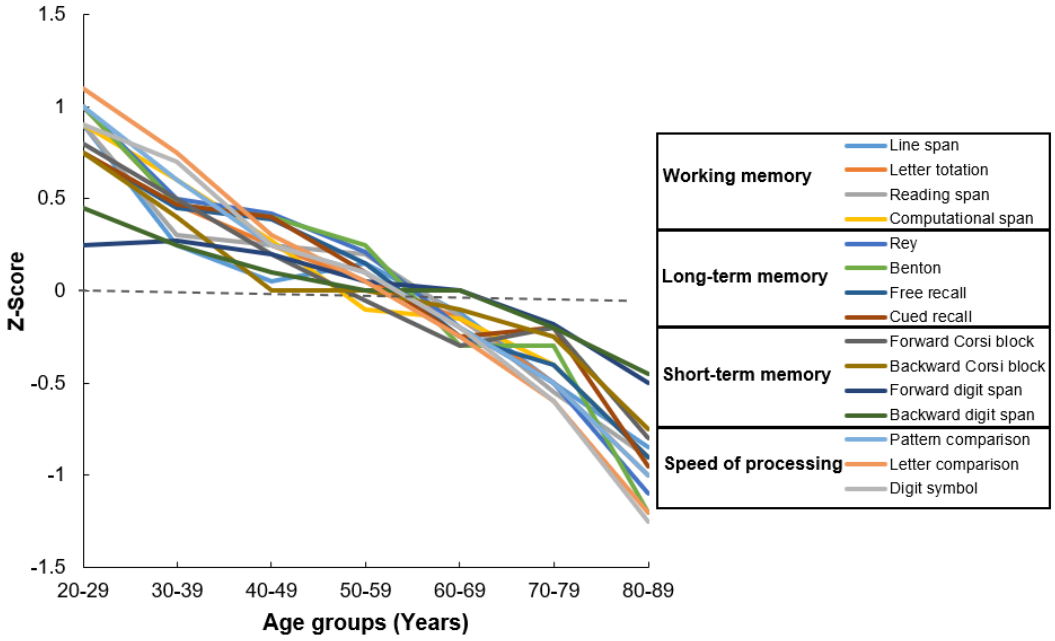


Figure 4: Behavioral performance on measures of cognitive function (fluid intelligence) across life span. *Adapted from Park et al. (2002)*

Along with the decline in cognitive functions, the brain's size and/or its weight decreases with age. It has been reported that brain atrophy is estimated to occur at a rate of approximately 5% per decade after the age of 40 (Peters, 2006). The shrinking of grey matter is one of the most significant brain structural deteriorations with increasing age, which may be due to the brain atrophy stemming from changes in neurons (e.g., shrinkage of neurons and neuronal cell death), dendrites (decreases in the number and length), synaptic spines, and synapses (Peters, 2006; Shock, 2020). Age-associated changes in brain structure have been reported both globally and regionally, however, the changes are not uniform across the whole brain. In other words, neuroanatomical changes do not occur to the same extent in all brain regions. With aging, certain regions of the brain experience shrinkage, especially those that are important to learning complex mental activities. Previous studies have shown that the prefrontal and temporal cortex, as well as subcortical cortex (e.g., putamen, thalamus, and accumbens), are the areas most affected by age (Fjell & Walhovd, 2010). In fact, the age-related neuroanatomical changes, to a substantial degree, could

explain the reductions in selected cognitive functions in the elderly population (for a review see Fjell & Walhovd (2010)). For example, with aging neurons in specific regions, or/and the number of synapse/synaptic dendrites may be reduced, which can cause communication issues between neurons or cells. These changes can affect cognitive functions. Actually, Nissim et al. (2016) reported that the worse performance on WM tasks was associated with a reduction in cortical surface areas of the frontal cortex.

Cognitive declines and neurostructural deficits associated with aging, increase susceptibility to and frequency of disease, frailty, or disability. In fact, aging is a leading risk factor for a variety of human diseases, especially chronic diseases. For instance, dementia becomes more prevalent with advancing age (Larson et al., 2013). Approximately 3% of people aged 65-74 years, 19% of those aged 75-84, and nearly half of those over 85 years old have dementia. Almost all the age-related cognitive, biological, neurostructural, and behavioral changes are related. With aging, there is a dynamic interplay between factors that lead to neurodegeneration and cognitive impairments and factors that lead to neuroplasticity and improved cognitive function (see Figure 5).

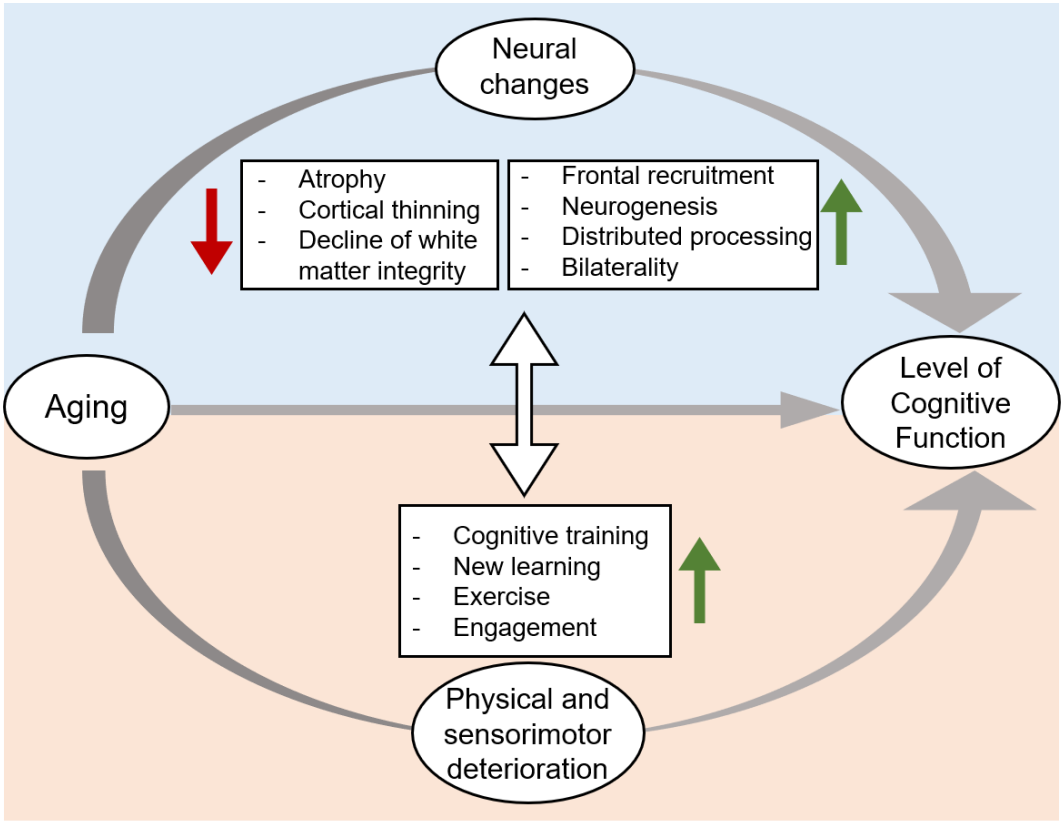


Figure 5: Aging related behavioral and neural changes as well as modifying factors. *Adapted and modified from Kraft (2012) and Park et al. (2009).*

In the light of the global aging phenomenon and the gradual deterioration of cognitive abilities with age, as well as the critical impact of cognitive functions on quality of life in the elderly population, particularly elderly individuals with age-related diseases (e.g., cognitive impairments, dementia), techniques to improve and maintain cognitive abilities, are gaining increasing importance (McNab et al., 2015). Furthermore, it is desirable to understand the neural mechanisms underlying aging-related changes as well as the neuroplasticity of the aging brain. In fact, there is a range of evidence suggesting that even the older brain has considerable plasticity or is able to adapt to new challenges/tasks (Park & Bischof, 2013).

1.3 Neuroanatomical measures

Grey matter and white matter are the major components of the central nervous system. White matter consists of axons that are coated with myelin, while grey matter consists of neural cell bodies, dendrites, synapses, and unmyelinated axons (Schultz, 2001). Both grey matter and white matter are essential components of the brain, however, grey matter plays the most significant part in allowing humans to function normally daily (Mercadante & Tadi, 2021).

Magnetic resonance imaging (MRI) is a powerful brain imaging technique invented by Peter Mansfield and Paul Lauterbur that utilizes magnetic fields and radio waves to produce high quality two-dimensional or three-dimensional images of brain structures/functions without the use of ionizing radiation or radioactive tracers (Lauterbur, 1989; Weishaupt et al., 2007). Thus, being non-invasive and posing little health risk, MRI is a safe technique which can be used even on infants. MRI has been widely applied in medical diagnosis (e.g., tumor and injury) as well as in academic researches. By using specific MRI sequences, different MRI signals can be acquired from tissue types (i.e., using structural MRI) or from metabolic changes (i.e., using functional MRI). Specifically, structural MRI (sMRI) provides detailed information to qualitatively and quantitatively evaluate the shape, size, location, and integrity of grey and white matter structures of the brain by using different types of sMRI sequences (e.g., T1-weighted sMRI, T2-weighted sMRI, and diffusion tensor imaging) (Mukherjee et al., 2008; Torkzad et al., 2014). Hereas, I will focus primarily on T1-weighted sMRI, which measures spin-lattice relaxation by using a short echo time (TE) and repetition time (TR). The two most prominent approaches

(i.e., Voxel-Based Morphometry and Surface-Based Morphometry) used to analyze high-resolution T1-weighted data will be described below.

1.3.1 Voxel-based morphometry

Voxel-based morphometry (VBM) is one of the key computational approaches in neuro-anatomy to investigate the differences in local distribution of grey matter density or grey matter concentration by comparing image intensities voxel by voxel (Ashburner & Friston, 2000). Unlike traditional morphometric methods which measure specific brain structures, VBM provides a comprehensive assessment of neuroanatomical differences throughout the entire brain.

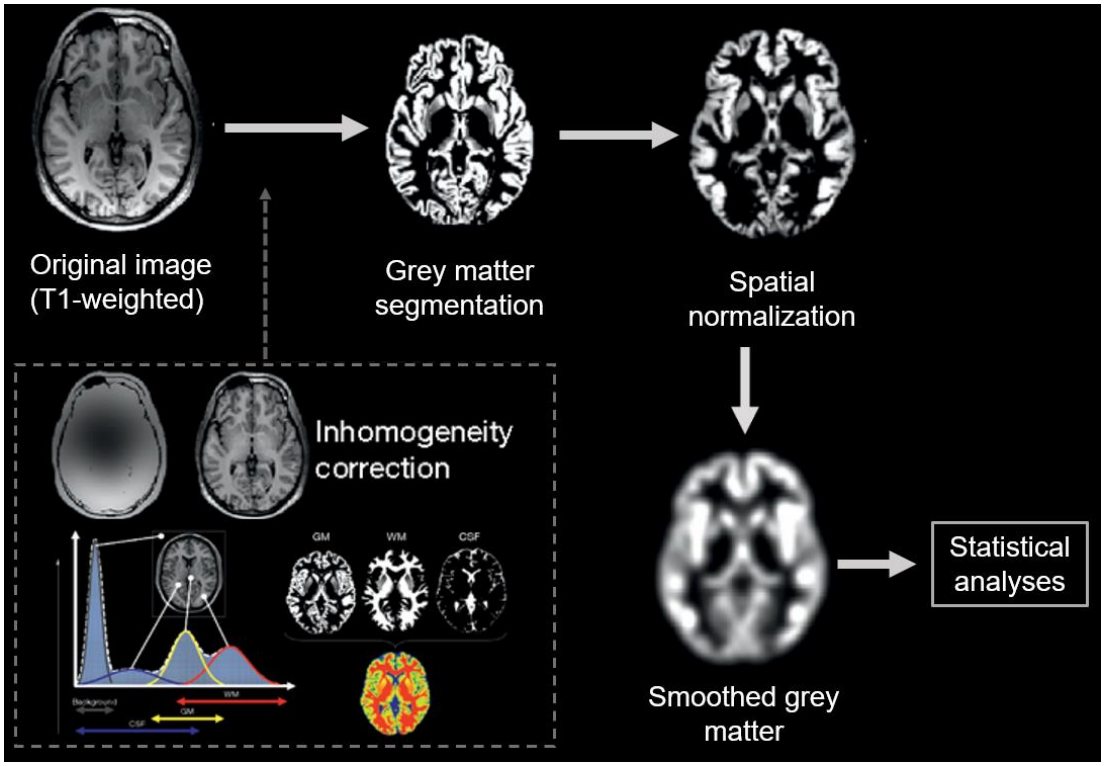


Figure 6: Overview of voxel-based morphometry (VBM) analysis. *Adapted from Kurth & Luders (2015)*

The concept of VBM is composed of three key processing steps (Figure 3). Briefly, after correcting for inhomogeneities, the high-resolution T1-weighted images are segmented into grey matter, white matter, and cerebrospinal fluid. The obtained gray matter segment is then registered to a standard template. Afterwards, the spatially normalized data are smoothed with an isotropic Gaussian Kernel so that each voxel represents the average of

itself and its neighbors. Finally, the smoothed images are used for further voxel-wise statistical analysis (Kurth & Luders, 2015; Andrea Mechelli et al., 2005).

Of note, though VBM is methodologically simple and provides comprehensive information about grey matter intensity globally, it's harder to interpret the results because grey matter density/concentration is a mixture of thickness, surface area, gyrification registration, volume-based smoothing, and intensity. In other words, VBM is incapable of isolating the geometrical basis underlying cortical changes, which means that changes in local grey matter density or concentration may be caused by variations in cortical thickness, surface area, cortical folding, signal intensity, or any possible combination of these measures.

1.3.2 Surface-based morphometry

Surface-based morphometry (SBM) or surface-based analysis (SBA), differing from VBM described above which ultimately analyzes brain properties at the voxel level, is a set of brain morphometric approaches used to construct and analyze surfaces that are representative of structural boundaries within the brain (Dale et al., 1999; Fischl et al., 1999). The boundaries are generated from a cortical surface model, where a grid consisting of a set of vertices and the adjacencies of each vertex is used to define the boundaries between different tissue types.

The boundaries between white matter and grey matter or between grey matter and cerebrospinal fluid (CSF) are referred to as white surface and pial surface respectively, which are mainly involved in SBM analyses (Dale et al., 1999). The major steps involved in SBM analysis includes surface reconstruction (The reconstructed surfaces, i.e., pial surface and white surface can be used to calculate different cortical metrics, for instance thickness, surface area, etc.), surface inflation and surface mapping (Figure 4).

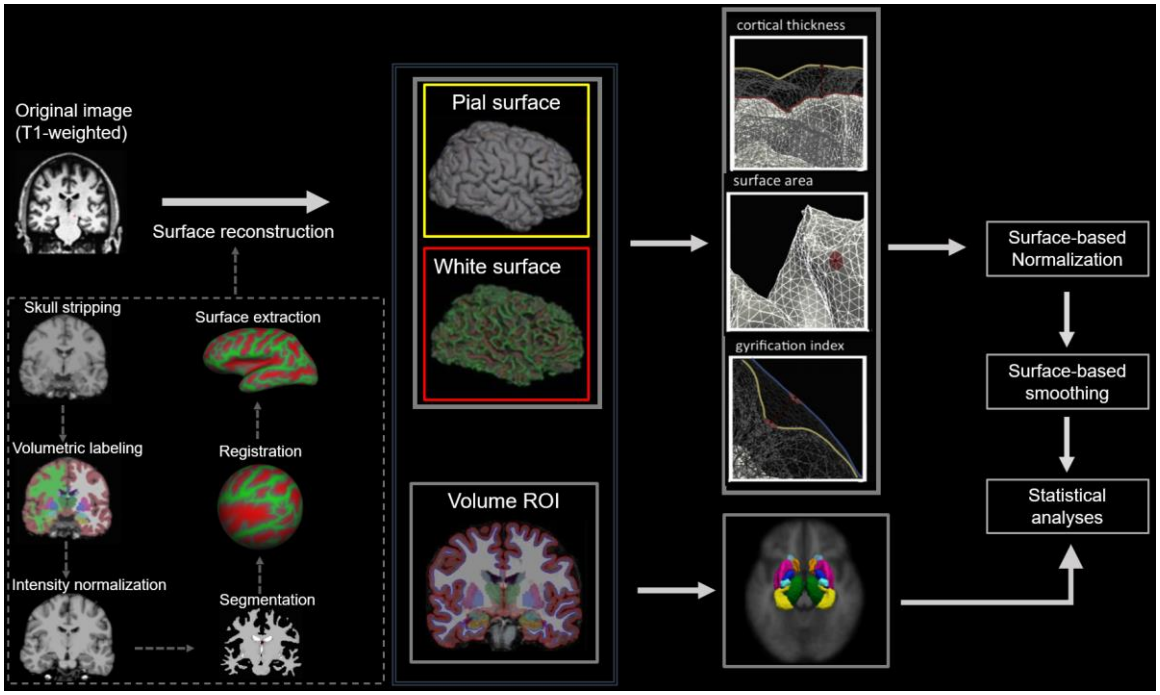


Figure 7: Workflow of surface-based morphometric analyses.

SBM enables researchers to estimate properties of brain structure by using more specific surface-based metrics including cortical thickness (CT), cortical volume (CV), cortical surface area (CSA), and local gyrification index (LGI) (Fischl & Dale, 2000). CT refers to the shortest distance between gray-white boundary (white surface) and the gray-cerebrospinal fluid interface (pial surface), whereas CSA (the total area of the surface encompassing a brain region) was calculated as the sum of the area of the vertices within a given region on the white surface (Winkler et al., 2012). The local gyrification index (LGI) was calculated as the ratio of the folded pial surface (25mm radius circular region of interest) to the surface of the corresponding smoothed outer surface using surface-based, 3D gyrification measurements (Schaer et al., 2008). The values of LGI indicate the degree of complexity of folding at a given pial surface, and LGI values can range between 1 and 5, with greater LGI values being buried in the sulcal folds (Schaer et al., 2012).

SBM has several advantages over VBM. First, it has been demonstrated that brain function has not only voxel-based organization but also surface-based organization (Sereno et al., 1995). Thus, SBM contributes to the understanding of the cortical mechanisms related to specific functions. Second, SBM can provide a more precise and accurate interpretation of cortical morphometry through different measurements of CT, CSA, and CV, which allows for the differentiation of CT and CSA contributions to CV. CT and

CSA have non-identical genetic backgrounds, cellular mechanisms, as well as developmental trajectories (Panizzon et al., 2009). Third, the surface-based methods address a number of the constraints and methodological issues inherent to VBM (e.g., significantly higher accuracy in registration than any form of volume-based registration) (Ghosh et al., 2010; Montal et al., 2018). Additionally, SBM enables the evaluation of cortical folding which is quantified using the measure cortical folding (Schaer et al., 2008; Zilles et al., 2013).

1.3.3 Structural covariance

The structural covariance (SC) analysis is a well-established and widely used structural MRI measure to infer cortico-cortical connectivity, despite the fact that the neurobiological mechanisms underlying the inter-regional SC have yet to be well elucidated (Alexander-Bloch et al., 2013). SC characterizes the relationship between pairs of brain regions in morphological terms (e.g., CT, CV, etc.) based on the assumption that inter-individual differences in morphology (i.e., regional structure) covary within communities of brain regions (Alexander-Bloch et al., 2013). For instance, the changes of cortical thickness or cortical volume in one region have impact on the volume or thickness of other regions which are structurally and functionally connected (Geerligs et al., 2016; A. Mechelli et al., 2005). It has been reported that SC is related to functional connectivity as well as structural connectivity captured by white matter tractography (Romero-Garcia et al., 2018). Nevertheless, SC is a unique metric for assessing cortico-cortical connectivity on the grounds that it represents, to a certain extent, the outcome of a mutually trophic benefit to distant regions that are anatomically connected, in a way that other metrics cannot. The SC is related to synchronous changes between neurons during development. It is hypothesized that synapses between distant neurons during development may result in mutually reinforcing trophic effects under the influence of common factors (e.g., genetic, environmental, functional activation, white matter connectivity, and so on), leading to structural covariation at the macroscale level. (Alexander-Bloch et al., 2013). In addition, this connectivity measure (i.e., SC) is sensitive to altered connectivity and brain network organization (Bethlehem et al., 2017; Wannan et al., 2019).

The concept of SC analysis is composed of three key processing steps: 1) Parameter (e.g., CT, CV, LGI, etc.) estimation of each predefined brain region; 2) Computing the inter-regional correlations of the parameter estimation; 3) Brain-wise correlation matrix of each

group (i.e., group-wise SC matrices were created). Please see Figure 8 that illustrates the workflow of SC analysis (Alexander-Bloch et al., 2013).

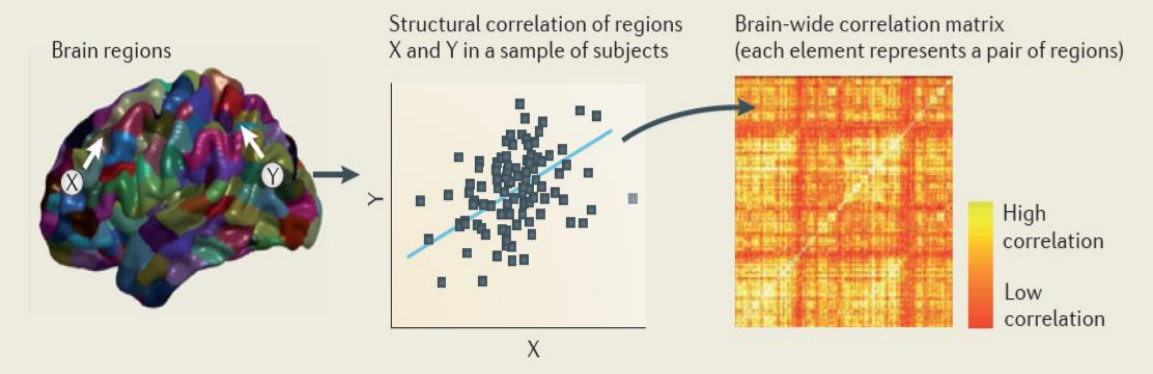


Figure 8: Overview of structural co-variance measurement in human brain MRI data. *With permission from Alexander-Bloch (2013).*

1.4 Working memory training

Working memory training (WMT) is aimed to improve the performance of WM. In recent years, WMT targeting to improve the WM capacity has been an important topic, especially the transfer effects of WM.

As mentioned in section 1.1, several theoretical models have been proposed to explain how WM functions, which are based on different assumptions. Notably, all the theoretical models assume that the amount of accessible information used for manipulation and maintenance (i.e., WM capacity) is limited and varies considerably across individuals. Additionally, WM capacity is closely related to other higher-order cognitive functions (e.g., reading, fluid intelligence, comprehension, and reasoning abilities) that are crucial for each day life functioning (Fukuda et al., 2010; Johnson et al., 2013; Süß et al., 2002). Thus, WM capacity not only can predict how WM performance and performance on other high-level cognitive abilities change across the life-span, but also can predict individual differences in other cognitive abilities (Cowan et al., 2005; Krogsrud et al., 2021).

Given the link between WM capacity and higher-order cognitive functions, the limitations of WM may place restrictions on higher-level cognitive functioning. This suggests that if WM capacity can be improved by training, this should generalize benefits to other cognitive skills as well (Shipstead et al., 2010). Thus, WM training (WMT) with the goal of improving WM capacity has become an important and hot topic (von Bastian & Oberauer, 2014). A variety of tasks, such as the delayed match-to-sample task, Sternberg, N-back

task, and span tasks can be used to assess WM capacity as well as be used as WMT tasks (Oberauer, 2005; Wilhelm et al., 2013).

The transfer effects induced by WMT have become one of the key research focuses. According to the similarity between the transfer and the trained tasks, the effects of WMT can be categorized into practice effects, near, and far transfer effects. Practice effects refers the cognitive improvements in the trained task (Jolles et al., 2012), whereas the improvements in tasks with similar materials are near effects, far transfer effects are those improvements on other cognitive domains (e.g., improvements on fluid intelligence, academic and behavioral outcomes) that differ from the WMT programs (Melby-Lervag et al., 2016). The key for WMT is the possibility that the training induced improvements will not only transfer to tasks with different materials but also lead to improvements on other cognitive abilities like fluid intelligence, reasoning, and decision making (Jaeggi et al., 2008).

1.5 Previous studies – working memory training effects

As mentioned above, on the behavioral level, the primary goal of WMT studies is to generalize transfer effects, particularly far transfer effects that may manifest as enhanced abilities for daily life functioning (Jobe et al., 2001). Previous studies have shown consistent and repeated evidence that WMT can produce strong practice effects (i.e., WMT induced cognitive improvements in the training tasks) (Sala et al., 2019; Soveri et al., 2017). However, the findings of transfer effects induced by WMT are inconsistent, even the conclusions of meta-analyses are contradictory. Inconsistencies in these findings have been attributed to a number of factors (e.g., methodological differences), including the existence or lack of an active control group, training tasks, training intensity, duration, and so on. Notably, among these methodological differences, the presence and type of the control group is the primary contributor to the inconsistent results of previous studies (Soveri et al., 2017). Significant improvement in fluid intelligence in healthy young adults was reported in one meta-analysis study by Au et al. (2015), though the training induced transfer effect was small. Nevertheless, other meta-analyses did not find significant improvements in any measure of ‘far transfer’ (Melby-Lervag et al., 2016; Sala et al., 2019; Soveri et al., 2017).

Regarding neuroimaging studies of WMT, most studies investigating the neural effects of WMT were based on task-based fMRI. A meta-analysis by Salmi et al. (2018) reported changes in brain activity induced by WMT within different networks related to WM, such as the dorsal attention and salience network and so on. Previous WMT investigations, particularly those employing n-back tasks as the training paradigm, indicate that training-induced activation of WM-related areas appears to decline under low and moderate demands (e.g., no higher than 3-back) (Aguirre et al., 2019; Clark et al., 2017; Heinzel et al., 2016; Miro-Padilla et al., 2019; Schneiders et al., 2011; Schneiders et al., 2012; Schweizer et al., 2013), but increase under higher loads (e.g., 4-back and 5-back) (Buschkuehl et al., 2014; Schweizer et al., 2013). Our group reported significantly decreased neural activity in WM characteristic regions in the experimental group compared to the active control group based on verbal WM task fMRI data (i.e., when comparing the activity of 3-back vs. 0-back) (Emch, Ripp, et al., 2019).

The effects of WMT on anatomical structure have yet been investigated only by a handful of research to date, and even scarcer in healthy elderly. Moreover, the findings of these restricted investigations differed from one another. Takeuchi and his colleagues observed a decrease in grey matter volume in frontoparietal areas following mental calculation training for five days in a group of healthy young population (Takeuchi et al., 2011). Whereas, in a relatively recent investigation, greater grey matter volume was observed in several clusters located in posterior cingulate, the cerebellum, and the temporal lobe in WMT group following a three-month adaptive training, compared to a passive control training (Colom et al., 2016). Additionally, they reported significant changes in CT and CSA by performing surface-based analysis on the same dataset with a-priori region of interests (ROIs) (Roman et al., 2016). Of note, both of the two studies used a young healthy cohort with restriction to female college students, limiting their conclusions/discoveries were not comparable to other populations (e.g., male participants or other groups with different age). In addition, because the supervised training was conducted in the laboratory, the findings may not generalize to more natural environments (e.g., home-based training). Engvig et al. (2010) found increased thickness in the right fusiform and insula following an 8-week WMT in a healthy elderly population were accompanied by reduced thickness in a passive control group. Metzler-Baddeley et al. (2016a, 2016b) discovered that WM training-related increased CT locating in right caudal middle frontal cortex, increased CV in the left pallidum, while decreased CT in the right insula, by using

a-priori ROIs. However, another recent ROI-based study found no evidence of significant grey matter plasticity (i.e., in terms of changes in grey matter volume, CSA, and CT) following a 6-week WMT with n-back paradigm (Lawlor-Savage et al., 2019). In general, the findings of these small investigations did not corroborate one another (e.g., training induced changes in brain regions were heterogeneous both spatially and in the direction of changes (i.e., increase vs. decrease)). Notably, most of the above reported structural changes in brain regions are also frequently reported to have changes in brain activation as revealed by fMRI studies.

In addition to training induced regional changes (i.e., changes at the vertex level), it is critical to investigate and quantify the relationship between WMT-induced changes in different brain regions, as this reveals training-related changes in topology. The SC is a more appropriate model for illustrating how training-induced changes in ROIs interact (i.e., training induced topological changes). To our knowledge, no study has been conducted to date on the topological changes induced by WMT. Previous studies have found that changes in structural covariance are associated with cognitive abilities, ageing, and age-related disorders (e.g., cognitive impairments and Alzheimer's disease (AD)) (DuPre & Spreng, 2017; Pichet Binette et al., 2020; Qing et al., 2021). Thus, if we can demonstrate that non-pharmacological interventions such as WMT can affect topology, this will aid in our understanding of the neural mechanisms underlying learning and aging.

Taken together, given the context of global aging as well as the aging related changes in the brain and WM, it is critical to develop effective interventions to preserve health and cognitive function, as well as to prevent or even help alleviate the burden of age-related diseases. Of those interventions, WMT has become an important and hot topic since WM has been assumed as the fundamental source of age-related impairments in a variety of cognitive abilities that are crucial for daily life. According to the above literature review, the grey matter structural effects induced by WMT have not been thoroughly investigated, particularly in middle-aged and elderly individuals. Previous evidence for the neural structural effects of WMT on grey matter was not congruent. Variations in training approaches (e.g., active vs. passive control groups, training paradigms, intensity, location, duration, and supervision), populations (e.g., specific age groups, pure male/female cohorts), and analyzing methods (e.g., a-priori ROIs vs. whole brain approaches, voxel-based vs. surface-based methods) may account for some of these inconsistencies and suggest the necessity of additional empirical evidence based on well-controlled studies.

2. Purposes of the thesis

Given the foregoing, particularly the contradictory literature, it seems worthwhile to explore the WMT induced grey matter plasticity at multiple levels (i.e., vertex-level, regional-level, global-level). The purpose of this thesis was of twofold.

Firstly, the study one aimed to assess if there is WMT-induced grey matter plasticity in a middle-aged group. If so, which neural metric is the most relevant and most plastic characteristic in terms of working memory and learning. To this end, a working memory group and an active control group of healthy volunteers (50-65 years old) completed neuroimaging as well as cognitive testing before and after an 8-week WMT. The WMT group received adaptive n-back training, while the CON group received non-adaptive training with a low-level of fixed difficulty by using the equivalent stimuli. We utilized adaptive n-back training because it is widely used and considered to be one of the most efficient WMT paradigms. We chose this particular age group (50–65 years old) for several reasons. First, this age group occurs immediately before the onset of aging, which is the primary risk for a variety of neurodegenerative diseases (e.g., dementia). Thus, early prevention is necessary to protect the brain from age-related damage, and the age range chosen appears to be optimal for an early but not excessively early prevention. Second, the human brain is dynamic and plastic throughout life, which means that neural plasticity varies across the lifespan. Thus, the mechanisms underlying young adult brain plasticity may not generalize to elderly adults. Given the relatively intact cognition and lack of significant atrophy in middle-aged individuals, training in this restricted age group may be more promising than training in older adults, thereby excluding potentially confounding effects on WM-related neural plasticity. Therefore, WMT in this age group, if proven to be successful, could result in a delay of cognitive decline due to age or disease. Surface-based morphometry was employed to investigate the neuroplastic effects due to WMT on grey matter structure. Specifically, we investigated the WMT related changes in vertex-wised grey matter metrics (CT, VSA, CV, and LGI) as well as subcortical volumes. Additionally, cognitive performance on an extensive cognitive test battery were accessed before and after the intervention in order to capture the transfer effects of WMT.

Secondly, based on the findings from study one, we aimed to capture whether grey matter plasticity in cortical folding at vertex level co-occurs with plasticity at a network level. The vertex-level results indicate that cortical folding might represent the most relevant

and most plastic characteristic of working memory and learning, reflecting WM training effects to a greater extent than the other metrics (i.e., CV, CT and CSA) at the vertex level. In light of the vertex-level findings, we further asked whether the WMT-induced grey matter plasticity observed in cortical folding also occurs at the network level. When compared to analyses at the vertex level, which miss out on quantifying the relationship between changes across different cortex regions, the structural covariance analysis is a more robust method for capturing the pattern of coordinated changes between ROIs due to training. In addition, cognitive functions, especially higher order cognitive functions, instead of being determined by separate processing in specialized subsystems (i.e., function segregation), rely on the communications and the functional integration of different brain regions (i.e., global cooperation between different subsystems or function integration). Thus, it's of importance to characterize whether WMT could produce grey matter plasticity of large-scale neural connectivity (cortico-cortical connectivity), or whether network-based structural connectivity inferred from structural covariance could explain the topological distribution of WMT induced grey matter effects across the cortical cortex. These can provide further insight into WM training-related neural plasticity by evaluating interregional relationships in grey matter structure. We hypothesized that network-based effects (i.e., cortico-cortical connectivity) induced by WMT would be distributed in 'WM neural network', which means that the structural connectivity among cortical regions of frontoparietal network would be changed after WMT.

In summary, based on findings of these two studies, which could shed light on the neural mechanisms underlying grey matter plasticity caused by WMT in middle-aged adults.

3. Material and Methods

3.1 Participants

Participants were recruited through hospital bulletin boards or online advertisements. Prior to the enrollment, all volunteers underwent cognitive and neuropsychiatric screening tests, including the Mini-International Neuropsychiatric Interview (M.I.N.I), the short form of the geriatric depression scale (GDS), the Mini-Mental State Examination (MMSE), the Clock Drawing Test (CDT), and Edinburgh Handedness Inventory (EHI) (Agrell & Dehlin, 2012; Burke et al., 1991; Folstein et al., 1975; Sheehan et al., 1998; Veale, 2014). Volunteers who met the following inclusion criteria were included in our project: 1) No neurological or psychiatric illness; 2) No cognitive impairment; 3) No contraindication to MRI; 4) right-handedness; 5) German speakers; 6) Medication naïve during the study. Participants were assigned pseudo-randomly to either a working memory training group or an active control group using a single-blinding procedure (gender- and age- matched). Finally, fifty-nine participants were included in the analyses: twenty-eight in the active control group and thirty-one in the working memory training group (please see Figure 9 for details).

All participants were informed of the purpose of the current study and provided written informed consent. The study was approved by the federal office for radiation protection and the Ethics Committee of the Klinikum Rechts der Isar, Technische Universität München.

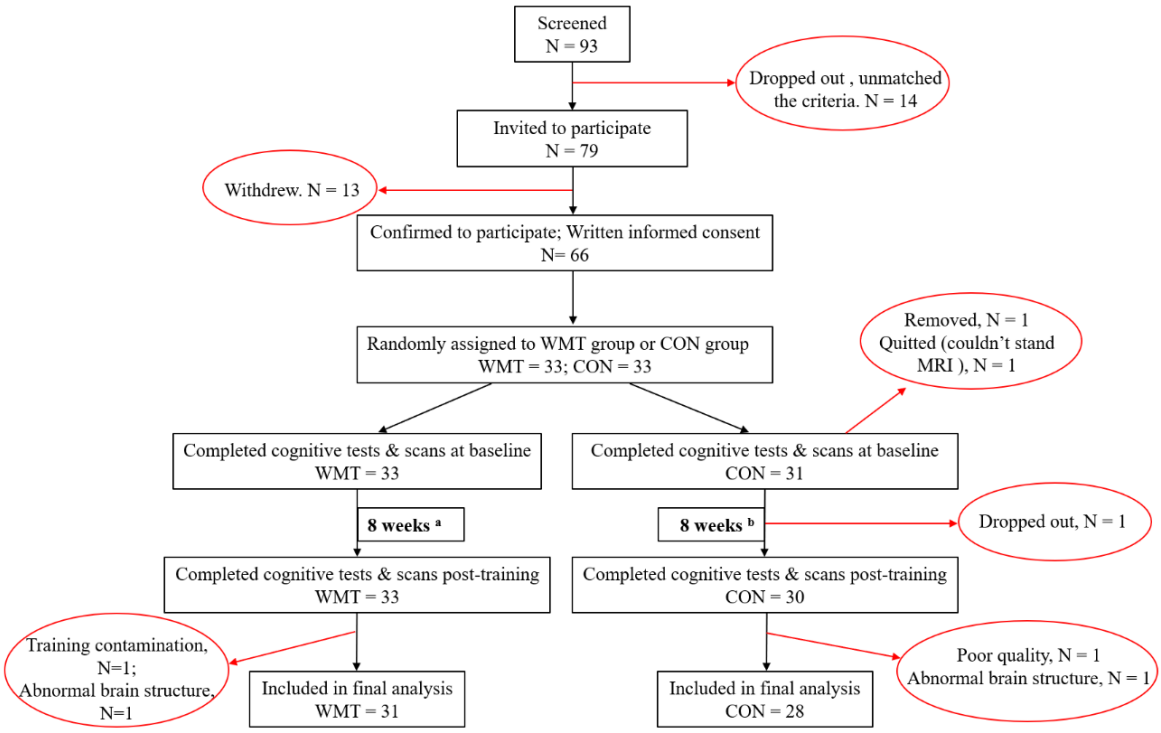


Figure 9: Flow chart of the study design.

WMT, working memory training; CON, control training; [a] adaptive n-back task training; [b] non-adaptive n-back task training.

3.2 Working memory training procedure

All participants received an 8-week supervised working memory training (WMT) that was conducted at home. The n-back task (i.e., visual n-back and verbal n-back) paradigm, which was adapted from Jaeggi et al.(2010), was used as training paradigm in the current study, Figure 10. The stimuli of both the visual and verbal tasks for both groups were equivalent.

The WMT group underwent an adaptive n-back training paradigm consisting of nine blocks per task type (i.e., nine blocks visual n-back tasks and nine blocks verbal n-back tasks), for a total of eighteen blocks each training session. Each block included a randomised sequence of six target trials as well as fourteen non-target trials. The adaptive n-back level ranged from one to nine. Participants began each session with a 1-back level and difficulty level (i.e., n-back) was increased or decreased adaptively based on the performance of participants. Specifically, if the correct response rate was greater than 90%, the level of n-back raised by one level in the following block, and if the correct response rate was less than 80%, the level of n-back lowered by one level. Or else, the level of n-back

remained constant. Figure 10B illustrates the example of 3-back verbal and visual tasks. The CON group received non-adaptive training (i.e., 1-back verbal task and X-back visual task), which meant that each task's difficulty level was set to a lower value which did not change (see Figure 10A). The X-back (i.e., 0-back) visual task required participants to give response whenever the target shape was presented. Throughout the entirety of the training, the instruction for the target shape was displayed at the start of each X-back block.

Each training session lasted approximately twenty minutes. The order of training tasks was counterbalanced between participants in each group. Participants were instructed to complete four training sessions per week and no more than one session each day. Following each training session, each participant's training data was saved in logfiles and automatically uploaded to the Millisecond Software website (https://www.millisecond.com/). The training status and performance were monitored, and all participants received a weekly training progress report via email.

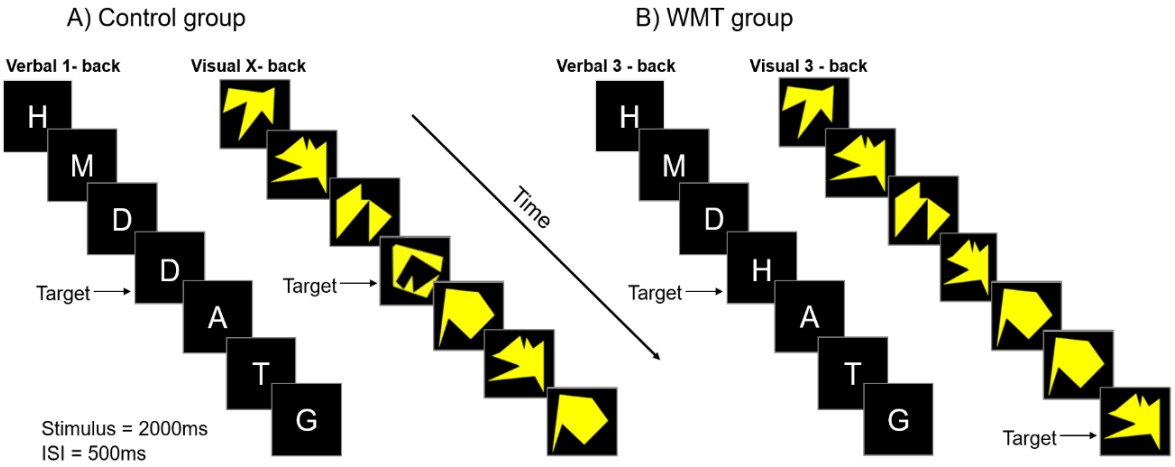


Figure 10: A schematic illustration of working memory training procedure.
ISI, Interstimulus Interval

3.3 Cognitive test battery

In order to investigate whether the 8-week WMT intervention could potentially induce transfer effects, all volunteers completed a cognitive test battery consisting of 9 cognitive assessments at baseline as well as after training. The interval between the cognitive assessment and training did not exceed one week (i.e., the interval between first session of cognitive assessment and start of training; the interval between second session of

cognitive assessment and the end of training). An experimenter explained each task to the participants and the instructed them to practice a short version of each task prior to the formal task. Cognitive testing took approximately one hour twenty minutes. In these nine cognitive tests:

1) Three cognitive tests were used to assess the nearest transfer effects. The Digit Span Test (both forward subtest and backward subtest), a subtest of German version of Wechsler Adult Intelligence Scale, HAWIE-R (Tewes, 1994), and the Corsi-block Tapping test (Corsi, 1973) were used to measure verbal working memory and visual-spatial working memory, respectively. The number of correct answers for Digit span and the total score of Corsi-block test (i.e., achieved block span x number of correct answers) were taken as the outcome measures. The Simple Visual Reaction Time (SVRT) task was used to detect the speed of response and attention. The outcome measure was the mean latency (Bleecker et al., 1987).

2) Four cognitive tests, including Color Word Stroop task (CWST), Visual Simon task (VST), Rapid Visual Information Processing (RVIP) and the German version of Verbal Learning and Memory test (VLMT), were used to investigate near transfer effects (Bialystok et al., 2004; Coull et al., 1996; Helmstaedter & Durwen, 1990; Simon & Berbaum, 1990; Uttl & Graf, 1997). CWST and VST were applied to explore interference inhibition, and the percentage of correct answers as well as the mean reaction time of corresponding conditions (e.g., congruent, incongruent and neutral) were calculated as the indicators. The RVIP was used to assess sustained attention, the outcome measure of which was the accuracy as well as mean reaction time. The VLMT was used to assess verbal memory, which consisted of five repeated auditory presentation of word list A and interfering word list B. Participants needed to recall the words from list A and list B following the investigator's instructions. As outcome indicators, we used the difference in the number of correct responses between the recall before and after the interference list presentation (Dg5-Dg6), the difference in the number of correct responses between the recall before and 20-30 minutes after the interference list presentation (Dg5-Dg7), and the values from the Word Recognition List (WR).

3) Two cognitive tests were used to investigate far transfer effects. The short version of the Raven's Advanced Progressive Matrices Test (APM) (Arthur & Day, 1994) and

the Iowa Gambling Task (IGT) (Bechara et al., 1994) were used to assess fluid intelligence and decision making respectively. The outcome measures were the number of correct answers for APM and the net score for IGT (which is good play – bad play).

3.4 Image acquisition and processing

3.4.1 Image acquisition

Imaging data were collected using a 3T hybrid PET/MR Siemens Biograph mMR scanner with a vendor-supplied 16-channel head coil at the Klinikum rechts der Isar, Munich, Germany. All participants underwent high resolution structural imaging with a three-dimensional, T1-weighted magnetization prepared – rapid gradient echo (MP-RAGE) sequence. The following parameters were included: repetition time (TR) = 2300 ms; echo time (TE) = 2.98 ms; flip angle (FA) = 9º; field of view (FOV) = 256mm; matrix size = 256 × 240 mm; slice thickness = 1.0 mm (no gap); voxel size = 1.0 × 1.0 × 1.0 mm^3 and 160 sagittal slices. Additionally, PET images, functional images, and diffusion tensor images were acquired in the same scanning session (results reported elsewhere, for task-based functional results please refer to (Emch, Ripp, et al., 2019; Ripp et al., 2022).

3.4.2 Data processing

A medical specialist reviewed all subjects' T1-weighted images to identify if there were any aberrant structural abnormalities. Two participants were omitted from the study due to massive calcification. We visually inspected each image carefully in MRIcron for motion-related artifacts (e.g., ghosting, blurring, stripping) to further ensure the quality of the acquired T1 images.

The cortical surfaces were anatomically reconstructed and volumetric segmentation was performed using FreeSurfer imaging analysis suite (Version 6.0.0, https://surfer.nmr.mgh.harvard.edu) following the longitudinal processing stream as previously described (Reuter & Fischl, 2011; Reuter et al., 2010; Reuter et al., 2012). Several preprocessing steps, including motion correction, skull stripping, image registration to Talairach space, and gray and white matter segmentation, were completed independently for both time points of all subjects. Then, for each subject, both timepoints were used to create a robust within-subject template that is unbiased (Reuter et al., 2012). Finally, each time point's longitudinal processing was initialized with the data from the preceding steps

to reduce variability over time and increase statistical power. The reconstructions were visually inspected and where necessary, manually corrected (e.g., boundaries found to be inaccurate upon visual inspection were corrected manually) (Wu et al., 2021).

After completing surface reconstructing steps, the reconstructed surfaces were used to evaluate the following three vertex-level metrics: cortical thickness (CT), the cortical surface area (CSA) and the cortical volume (CV).

In addition, volumes of seven subcortical regions of interests (ROIs), including the thalamus, putamen, caudate nucleus, pallidum, amygdala, hippocampus, and the nucleus accumbens, were obtained during the preceding preprocessing for use in volumetric measures implemented in Freesurfer. The caudate, putamen, pallidus, and nucleus accumbens are major components of the basal ganglia that are involved in the maintenance of working memory (Moore et al., 2013). Moreover, cortico-basalganglio-thalamic loops contribute to learning, WM control and response selection (Schroll et al., 2012). The amygdala-hippocampus complex is critical for memory encoding and consolidation, as well as for learning regulation (Richter-Levin & Akirav, 2000).

Lastly, the global cortical thickness for each hemisphere using the Freesurfer provided 'Mean Thickness' variable was calculated. Specifically, the global mean thickness was calculated the difference of the total thickness below the pial surface and the total thickness below the white surface (Fischl & Dale, 2000).

Subcortical volumes and global cortical thickness values were extracted and then analyzed with SPSS 19.0 (IBM Corporation, Somers, NY).

In order to investigate the macrostructural changes induced by WMT at the network level, the extracted cortical surfaces from the preprocessing phase described above were then parcellated into 148 regions (74 regions per hemisphere) based on the Destrieux altas (Destrieux et al., 2010). Following that, the mean LGI for each region was estimated and extracted, yielding 148 regional LGI estimates for each participant at each timepoint (i.e., pre-training and post-training). The extracted LGIs were then used for further SC analysis on a group-by-group basis.

3.5 Statistical analyses

3.5.1 Statistical analyses of behavioral data

3.5.1.1 Demographic data

At baseline, demographic data were analyzed using chi-square (gender) or independent sample t-tests (age), which were carried out with SPSS 19.0 (IBM Corporation, Somers, NY).

3.5.1.2 Working memory training data

The improvements induced by WM intervention on trained tasks were measured by means of *d* prime (d') and achieved n-back level. *d*' takes the range for both *hits* and *misses* into account by calculating the Z transformed *hit rate* minus *false-alarm rate* ($d' = Z_{Hit} - Z_{FA}$) (Haatveit et al., 2010; Meule, 2017). Higher values of *d*' indicate better performance, whereas lower values of *d*' values represent worse performance. We first calculated the average *d'* value of the first and last week (i.e., first 4 and last 4 training sessions) for each group and each WM training paradigm separately (e.g., verbal and visual n-back tasks). And then a two-tailed paired t-test between the mean *d*' values of the beginning and end of the training was conducted. For the WMT group, an additional t-test was calculated between the average achieved n-back level during the first and the last four training sessions. The CON group, on the other hand, did not undergo this test because they received fixed n-back training, which meant that their n-back level remained constant throughout the thirty-two training sessions.

3.5.1.3 Cognitive test battery

All behavioral data of the cognitive test battery were analyzed using a group (CON, WMT) by time (pre-training "Pre", post-training "Post") multivariate ANOVA (MANOVA) for each category of transfer effect (e.g., nearest, near, far) separately following ANOVA for each subtest. We considered the results as statistically significant at $p < 0.05$ Bonferroni corrected (3 categories for MANOVAs and all 21 subtests for ANOVAs). All statistical analyses were conducted by using SPSS 19.0 (IBM Corporation, Somers, NY).

3.5.2 Statistical analyses of neuroimaging data

3.5.2.1 Global cortical thickness and subcortical volumes

Global cortical thickness was analyzed statistically using group (WMT, CON) by time (Pre, Post) ANOVAs for left and right hemispheres separately. We performed repeated measures ANOVAs of group by time by ROIs for each hemisphere's subcortical volumes. The threshold for statistically significant results was set at $p < 0.05$ (Bonferroni corrected) for all ANOVAs.

3.5.2.2 Four vertex-wised parameters

We conducted longitudinal analyses using longitudinal two stage model with Freesurfer (http://freesurfer.net/fswiki/LongitudinalTwoStageModel). Firstly, each subject's repeated measures were reduced to a single statistic. At each vertex of each subject from both timepoints, symmetrized percent change (SPC) which is a dimensionless measure of change (i.e., the rate of change with respect to the average CT/CV/CSA/LGI), was calculated (Reuter et al., 2012). The formula of SPC calculation is:

$$SPC = 100 * \frac{(\mathrm{V2} - V1)}{(T2 - T1) * 0.5 * (V1 + V2)} = 100 * \frac{rate}{avg}$$

Where V1 is the vertex-wise measure (e.g., CT, CV, CSA and LGI) at baseline (T1) and V2 is the measure at 8-week follow-up (T2). The SPC represents the monthly rate of change with respect to the average CT/CV/CSA/LGI across the two time points. Secondly, within group analysis (within the CON group and WMT group separately) as well as group comparisons (comparisons between SPC in WMT group and SPC in CON group) of whole brain SPC in CT, LGI, CV and CSA were performed in Freesurfer using a standard QDEC (general linear model, GLM). CT, CV and CSA were smoothed using Gaussian smoothing kernels with a full-width/half-maximum (FWHM) of 10 mm, whereas the LGI was smoothed using Gaussian smoothing kernels with a FWHM of 5 mm (Schaer et al., 2012). The GLM analyses of each of above measures were performed for left and right hemispheres separately. For each GLM analysis, Monte Carlo simulation (Hagler et al., 2006), a cluster-wise correction, was used to correct for multiple comparisons. Only when the initially obtained clusters ($p < 0.05$ at vertex-wise level, two-tailed) met the additional cluster-wise threshold of $p_{cluster} < 0.05$ (two-tailed) and 1000 random permutations were the results considered significant (Wu et al., 2021).

3.5.2.3 Whole brain structural covariance analysis

The estimated LGI values of 148 regions of each subject at each time point were then used for structural covariance analysis. Here, we calculated structural covariance matrices separately for each group and each time point, as well as longitudinal structural covariance matrices.

In order to capture training-induced SC pattern within each group, the group-wise structural covariance matrices were generated using the inter-regional Pearson correlation of the estimated LGI values. Specifically, age, gender, and years of education were first regressed from the LGI estimates (Alexander-Bloch et al., 2013). For each pair of the 148 Destrieux-atlas cortical regions, the Pearson correlation coefficient was computed between the LGI values across all subjects within the WMT and the CON groups, and each timepoint separately, resulting in a 148 × 148 correlation matrix for each group each timepoint (i.e., the SC matrices for CON group pre-training, the SC matrices for CON group post-training, the SC matrices for WMT group pre-training, and the SC matrices for WMT group post-training). Each correlation matrix comprised 10878 (i.e., 148 (148-1) /2 = 10878) unique pairwise associations. Thereafter, a Fisher's Z transformation was performed on the correlation coefficients in order to improve normality. Finally, the group-wise structural connectivity matrices of each group at each time point were constructed.

The longitudinal structural covariance matrices were generated by computing the inter-regional Pearson correlation coefficient between the degree of LGI change (ΔLGI) for each pair of the atlas regions. Briefly, at the individual level, the LGI change over the 8-week WM training for each ROI was computed by using post-training minus pre-training, yielding 148 ΔLGIs. By computing Pearson correlation coefficient between ΔLGI values and then transforming the data using Fisher's Z transformation, a matrix of correlation coefficients (longitudinal structural covariance) for the degree of training-induced changes in the LGI within each group was constructed. The higher values of SC captured the patterns of similar structural changes between ROIs over WMT.

A Z-test statistic was applied to compare the structural covariance matrices for statistically significant differences within each group as well as between groups. The formula for calculating the Z-test statistic is as follows:

$$Z = \frac{Z_1 - Z_2}{\sqrt{\frac{1}{n_1 - 3} + \frac{1}{n_2 - 3}}}$$

Where n denotes the group's sample size. The z value was converted to a p value by using a normal cumulative distribution function. For instance, to compare the intergroup difference of longitudinal SC, the Z-test was calculated as follows: $Z = (Z_{WMT} - Z_{CON}) / \sqrt{\frac{1}{N\_WMT-3} + \frac{1}{N\_CON-3}}$.

We considered the results as statistically significant at $p < 0.05$ FDR corrected. In addition, given that the multiple comparison correction was based on tens of thousands of paired connections, meaning that such a stringent correction tends to result in a lower survival outcome after correction. Alternatively, the training may have caused some pattern changes that were insufficient to withstand such stringent threshold. Thus, on the exploratory basis, we also considered the results with more liberal threshold (i.e., uncorrected $p < 0.005$), attempting to capture the potential training-related pattern changes. This analysis was performed using MATLAB v2019b (The MathWorks Inc., Natick, Massachusetts, USA).

3.5.3 Correlation analyses

To investigate a potential relationship between structural changes following the training and the improvements of working memory indued by training, the LGI/CT/CV/CSA values from all clusters exhibiting significant group by time interaction for each time point and each subject of the WMT group were first estimated and extracted. Then, the change scores for Digit Span (Post - Pre), as well as changes in LGI/CT/CV/CSA (Post - Pre) were computed. Correlations between behavioral changes and cortical changes in the WMT group were then performed using partial correlation after age, gender, and years of education were controlled with SPSS 19.0 (IBM Corporation, Somers, NY). We considered the results as statistically significant at $p < 0.05$ Bonferroni corrected.

4. Results

4.1 Behavioral results

4.1.1 Demographic characteristics

As shown in Table 1, the results revealed that the demographic varaibles including age, gender, and years of education did not differ between the WMT and the CON group at baseline.

Table 1: Demographics of two groups

	WMT (n=31)	**CON (n=28)**	***P* value**
	Mean ± SD	Mean ± SD	
Age	55.81 ± 4.23	56.00 ± 4.19	0.861
Gender (female/male)	15/16	14/14	0.902
YoE	17.03 ± 3.14	16.14 ± 3.06	0.276

WMT, working memory training; CON, active control group; SD, standard deviation; YoE, years of education; Gender (categorical data) was tested by using chi-squared tests (χ^2)

4.1.2 Working memory training

The results of training data revealed that after an 8-week WMT, participants' performance improved significantly in both visual n-back trained tasks ($t_{(30)}$ = -6.75, p < 0.0001) and verbal n-back trained task ($t_{(30)}$ = -6.9, p < 0.0001) (i.e., for the WMT group, the d' values were significantly higher at the end of the WMT group compared to the beginning). Additionally, significant improvements in achieved n-back level were observed for both verbal ($t_{(30)}$ = -7.13, p < 0.0001) and visual n-back training ($t_{(30)}$ = -6.14, p < 0.0001) (Figure 11). In the CON group, no significant difference in d' values were observed between the first four sessions and the last four sessions for verbal n-back training or visual n-back training.

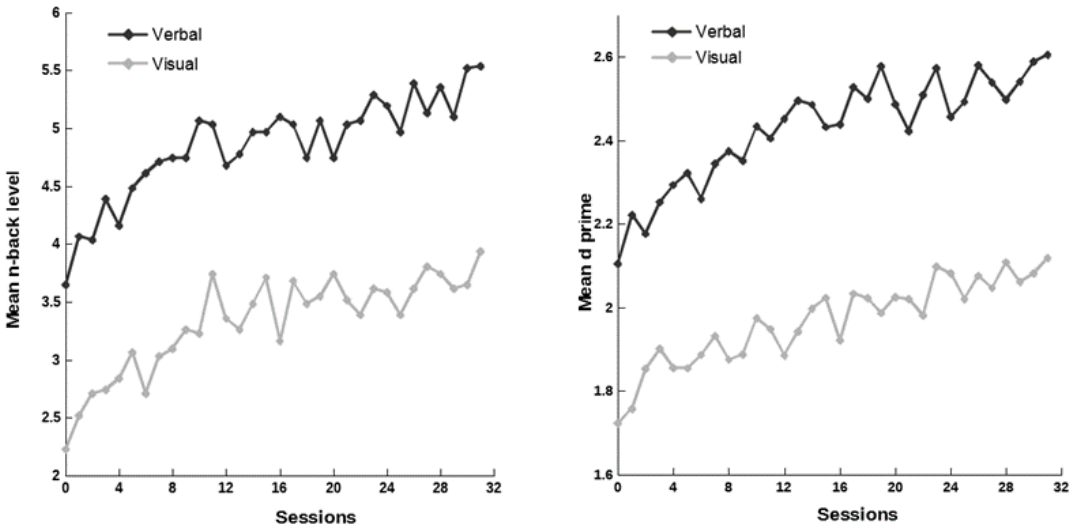


Figure 11: Training results of working memory training (WMT) group.
Mean achieved n-back level over 32 sessions for both verbal and visual WMT (left); Mean achieved d' values over 32 sessions for both verbal and visual WMT (right)

4.1.3 Cognitive test battery

The results of the cognitive test battery are summarized in Table 2. Briefly, no significant difference was found between the two groups (i.e., CON group and WMT group) at baseline across all cognitive tests as well as subtests. The MANOVAs revealed significant group × time interaction only in the nearest transfer effect category ($F_{(4.53)} = 5.93$, $p < 0.05$, Bonferroni corrected, partial $\eta^2 = 0.31$) and a significant group by time interaction was found only in the forward Digit span test ($F_{(1,58)} = 19.3$, $p < 0.01$, Bonferroni corrected, partial $\eta^2 = 0.26$) using follow-up ANOVAs for each subtest.

Table 2: T-tests (i.e., WMT vs. CON) at baseline and ANOVAs results of all cognitive tests

WMT effects	**Tests**	**WMT n = 31**		**CON n = 28**		**ANOVAs Interaction group × time**		**T-test at baseline**	
		Pre M (SD)	**Post M (SD)**	**Pre M (SD)**	**Post M (SD)**	***F***	***P* (partial η^2)**	***T***	***P***
Nearest-effects (3)	**Digit Span**								
	Forward	7.8 (2.1)	8.9 (1.7)	7.5 (2.2)	7.0 (2.7)	19.3	**<.0001* (.26)**	.54	.59

	Back-ward	6.7 (1.3)	7.5 (2.1)	7.1 (2.3)	7.6 (2.5)	.16	.69 (.003)	-.67	.51
	Corsi	46.6 (17.1)	47.6 (15.8)	43.9 (18.7)	44.0 (16.5)	.22	.64 (.004)	.32	.75
	SVRT								
	M-la-tency	287.2 (31.0)	305.1 (47.3)	292.0 (49.2)	288.5 (41.7)	4.84	.03 (.08)	-.44	.67
Near-trans-fer (4)	**VLMT**								
	Dg5-6	1.6 (1.7)	2.0 (2.8)	1.0 (1.8)	1.0 (1.3)	.26	.61 (.005)	1.32	.19
	Dg5-7	1.3 (1.6)	1.1 (1.7)	.9 (1.4)	1.0 (1.1)	.76	.39 (.01)	1.12	.24
	w-f	12.8 (2.5)	13.0 (2.2)	13.0 (3.0)	14.0 (1.4)	1.38	.25 (.02)	-.28	.78
	RVIP								
	Accu-racy	18.2 (7.1)	21.0 (4.9)	18.2 (7.1)	20.1 (5.7)	.11	.74 (.002)	.74	.46
	RT	521.0 (74.3)	527.8 (66.2)	512.6 (84.3)	492.9 (65.2)	1.98	.17 (.03)	.41	.69
	CWST								
	RT-cong	1320.4 (278.9)	1228.8 (271.6)	1331.6 (268.1)	1309.6 (300.6)	1.43	.24 (.03)	-.16	.88
	RT-in-cong	1578.7 (289.0)	1487.3 (317.1)	1531.1 (287.5)	1538.6 (299.3)	1.80	.19 (.04)	.63	.53
	RT-neu-tral	1239.5 (237.8)	1172.7 (236.2)	1228.9 (232.8)	1240.9 (262.4)	2.06	.16 (.04)	.17	.86
	%-cong	.996 (.01)	.988 (.03)	.994 (.02)	.996 (.01)	2.41	.13 (.04)	.44	.66
	%-in-cong	.937 (.07)	.933 (.07)	.952 (.06)	.950 (.05)	.02	.90 (.00)	-.84	.40
	%-neu-tral	.984 (.04)	.990 (.03)	.999 (.01)	.996 (.01)	2.05	.16 (.04)	-1.8	.08
	VST								
	RT-cong	453.8 (59.2)	424.5 (60.3)	449.3 (62.6)	407.7 (78.7)	1.03	.32 (.02)	1.59	.12
	RT-in-cong	502.5 (63.7)	467.2 (64.3)	493.4 (70.5)	452.1 (74.7)	.22	.64 (.004)	.22	.83
	%-cong	.982 (.04)	.988 (.02)	.943 (.13)	.982 (.02)	1.87	.18 (.03)	1.1	.29
	%-in-cong	.963 (.04)	.965 (.03)	.937 (.13)	.944 (.05)	.03	.86 (.001)	.51	.61

Far-trans-fer (2)	**APM**	5.6 (2.2)	6.5 (2.6)	5.3 (2.4)	5.7 (2.4)	.75	.39 (.01)	.63	.53
	IGT	6.0 (8.1)	10.8 (10.8)	5.4 (12.9)	10.6 (16.8)	.006	.94 (.00)	.21	.83

*WMT, working memory training; M (SD), mean (standard deviation);Corsi, Corsi-block Tapping test; SVRT, simple visual reaction time task; M-latency, mean latency; RVIP, the rapid visual information processing task; Accuracy = hits – FA; RT (ms), mean reaction time for correct responses in millisecond; CWST, the color-word stroop task; RT-cong; mean reaction time for congruent condition; RT-incong, mean reaction time for incongruent condition; RT-neutral, mean reaction for neutral condition; %-cong, percent correct for congruent condition; %-incong, percent correct for incongruent condition; %-neutral, percent correct for neutral condition; VST, visual Simon task; Short-APM, the short version of Raven's Advanced Progressive Matrices Test; IGT, Iowa Gambling Task, independent variable here is net score. * Significant at p < .05 (Bonferroni corrected).*

4.2 Results at neural level

4.2.1 Global cortical thickness & subcortical volumes

The results of global mean CT and subcortical volumes are summarized in Figure 12 and Figure 13, respectively. We did not detect significant training induced changes (i.e., significant group × time interaction) either in global mean thickness or in the selected subcortical volumes.

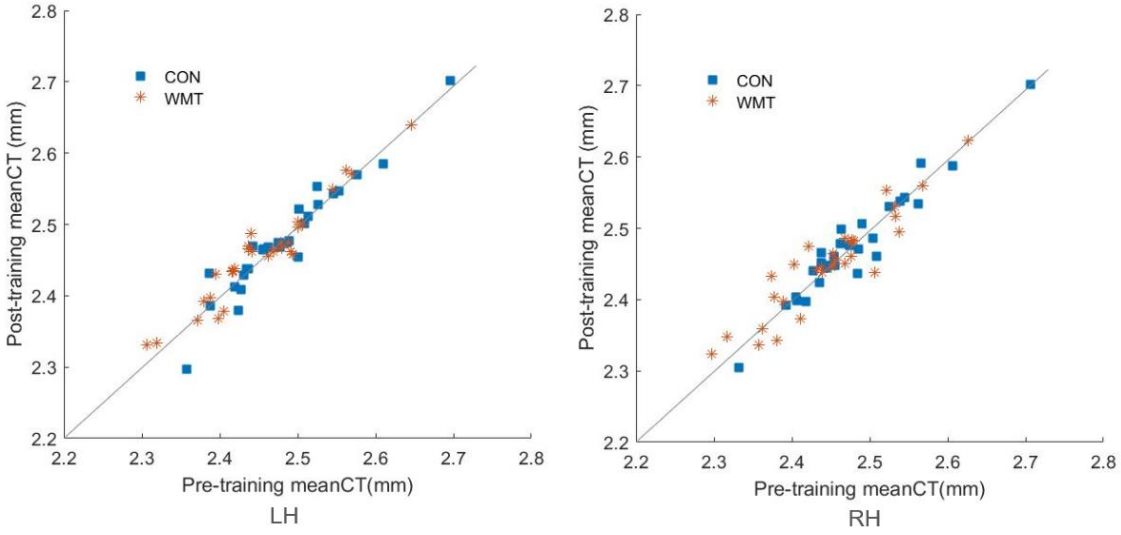


Figure 12: Global mean cortical thickness comparison, pre- as well as post-training of each group.

LH, left hemisphere; RH, right hemisphere; CON, active control group; WMT, working memory training group.

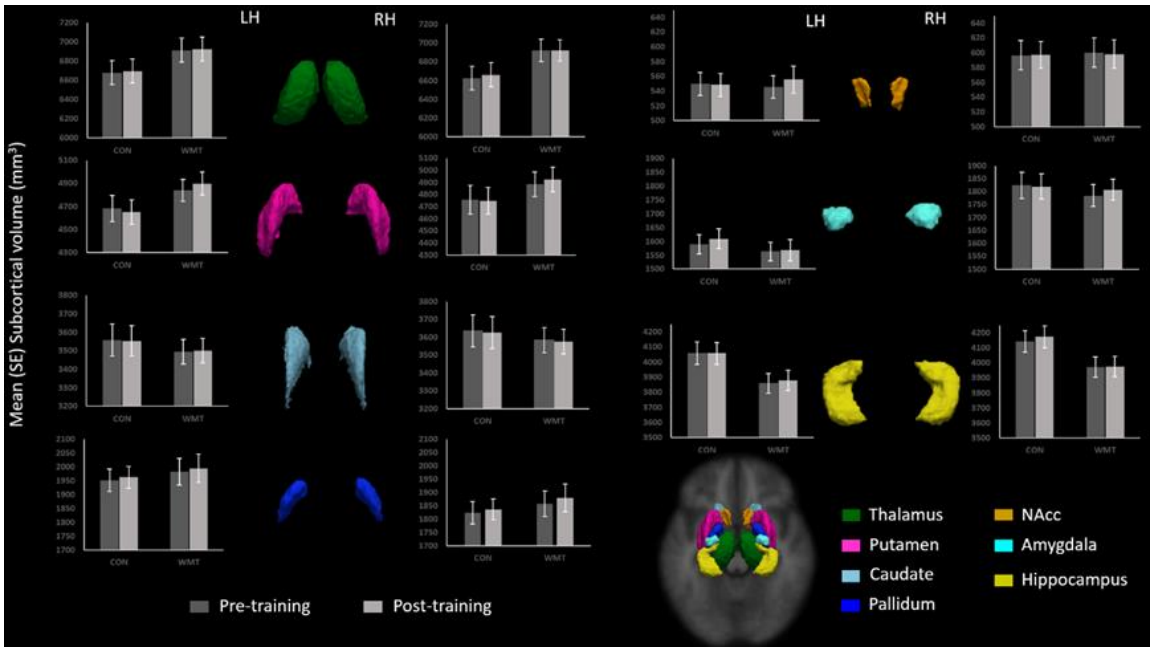


Figure 13: Bar graphs of the average subcortical volumes (standard error).
LH, left hemisphere; RH, right hemisphere; CON, active control group; WMT, working memory training group; NAcc, nucleus accumben

4.2.2 Four vertex-wised parameters

The results of WMT induced microstructural changes on vertex-level within each group are shown in Table 3 and Figure 14. Significant changes (i.e., SPC) were detected in the active control group only in terms of a greater LGI in the left lateral occipital cortex extending to the medial occipital cortex compared to baseline.

In the WMT group, in contrast, the LGI, the CT, and the CV were increased in several regions following training, in comparison to at baseline. Greater LGI clusters were observed in bilateral superior parietal cortex, as well as the left inferior parietal cortex and the right precuneus. Clusters in the left paracentral lobule and the right precentral gyrus demonstrated an increase in CT, corresponding to regions with a greater CV. Additionally, a reduction in CSA in bilateral visual cortex, in particular bilateral primary visual cortex as well as visual association area was observed (Wu et al., 2021).

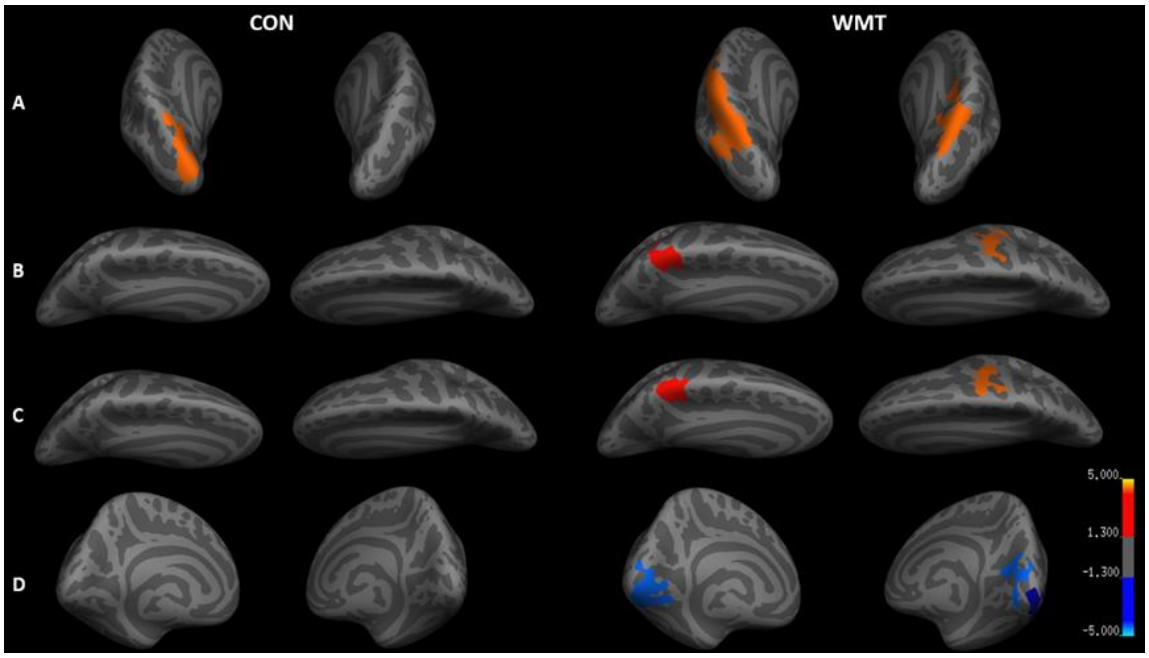


Figure 14: Gray matter changes between pre-training (baseline) and post-training in each group.

A) Local gyrification index; B) Cortical thickness; C) Cortical volume; D) Surface area. Colored regions are used to indicate significant changes between pre-training (baseline) and post-training. Red/yellow represents greater values for post-training compared with pre-training, while blue represents greater values at baseline (pre-training) compared with post-training. The value of the color bar is a log_{10}(p value). CON, active control group; WMT, working memory training group.

Table 3: Clusters of cortical changes in each group

Group	Cortical structures	Hemi-sphere	Max	Size (mm^2)	TalX	TalY	TalZ	No. Ver-tices	Annotation	
WMT	LGI	L	4.36	4943.93	-19.1	-69.4	39.9	10432	SPC, IPL	Post > Baseline
		R	3.11	2250.48	17.2	-69.4	39.4	9709.02	SPC, Precu-neus	
	CT	L	4.84	797.01	-11.7	-36.4	64.8	1959	PL	
		R	4.27	1124.41	33.9	-19.1	44.4	2577	PG	
	CV	L	4.98	784.32	-13.3	-36.4	63.7	1950	PL	
		R	4.93	1100.91	35.9	-18.2	50.8	2549	PG	
	SA	L	-3.79	2787.33	-22.9	-76.1	-0.8	3456	mOC	Baseline

		R	-3.19	1144.02	28.9	-92.2	-4.6	1470	lOC	>
		R	-3.43	1572.58	11.0	-81.4	12.7	2029	mOC	Post
CON	LGI	L	2.55	2465.34	-15.7	-92.1	20.6	3514	lOC, mOC	Post > Baseline

WMT, working memory training group; CON, active control group; LGI, local gyrification index; CT, cortical thickness; CV, cortical volume; SA, surface area; SPC, superior parietal cortex; IPL, inferior parietal lobule; PL, paracentral lobule; PG, precentral gyrus; mOC, medial occipital cortex; lOC, lateral occipital cortex; L, left; R, right; Max, log_{10} (p value); Tal (X, Y, Z), Talairach (X, Y, Z); Post, post-training.

Table 4 and Figure 15 provide a summary of the results of SPC group differences. The group comparison results for these four metrics were in accord with the findings of the WMT group. In the WMT group, the clusters showing greater SPC in LGI were located in bilateral superior parietal cortex and the right precentral gyrus, compared to the CON group. In contrast, one cluster, the left cuneus, showed smaller SPC in LGI in WMT group, compared to the CON group. The WMT group showed increased SPC in CT as well as in CV in the left paracentral lobule and the right precentral gyrus, compared to the CON group. Additionally, one cluster locating in left precuneus showed increased SPC in CV in the WMT group compared to the CON group. Compared to the CON group, one cluster of the right lateral occipital cortex showed decreased SPC in CSA in the WMT group (Wu et al., 2021).

Monte Carlo simulations were used to adjust all of the results for the four vertex-wise cortical metrics (i.e., LGI, CV, CT, and CSA), both for the within-group results as well as for group-time interaction results. At a threshold that was considered to be more conservative (i.e., FDR), there were no significant results observed.

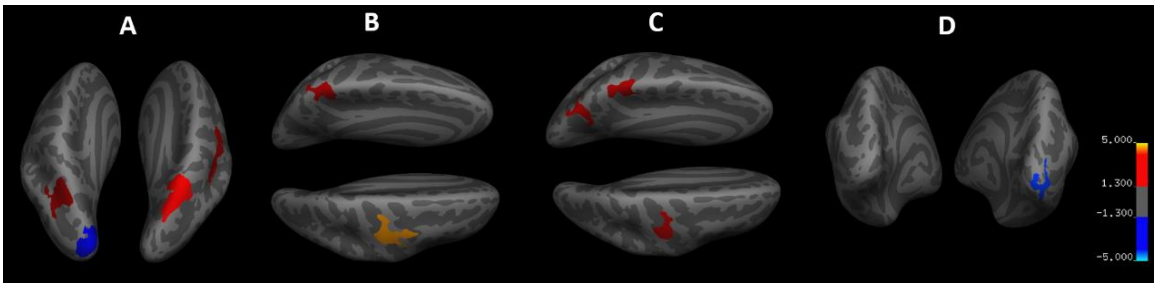


Figure 15: Differences of gray matter changes between the groups.

A) Local gyrification index; B) Cortical thickness; C) Cortical volume; D) Surface area. Colored regions are used to indicate significant "group by time interaction". Red/yellow represents greater values of symmetrized percent change for WMT group compared CON group, while blue represents greater values of symmetrized percent change for the CON group compared with the WMT group. The value of the color bar is a log_{10}(p value). CON, active control group; WMT, working memory training group.

Table 4: Differences in gray matter changes between groups

Cortical structures	Hemisphere	Max	Size (mm^2)	TalX	TalY	TalZ	No. Vertices	Annotation	
LGI	L	3.51	1044.75	-18.9	-68.4	39.2	2042	SPC	WMT > CON
	L	-3.01	1372.94	-5.3	-90.8	13.6	1735	Cuneus	CON > WMT
	R	2.97	1465.38	16.4	-70.3	42.9	2858	SPC	WMT > CON
	R	2.70	1334.99	33.0	-18.7	55.2	3287	PG	WMT > CON
CT	L	3.74	552.86	-11.9	-36.2	66.8	1344	PL	WMT > CON
	R	4.25	1083.04	35.1	-23.7	44.0	2406	PG	WMT > CON
CV	L	3.26	527.40	-10.6	-36.8	62.1	1262	PL	WMT > CON
	L	2.63	725.55	-5.8	-66.0	42.5	1421	precuneus	WMT > CON
	R	4.72	691.73	34.4	-21.4	42.2	1522	PG	WMT > CON
CSA	R	-2.45	653.52	16.6	-95.7	-2.3	841	lOC	CON > WMT

WMT, working memory training group; CON, active control group; LGI, local gyrification index; CT, cortical thickness; CV, cortical volume; SA, surface area; SPC, superior parietal cortex; PL, paracentral lobule; PG, precentral gyrus; lOC, lateral occipital cortex; MTC, middle temporal cortex; L, left; R, right; Max, log_{10} (p value); Tal (X, Y, Z), Talairach (X, Y, Z)

4.2.3 Network-level – structural covariance

The SC matrices of LGI for each group before and after training were summarized in Figure 16. No significant training induced changes were observed within group comparison, neither in the CON group or the WMT group.

The results of WMT induced structural changes on network-level as well as the longitudinal SC matrices for each group were shown in Figure 17. Briefly, no significant training-induced group differences were observed on longitudinal SC, however, at an uncorrected level (i.e., $p < 0.005$), significant group differences of longitudinal structural covariance were observed in several pairs of cortical regions (e.g., parietal regions, frontal regions) between the CON and WMT groups.

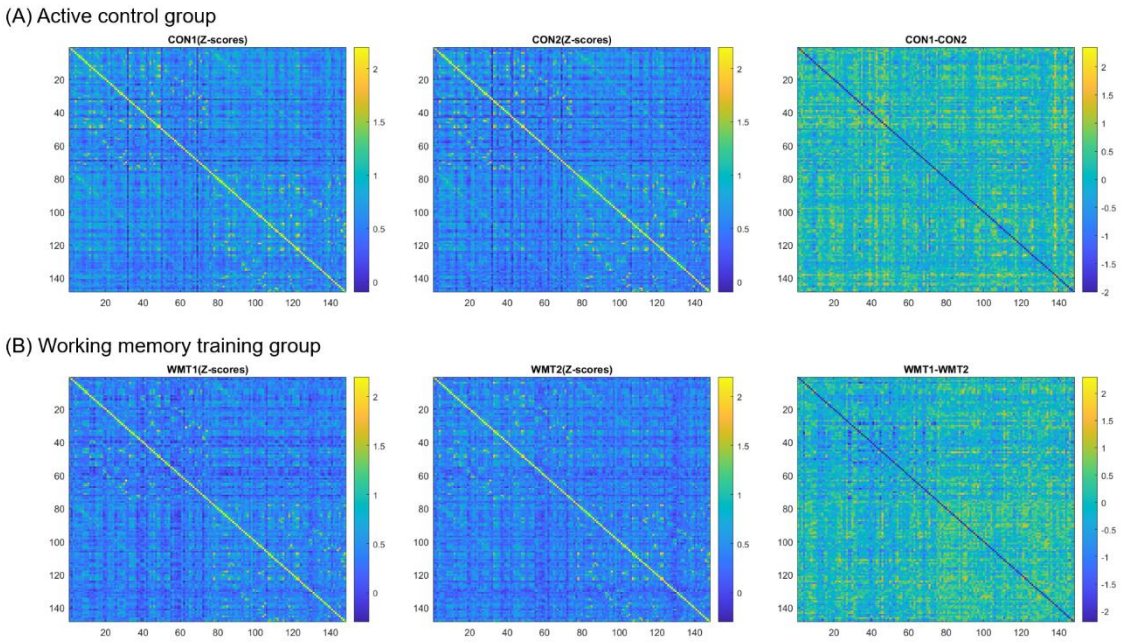


Figure 16: Structural covariance matrices of cortical gyrification for each group pre-training and post-training.

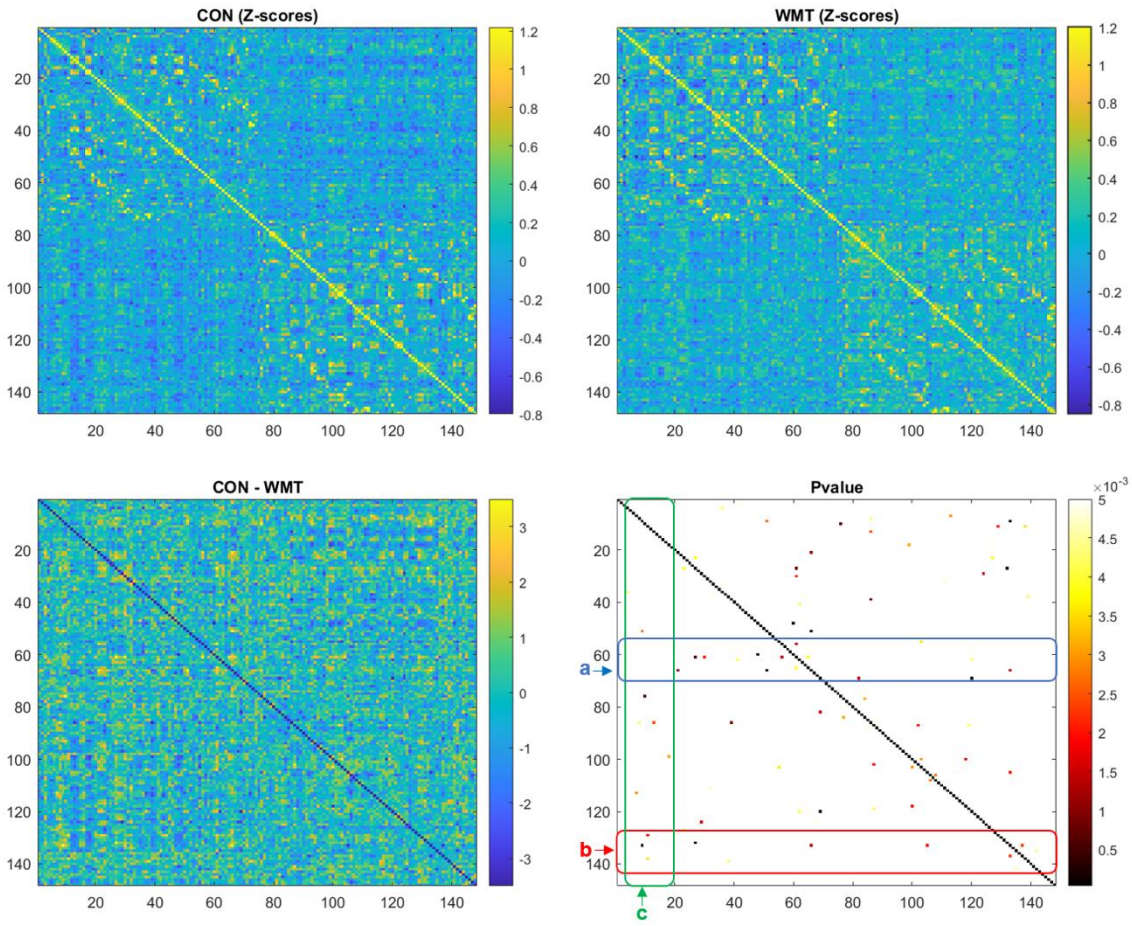


Figure 17: Longitudinal structural covariance matrices for CON and WMT groups.

CON, active control group; WMT, working memory training group; The threshold of P-values shown here is p < 0.005 without multiple correction; a represents group differences of longitudinal structural covariance between left parietal regions and other cortical regions; b represents group differences of longitudinal structural covariance between right parietal regions and other cortical regions; and c represents the group differences of longitudinal structural covariance between left frontal regions and other cortical regions.

4.3 Association of behavioral changes and vertex-wised cortical changes

No significant correlations between microstructural changes and forward Digit Span change scores were observed after correcting for multiple comparisons. However, on an uncorrected level, we did detect that the change in the LGI of the right superior parietal cortex positively correlated with the change in forward Digit Span (r = 0.483, *p* = 0.014, uncorrected).

5. Discussion

5.1 Behavioral effects induced by WMT

On the behavioral level, in comparison with the CON group, participants of the WMT group performed significantly better on the training tasks (i.e., trained verbal and visual n-back tasks) and on a cognitive test (i.e., Digit Span Test) with a high degree of similarity to training tasks following the 8-week WMT. However, neither near- or far- transfer effects were detected.

On the one hand, these findings support the efficacy of WMT in elderly populations, particularly in terms of the practice effects that WMT-induced has on those populations, which corroborate replicated prior evidence (Dahlin et al., 2008; Sala et al., 2019; Tusch et al., 2016).

On the other hand, our data do not support the transfer efficacy of WMT, at least, in this specific population (i.e., healthy adults aged 50-65 years). Even so, it is worth noting that the results should be interpreted with caution, that is to say while we did not observe any near- or far- transfer effects in the present study, we cannot conclude that transfer effects are completely absent because these findings were based on a specific population (i.e., healthy middle-aged individuals) and training procedures (i.e., N-back training paradigm), as well as the use of specific cognitive test battery to assess transfer effects. As described previously (please see instruction section), although there are numerous WMT studies and an increasing number of meta-analyses investigating whether WMT can generate transfer effects, the evidence is still not as conclusive as that for training-induced practice effects. And several reasons, especially heterogeneity of methodology and research subjects may contribute to the inconsistency of the findings. In addition, when we compared participants' performance on all cognitive tests before and after training separately within each group, we did observe that participants in the WMT group demonstrated a trend toward superior performance on the majority of these cognitive tests following the training, but not in the CON group. When all of the results are combined, it may not be appropriate to conclude that WMT has no transfer effect at all, but it may indicate that WMT has a very limited transfer effect. Further research is required to determine whether WMT can generate transfer effects and, if so, to further investigate the magnitude of the transfer,

the populations most susceptible to transfer, and the most effective training paradigms, etc.

5.2 Neural structural effects at vertex level

5.2.1 Cortical folding

One of the most important findings of the current study was that, following the intensive adaptive working memory intervention for eight weeks, we found that the WMT group demonstrated an increase in LGI in bilateral parietal regions, whereas the active control group showed greater cortical folding in only one cluster located in the left lateral occipital cortex (Figure 15A). Furthermore, the findings from the group by time interaction were consistent from the findings within each group, with the exception of one additional finding (i.e., the WMT group showed increased in gyrification in the right precentral gyrus after training compared to the active control). The spatially smaller regions of group × time interaction indicated the effects induced by training after adjusting for non-adaptive training effects in the active control (Figure 16A).

These findings suggest that long-term intensive WM training with adaptive difficulty level tends to increase the extent of gyrification in brain areas which are known to be crucial for processing higher-load WM tasks, whereas intensive WM training with low difficulty level only generates changes of cortical folding in a visual cortex. This discovery stands to reason, given that when participants were trained in adaptive WM, the difficulty increased with their performance, requiring them to concentrate on progressively higher levels of n-back, which placed greater demands on cognitive abilities such as continuous updating and processing of information, higher processing speed and WM capacity, decision making, etc. (Gajewski et al., 2018). Previous research has found a correlation between increased cortical folding and enhanced cognitive performance, specifically a positive correlation between the degree of cortical folding in parietal-prefrontal regions and the capacity of working memory (Green et al., 2018). While the precise mechanisms of cortical folding remain unknown, but there is evidence suggesting that, in contrast to other cortical metrics that are strongly determined by genetic variations, cortical folding appears to be primarily determined by the lifelong experience or environmental correlates (Gautam et al., 2015; Green et al., 2018; Kochunov et al., 2010; Luders et al., 2012; Rogers et al., 2010; White et al., 2002). Thus, the cortical folding is the hallmark feature

of the cortex surface, reflecting the dynamic reorganization of the morphological cortex of the brain as a result of training/learning processes in ontogeny. The gyri bring distinct brain areas of grey matter closer together, potentially increasing their communication efficiency and enabling more efficient cognitive processing. It's possible that changes in either domain-general or domain-specific functions are reflected by changes in cortical regional convolutional variability. As previously stated, the CON group received a very low-load WMT that consisted solely of fundamental processing of WM. It is believed that occipital regions contribute significantly to fundamental visuo-attentional WM processes by forwarding and transforming information along two processing pathways (e.g., occipito-parietal and occipito-temporal pathways) (Ungerleider et al., 1998). Consequently, the observed greater LGI in the visual cortex may facilitate the information processing of transformative low-level inputs, which leads to more efficient and robust processing of relevant information at lower levels. On the other hand, training more complex WM processes was related to the gyrification remodeling in parieto-frontal networks. The parietal areas integrate sensory information, distribute attention, and promote efficient encoding, retrieval as well as feedback processes (Bajaj et al., 2018; Gevins & Smith, 2000; Graham et al., 2010). Thus, our finding that the greater degree of cortical folding associated with WMT group's improved working memory performance can be interpreted as evidence for the distinct but limited WM-induced cognitive-neurobiological benefits. Which means, the increased gyrification observed in the specific regions may imply that individuals are better able to integrate information via the parietal-prefrontal network/pathways in order to produce optimal responses. Following this line, the result that training-related changes confined to WM-related regions coincides with the discovery that WMT did have an effect on working memory performance (i.e., performance in forward digit span task). The confined cognitive-neurobiological effect induced by WMT was further supported by a trend association between increase cortical folding in right superior parietal cortex and training-induced improved performance in digit forward span. The link may suggest that the effects on cortical folding induced by WMT, at least in superior parietal areas, are strongly related to the enhancement of cognitive ability, particularly in domains that are identical or comparable to trained tasks. As this is the first study to look into the neuroplastic effects on cortical folding induced by WMT, additional research is required to elucidate the precise mechanisms underlying cortical folding and training-associated cortical folding changes, and the relationship between the degree of

cortical folding changes and other alterations (e.g., alterations on neural level and behavioral level) caused by WMT.

5.2.2 Cortical thickness & cortical volume

Following the 8-week WMT, similar training induced changes were observed in CV and CT within the WMT group (Figure 15 B and C), of note, which were also discernable in group comparison (i.e., the training group vs. the active control) (Figure 16 B and C). Specifically, we observed training-induced increases in both CT and CV locating in the left paracentral lobule as well as the right precentral cortex in the WMT group, which coincided with the results of group-by-time interaction. Furthermore, in the left precuneus, the WMT group showed higher CV than the CON group.

Several significances follow from these findings. *Firstly*, the results demonstrate a close interdependence between the two measures, implying that changes in CT due to WMT contribute to changes in cortical volume. As previously reported, the change in thickness is highly positively associated with the change in volume, and the findings of current study is consistent with prior research (Storsve et al., 2014). The alterations in thickness and volume may be related to increased dendritic branching, synaptogenesis, angiogenesis or other processes (Zatorre et al., 2012). In particular, grey matter changes associated with practice or training may be predominantly attributable to synaptic reorganization in particular processing regions (Ilg et al., 2008). *Secondly*, the findings reveal grey matter alterations in only those that are believed to be relevant to WM processing. In the current study, we found that, compared to the CON group, participants in the WMT group showed a greater CV in the left precuneus following the 8-week WMT. Additionally, increased CT was observed in the paracentral lobule and precentral gyrus, both of which are critical components of primary motor cortex (PMC). The precuneus has been demonstrated being a critical brain region involved in WM processing, particularly during the processing of visuo-spatial working memory (Cavanna & Trimble, 2006; Lundstrom et al., 2005; Schott et al., 2019; Silk et al., 2006). The PMC, in addition to be in charge of planning and executing movement, also participates in higher order cognition such as learning, movement inhibition, etc. (Bhattacharjee et al., 2020; Hoshi & Tanji, 2006; Jeannerod, 2001). Moreover, the balance of the neural activation and inhibition in the PMC is closely linked to high load WM-related neural activity (Freeman et al., 2016). Specifically, greater activation in the PMC has been linked to quicker reaction times as well as higher intelligence

level (Bajaj et al., 2018; Emch, von Bastian, et al., 2019). Consequently, the findings of the present study may imply that increases in thickness in bilateral PMC contribute to optimizing the balance of activation and inhibition in specific neurons through synaptic reorganization, thereby resulting in improved performance in specific cognitive tasks (e.g., response faster Emch et al. (2019)).

5.2.3 Cortical surface area

Unexpectedly, after the training, the WMT group had a lower CSA bilaterally in occipital cortex than the CON group (Figure 15 D and Figure 16 D). Prior research has found that the surface area is a dynamic process associated with variations in local gyrification, specifically the CSA is increasing with LGI (Green et al., 2018; Wierenga et al., 2014). We observed the WMT group showed cortical contraction in the visual-attentional regions after WMT, which may suggest that the dynamic organization process of cortical folding of the cortical mantle induced by training. Particularly, as discussed earlier, increased cortical folding in bilateral parietal cortex may bring brain regions closer together. During this dynamic reorganization process, portions of the occipital cortex may have been stretched and pulled closer to parietal regions, leading to a reduction in the surface area of the occipital cortex. In this light, the findings are plausible and consistent with cortical folding findings reported above. To date, only two studies have reported the effects induced by WMT on CSA. Román and colleagues (2016) discovered a small surface expansion in the right middle temporal cortex in the training group, while mixed findings (i.e., a tendency for expansion in the right frontal and anterior medial temporal areas, and a tendency for contraction in the left temporal-parietal cortex) were observed in the control group. However, no changes in the CSA were found following an n-back training (Lawlor-Savage et al., 2019). Inconsistencies may be partially explained by variations in methodology, as stated previously. Due to the paucity of research on the neural structural effects of WMT on surface area, additional research is required to identify the key brain areas and the extent of alterations in surface area that reflect the neural substrates underlying WMT.

5.3 Neural structural effects at network level – Structural Covariance

The results of the first study (i.e., the WMT induced plasticity on cortical structures at vertex level) indicated that WMT can produce plasticity in cortical structures at vertex level. In addition, the cortical folding seems to be the most relevant or sensitive cortical characteristic related to WMT in comparison to other metrics.

Based on the findings above observed, we aimed to capture whether grey matter plasticity in cortical folding at vertex level co-occurs with plasticity at a network level by using structural covariance analysis, in other words, whether WMT induced plasticity of cortical reorganization in a network-level topology. To date, structural covariance has not been studied in terms of the neural effects induced by working memory training (neither thickness-based SC, nor LGI -based SC).

The results of the LGI-based SC analysis within each group revealed no significant WMT induced changes in cortical-cortical connections, either in the WMT group or the CON group. In the longitudinal SC analysis, after correcting for multiple corrections, no significant results were found. However, at the uncorrected level (i.e., $p < 0.005$), the training induced changes of cortical folding intensity showed significant difference between pairs of parietal regions as well as pairs of frontal regions. The results observed at the uncorrected level seem to be important in two folds. First, they indicated that the longitudinal SC could capture the pattern of topological changes due to WMT (i.e., the pattern of similar structural changes between ROIs). Specifically, combined the results obtained from study one, where WMT resulted in a significant increase in cortical folding, which was accompanied by the pattern of similar structural changes between ROIs in the areas where this occurred over the 8-week working memory training. Second, these cortical regions (i.e., parietal regions) might be the hub associated with WM training/learning at both vertex- and network-level. The magnitude of the changes in these regions may serve as a predictor of changes in other related regions, particularly those associated with processing improvement. As this is the first study to investigate neural effects in network-level topology by using SC, more work will be required to fully understand these issues.

The neuroplasticity induced by WMT might manifest itself in a variety of ways. Firstly, it is possible that training-induced neural structural plasticity may be associated with a variety of metrics, including cortical thickness, cortical volume, cortical folding, surface

area etc. What's more, training-induced plasticity in various metrics might be characterized in a variety of ways at various scales, which means that WMT may result in a more optimal configuration of various metrics at various levels during the cognitive processes following the training. For instance, we observed significantly increased cortical folding in cortical regions associated with better WM performance at vertex level, but not at the network level (e.g., within group SC comparisons), revealed on global structural covariance. The following are several possible explanations for the results: 1) The training-induced effects on global structural covariance may be too subtle to detect; 2) Changes in structural coordination induced by WMT may not occur at the whole-brain level, but rather within regions with significant localized (i.e., vertex-level) changes. This pattern (i.e., no changes in global SC but only within regions with significant local changes) was reported recently in a study – the thickness-based structural covariance was not altered at the whole brain level but only in regions with significantly reduction of thickness in schizophrenia compared to controls (Wannan et al., 2019); 3) Cortical folding might be the most relevant and plastic feature of working memory and learning at the vertex-level, reflecting WM training effects to a greater extent than the other metrics. However, it may not be the optimal indicator for characterizing training-induced changes in structural coordination, alternative metrics (e.g., cortical thickness, cortical volume, etc. may be more appropriate. 4) Structural covariance analysis (i.e., direct comparison of SC matrices within and between groups) might not be sufficient to detect the topological changes induced by WMT, as SC analysis does not allow for the evaluation of a variety of topological properties (e.g., global efficiency, clustering coefficient, modularity etc.) that can provide insights into the topological changes. Given that this is the first study to investigate WMT-induced neural topological plasticity using structural covariance, additional work is needed to replicate and validate this finding, as well as to use a more comprehensive approach to explore training induced topological changes by combing different metrics and properties. The points raised above can serve as inspiration for future research directions and topics. Prospects for future research are outlined in the outlook section (please see section 5.6 Strengths, limitations and future prospects for details.)

5.4 Strengths, limitations and future prospects

Several strengths of studies within this thesis are worth noting. To begin, this is the first study to examine behavioral effects as well as neural structural plasticity at the vertex,

network, and global levels due to WMT, providing a more complete picture of the mechanisms underlying WMT. In addition, instead of a non-contact control or passive control, the control group in current studies were active control, meaning volunteers in the active control group underwent same intervention as the training group, except the training difficulty in the control group was not adaptive. Furthermore, this study focused on a specific middle-aged group (i.e., 50 65 years) that occurs prior to the onset of aging as well as is strongly associated with the onset of a variety of neural degenerative diseases. Lastly, the sample size was adequate in comparison to other longitudinal intervention studies in neuroimaging.

This study does have few limitations. Firstly, regarding the vertex-wise structural analysis, we used a longitudinal two stage model which relatively simple in comparison to a linear mixed effects (LME) model, due to the design (two-timepoint repeated measures design) and balanced data with approximately equally spaced. The LME model is relative more complex but more powerful in studies with multiple timepoints or unbalanced data (Bernal-Rusiel et al., 2013). The LME model is capable of handling both unequal timing and unbalanced data, allowing for the inclusion of participants with as few as one timepoint in the analyses. Secondly, since we aimed to investigate whether WMT induced changes in cortical folding at vertex level were companied by changes in network-level topology. It was therefore decided to use the LGI exclusively for the purpose of constructing structural covariance matrices, rather than other metrics such as CV, CT, or CSA.

In the future, further research is needed to investigate training-induced topological changes using a more comprehensive approach that combines different metrics and properties. According to the findings of the current study, cortical folding might more accurately reflect the effects of WMT-induced at the vertex level than other metrics; however, it might be restricted to the vertex level rather than the topological level, implying that the most appropriate metric for training-induced structural coordination changes may be another metric. Thus, the SC analyses need to be conducted using all available metrics. Moreover, in addition to global SC, SC analysis should be also restricted to regions with significant vertex-level changes, as WMT may result in changes in structural coordination only within regions with altered localized changes. Additionally, along with SC analysis, it is worthwhile to investigate training-induced neural structural plasticity at the network level using graphic theory approach, which allows for a broader range of topological properties than the SC. The following topological properties are used to characterize the

topological organization of structural covariance networks (SCNs): network segregation (clustering and modularity), network integration (global efficiency), and the balance between segregation and integration (small-world topology) (Alexander-Bloch et al., 2013). By examining how these properties change in response to WMT, we can gain a better understanding of how the brain dynamically reconfigures its structural organization, thereby providing a better platform for better performances on cognitive tasks.

6. Conclusion

In current thesis, we combined cognitive testing and grey matter metrics to look into the behavioral effects induced by WMT, as well as neural structural plasticity at multiple levels (i.e., vertex, network, and global levels). The results revealed that, in a group of older adults, extensive high-load working memory intervention resulted in creased cortical folding, volume, and thickness, as well as changes in surface area in several core regions. In addition, the morphometric changes induced by the intervention were accompanied by improvements in training performance. In particular, training-induced localized (i.e., vertex-level) changes in cortical folding were restricted to a network of regions known to be critically involved in WM processing. These findings at vertex level indicate that the cortical folding, but not other metrics, might represent the most relevant and plastic features of working memory and learning, and might reflect neuroplastic effects induced by working memory intervention to a greater extent than the other metrics (i.e., CV, CT and CSA). Moreover, the results of longitudinal structural covariance analysis revealed that the significant increase in cortical folding in vertex-level observed during the 8-week WMT was accompanied by a similar pattern of structural changes across ROIs in these regions. Overall, combined the results from study one and study two, these cortical regions (i.e., parietal regions, especially superior parietal cortex and inferior parietal lobule) may act as hubs for WM training/learning, and they may play a critical role in reconfiguring structural organization to optimize the functional organization and thereby to support cognitive processes with higher load.

Further research is required to: 1) replicate and validate the findings observed in the current study; 2) determine whether WMT can generate transfer effects and, if so, to further investigate the magnitude of the transfer, the populations most susceptible to transfer, and the most effective training paradigms, etc.; 3) investigate training-induced topological changes using a more comprehensive approach that combines different metrics and properties.

Reference

Agrell, B., & Dehlin, O. (2012). The clock-drawing test. 1998. *Age Ageing, 41 Suppl 3*, iii41-45. doi:10.1093/ageing/afs149

Aguirre, N., Cruz-Gomez, A. J., Miro-Padilla, A., Bueicheku, E., Broseta Torres, R., Avila, C., Sanchis-Segura, C., & Forn, C. (2019). Repeated Working Memory Training Improves Task Performance and Neural Efficiency in Multiple Sclerosis Patients and Healthy Controls. *Mult Scler Int, 2019*, 2657902. doi:10.1155/2019/2657902

Alexander-Bloch, A., Giedd, J. N., & Bullmore, E. (2013). Imaging structural co-variance between human brain regions. *Nature Reviews Neuroscience, 14*(5), 322-336. doi:10.1038/nrn3465

Arthur, W., & Day, D. V. (1994). Development of a short form for the Raven Advanced Progressive Matrices Test. *Educational and Psychological Measurement, 54*(2), 394-403. doi:10.1177/0013164494054002013

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. *Neuroimage, 11*(6 Pt 1), 805-821. doi:10.1006/nimg.2000.0582

Atkinson, R. C., & Shiffrin, R. M. (1968a). Human Memory: A Proposed System and its Control Processes. In K. W. Spence & J. T. Spence (Eds.), *Psychology of Learning and Motivation* (Vol. 2, pp. 89-195): Academic Press.

Atkinson, R. C., & Shiffrin, R. M. (1968b). Human Memory: A Proposed System and its Control Processes11This research was supported by the National Aeronautics and Space Administration, Grant No. NGR-05-020-036. The authors are indebted to W. K. Estes and G. H. Bower who provided many valuable suggestions and comments at various stages of the work. Special credit is due J. W. Brelsford who was instrumental in carrying out the research discussed in Section IV and whose overall contributions are too numerous to report in detail. We should also like to thank those co-workers who carried out a number of the experiments discussed in the latter half of the paper; rather than list them here, each will be acknowledged at the appropriate place. In K. W. Spence & J. T. Spence (Eds.), *Psychology of Learning and Motivation* (Vol. 2, pp. 89-195): Academic Press.

Reference

Au, J., Sheehan, E., Tsai, N., Duncan, G. J., Buschkuehl, M., & Jaeggi, S. M. (2015). Improving fluid intelligence with training on working memory: a meta-analysis. *Psychon Bull Rev, 22*(2), 366-377. doi:10.3758/s13423-014-0699-x

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends Cogn Sci, 4*(11), 417-423. doi:10.1016/s1364-6613(00)01538-2

Baddeley, A. (2010). Working memory. *Current Biology, 20*(4), R136-140. doi:10.1016/j.cub.2009.12.014

Baddeley, A. (2012). Working memory: theories, models, and controversies. *Annu Rev Psychol, 63*, 1-29. doi:10.1146/annurev-psych-120710-100422

Baddeley, A. D. (2000). Short-term and working memory *The Oxford handbook of memory.* (pp. 77-92). New York, NY, US: Oxford University Press.

Baddeley, A. D., & Hitch, G. (1974). Working Memory. In G. H. Bower (Ed.), *Psychology of Learning and Motivation* (Vol. 8, pp. 47-89): Academic Press.

Bajaj, S., Raikes, A., Smith, R., Dailey, N. S., Alkozei, A., Vanuk, J. R., & Killgore, W. D. S. (2018). The Relationship Between General Intelligence and Cortical Structure in Healthy Individuals. *Neuroscience, 388*, 36-44. doi:https://doi.org/10.1016/j.neuroscience.2018.07.008

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1-3), 7-15. doi:10.1016/0010-0277(94)90018-3

Bernal-Rusiel, J. L., Greve, D. N., Reuter, M., Fischl, B., Sabuncu, M. R., & Alzheimer's Disease Neuroimaging, I. (2013). Statistical analysis of longitudinal neuroimage data with Linear Mixed Effects models. *Neuroimage, 66*, 249-260. doi:10.1016/j.neuroimage.2012.10.065

Bethlehem, R. A. I., Romero-Garcia, R., Mak, E., Bullmore, E. T., & Baron-Cohen, S. (2017). Structural Covariance Networks in Children with Autism or ADHD. *Cereb Cortex, 27*(8), 4267-4276. doi:10.1093/cercor/bhx135

Bhattacharjee, S., Kashyap, R., Abualait, T., Annabel Chen, S. H., Yoo, W. K., & Bashir, S. (2020). The Role of Primary Motor Cortex: More Than Movement Execution. *J Mot Behav*, 1-17. doi:10.1080/00222895.2020.1738992

Reference

Bialystok, E., Craik, F. I., Klein, R., & Viswanathan, M. (2004). Bilingualism, aging, and cognitive control: evidence from the Simon task. *Psychol Aging, 19*(2), 290-303. doi:10.1037/0882-7974.19.2.290

Bleecker, M., Agnew, J., & Meyers, D. (1987). Simple visual reaction time: Sex and age differences. *Developmental Neuropsychology - DEVELOP NEUROPSYCHOL, 3*, 165-172. doi:10.1080/87565648709540372

Burke, W. J., Roccaforte, W. H., & Wengel, S. P. (1991). The short form of the Geriatric Depression Scale: a comparison with the 30-item form. *J Geriatr Psychiatry Neurol, 4*(3), 173-178. doi:10.1177/089198879100400310

Buschkuehl, M., Hernandez-Garcia, L., Jaeggi, S. M., Bernard, J. A., & Jonides, J. (2014). Neural effects of short-term training on working memory. *Cogn Affect Behav Neurosci, 14*(1), 147-160. doi:10.3758/s13415-013-0244-9

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain, 129*(Pt 3), 564-583. doi:10.1093/brain/awl004

Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working Memory From the Psychological and Neurosciences Perspectives: A Review. *Front Psychol, 9*, 401. doi:10.3389/fpsyg.2018.00401

Clark, C. M., Lawlor-Savage, L., & Goghari, V. M. (2017). Functional brain activation associated with working memory training and transfer. *Behav Brain Res, 334*, 34-49. doi:10.1016/j.bbr.2017.07.030

Colom, R., Martinez, K., Burgaleta, M., Roman, F. J., Garcia-Garcia, D., Gunter, J. L., Hua, X., Jaeggi, S. M., & Thompson, P. M. (2016). Gray matter volumetric changes with a challenging adaptive cognitive training program based on the dual n-back task. *Personality and Individual Differences, 98*, 127-132. doi:10.1016/j.paid.2016.03.087

Corsi, P. M. (1973). *Human memory and the medial temporal region of the brain.* (34), ProQuest Information & Learning, US.

Coull, J. T., Frith, C. D., Frackowiak, R. S., & Grasby, P. M. (1996). A fronto-parietal network for rapid visual information processing: a PET study of sustained

attention and working memory. *Neuropsychologia, 34*(11), 1085-1095. doi:10.1016/0028-3932(96)00029-2

Cowan, N. (1999). An Embedded-Processes Model of working memory *Models of working memory: Mechanisms of active maintenance and executive control.* (pp. 62-101). New York, NY, US: Cambridge University Press.

Cowan, N. (2005). *Working memory capacity*. New York, NY, US: Psychology Press.

Cowan, N., Elliott, E. M., Scott Saults, J., Morey, C. C., Mattox, S., Hismjatullina, A., & Conway, A. R. A. (2005). On the capacity of attention: its estimation and its role in working memory and cognitive aptitudes. *Cognitive psychology, 51*(1), 42-100. doi:10.1016/j.cogpsych.2004.12.001

Dahlin, E., Nyberg, L., Backman, L., & Neely, A. S. (2008). Plasticity of Executive Functioning in Young and Older Adults: Immediate Training Gains, Transfer, and Long-Term Maintenance. *Psychol Aging, 23*(4), 720-730. doi:10.1037/a0014296

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage, 9*(2), 179-194. doi:10.1006/nimg.1998.0395

Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage, 53*(1), 1-15. doi:10.1016/j.neuroimage.2010.06.010

Diamond, A. (2013). Executive functions. *Annu Rev Psychol, 64*, 135-168. doi:10.1146/annurev-psych-113011-143750

DuPre, E., & Spreng, R. N. (2017). Structural covariance networks across the life span, from 6 to 94 years of age. *Network Neuroscience, 1*(3), 302-323. doi:10.1162/NETN_a_00016

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. *Front Aging Neurosci, 11*, 300. doi:10.3389/fnagi.2019.00300

Reference

Emch, M., von Bastian, C. C., & Koch, K. (2019). Neural Correlates of Verbal Working Memory: An fMRI Meta-Analysis. *Front Hum Neurosci, 13*, 180. doi:10.3389/fnhum.2019.00180

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, O., Larsen, V. A., & Walhovd, K. B. (2010). Effects of memory training on cortical thickness in the elderly. *Neuroimage, 52*(4), 1667-1676. doi:10.1016/j.neuroimage.2010.05.041

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America, 97*(20), 11050-11055. doi:10.1073/pnas.200033797

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage, 9*(2), 195-207. doi:10.1006/nimg.1998.0396

Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: courses, causes and cognitive consequences. *Rev Neurosci, 21*(3), 187-221. doi:10.1515/revneuro.2010.21.3.187

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198. doi:10.1016/0022-3956(75)90026-6

Freeman, S. M., Itthipuripat, S., & Aron, A. R. (2016). High Working Memory Load Increases Intracortical Inhibition in Primary Motor Cortex and Diminishes the Motor Affordance Effect. *J Neurosci, 36*(20), 5544-5555. doi:10.1523/JNEUROSCI.0284-16.2016

Froudist-Walsh, S., López-Barroso, D., José Torres-Prioris, M., Croxson, P. L., & Berthier, M. L. (2018). Plasticity in the Working Memory System: Life Span Changes and Response to Injury. *The Neuroscientist, 24*(3), 261-276. doi:10.1177/1073858417717210

Fukuda, K., Vogel, E., Mayr, U., & Awh, E. (2010). Quantity, not quality: the relationship between fluid intelligence and working memory capacity. *Psychon Bull Rev, 17*(5), 673-679. doi:10.3758/17.5.673

Reference

Gajewski, P. D., Hanisch, E., Falkenstein, M., Thönes, S., & Wascher, E. (2018). What Does the n-Back Task Measure as We Get Older? Relations Between Working-Memory Measures and Other Cognitive Functions Across the Lifespan. *Front Psychol, 9*(2208). doi:10.3389/fpsyg.2018.02208

Gautam, P., Anstey, K. J., Wen, W., Sachdev, P. S., & Cherbuin, N. (2015). Cortical gyrification and its relationships with cortical volume, cortical thickness, and cognitive performance in healthy mid-life adults. *Behav Brain Res, 287*, 331-339. doi:10.1016/j.bbr.2015.03.018

Geerligs, L., Cam, C. A. N., & Henson, R. N. (2016). Functional connectivity and structural covariance between regions of interest can be measured more accurately using multivariate distance correlation. *Neuroimage, 135*, 16-31. doi:https://doi.org/10.1016/j.neuroimage.2016.04.047

Gevins, A., & Smith, M. E. (2000). Neurophysiological measures of working memory and individual differences in cognitive ability and cognitive style. *Cereb Cortex, 10*(9), 829-839. doi:10.1093/cercor/10.9.829

Ghosh, S. S., Kakunoori, S., Augustinack, J., Nieto-Castanon, A., Kovelman, I., Gaab, N., Christodoulou, J. A., Triantafyllou, C., Gabrieli, J. D. E., & Fischl, B. (2010). Evaluating the validity of volume-based and surface-based brain image registration for developmental cognitive neuroscience studies in children 4 to 11 years of age. *Neuroimage, 53*(1), 85-93. doi:10.1016/j.neuroimage.2010.05.075

Glisky, E. L. (2007). Changes in Cognitive Function in Human Aging. In D. R. Riddle (Ed.), *Brain Aging: Models, Methods, and Mechanisms*. Boca Raton (FL).

Graham, S., Jiang, J., Manning, V., Nejad, A. B., Zhisheng, K., Salleh, S. R., Golay, X., Berne, Y. I., & McKenna, P. J. (2010). IQ-related fMRI differences during cognitive set shifting. *Cereb Cortex, 20*(3), 641-649. doi:10.1093/cercor/bhp130

Green, S., Blackmon, K., Thesen, T., DuBois, J., Wang, X., Halgren, E., & Devinsky, O. (2018). Parieto-frontal gyrification and working memory in healthy adults. *Brain Imaging Behav, 12*(2), 303-308. doi:10.1007/s11682-017-9696-9

Haatveit, B. C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., & Andreassen, O. A. (2010). The validity of d prime as a working memory index: results from the

"Bergen n-back task". *J Clin Exp Neuropsychol, 32*(8), 871-880. doi:10.1080/13803391003596421

Hagler, D. J., Jr., Saygin, A. P., & Sereno, M. I. (2006). Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *Neuroimage, 33*(4), 1093-1103. doi:10.1016/j.neuroimage.2006.07.036

Heinzel, S., Lorenz, R. C., Pelz, P., Heinz, A., Walter, H., Kathmann, N., Rapp, M. A., & Stelzel, C. (2016). Neural correlates of training and transfer effects in working memory in older adults. *Neuroimage, 134*, 236-249. doi:10.1016/j.neuroimage.2016.03.068

Helmstaedter, C., & Durwen, H. F. (1990). VLMT: Verbaler Lern- und Merkfähigkeitstest: Ein praktikables und differenziertes Instrumentarium zur Prüfung der verbalen Gedächtnisleistungen. [VLMT: A useful tool to assess and differentiate verbal memory performance.]. *Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie, 141*(1), 21-30.

Hoshi, E., & Tanji, J. (2006). Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. *J Neurophysiol, 95*(6), 3596-3616. doi:10.1152/jn.01126.2005

Ilg, R., Wohlschlager, A. M., Gaser, C., Liebau, Y., Dauner, R., Woller, A., Zimmer, C., Zihl, J., & Muhlau, M. (2008). Gray matter increase induced by practice correlates with task-specific activation: a combined functional and morphometric magnetic resonance imaging study. *J Neurosci, 28*(16), 4210-4215. doi:10.1523/JNEUROSCI.5722-07.2008

Izekenova, A. K., Kumar, A. B., Abikulova, A. K., & Izekenova, A. K. (2015). Trends in ageing of the population and the life expectancy after retirement: A comparative country-based analysis. *J Res Med Sci, 20*(3), 250-252.

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences of the United States of America, 105*(19), 6829-6833. doi:10.1073/pnas.0801268105

Jaeggi, S. M., Studer-Luethi, B., Buschkuehl, M., Su, Y. F., Jonides, J., & Perrig, W. J. (2010). The relationship between n-back performance and matrix reasoning -

implications for training and transfer. *Intelligence, 38*(6), 625-635. doi:10.1016/j.intell.2010.09.001

Jeannerod, M. (2001). Neural simulation of action: a unifying mechanism for motor cognition. *Neuroimage, 14*(1 Pt 2), S103-109. doi:10.1006/nimg.2001.0832

Jobe, J. B., Smith, D. M., Ball, K., Tennstedt, S. L., Marsiske, M., Willis, S. L., Rebok, G. W., Morris, J. N., Helmers, K. F., Leveck, M. D., & Kleinman, K. (2001). ACTIVE: a cognitive intervention trial to promote independence in older adults. *Control Clin Trials, 22*(4), 453-479. doi:10.1016/s0197-2456(01)00139-8

Johnson, M. K., McMahon, R. P., Robinson, B. M., Harvey, A. N., Hahn, B., Leonard, C. J., Luck, S. J., & Gold, J. M. (2013). The Relationship Between Working Memory Capacity and Broad Measures of Cognitive Ability in Healthy Adults and People With Schizophrenia. *Neuropsychology, 27*(2), 220-229. doi:10.1037/a0032060

Jolles, D. D., van Buchem, M. A., Rombouts, S. A., & Crone, E. A. (2012). Practice effects in the developing brain: a pilot study. *Dev Cogn Neurosci, 2 Suppl 1*, S180-191. doi:10.1016/j.dcn.2011.09.001

Kane, M. J., Brown, L. H., McVay, J. C., Silvia, P. J., Myin-Germeys, I., & Kwapil, T. R. (2007). For Whom the Mind Wanders, and When:An Experience-Sampling Study of Working Memory and Executive Control in Daily Life. *Psychol Sci, 18*(7), 614-621. doi:10.1111/j.1467-9280.2007.01948.x

Kim, C., Kroger, J. K., Calhoun, V. D., & Clark, V. P. (2015). The role of the frontopolar cortex in manipulation of integrated information in working memory. *Neurosci Lett, 595*, 25-29. doi:10.1016/j.neulet.2015.03.044

Kochunov, P., Glahn, D. C., Fox, P. T., Lancaster, J. L., Saleem, K., Shelledy, W., Zilles, K., Thompson, P. M., Coulon, O., Mangin, J. F., Blangero, J., & Rogers, J. (2010). Genetics of primary cerebral gyrification: Heritability of length, depth and area of primary sulci in an extended pedigree of Papio baboons. *Neuroimage, 53*(3), 1126-1134. doi:10.1016/j.neuroimage.2009.12.045

Kraft, E. (2012). Cognitive function, physical activity, and aging: possible biological links and implications for multimodal interventions. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 19*(1-2), 248-263. doi:10.1080/13825585.2011.645010

Reference

Krogsrud, S. K., Mowinckel, A. M., Sederevicius, D., Vidal-Piñeiro, D., Amlien, I. K., Wang, Y., Sørensen, Ø., Walhovd, K. B., & Fjell, A. M. (2021). Relationships between apparent cortical thickness and working memory across the lifespan - Effects of genetics and socioeconomic status. *Dev Cogn Neurosci, 51*, 100997. doi:https://doi.org/10.1016/j.dcn.2021.100997

Kurth, F., & Luders, E. (2015). *Voxel-Based Morphometry*.

Larson, E. B., Yaffe, K., & Langa, K. M. (2013). New insights into the dementia epidemic. *N Engl J Med, 369*(24), 2275-2277. doi:10.1056/NEJMp1311405

Lauterbur, P. C. (1989). Image formation by induced local interactions. Examples employing nuclear magnetic resonance. 1973. *Clin Orthop Relat Res*(244), 3-6.

Lawlor-Savage, L., Clark, C. M., & Goghari, V. M. (2019). No evidence that working memory training alters gray matter structure: A MRI surface -based analysis. *Behav Brain Res, 360*, 323-340. doi:10.1016/j.bbr.2018.12.008

Luders, E., Kurth, F., Mayer, E. A., Toga, A. W., Narr, K. L., & Gaser, C. (2012). The unique brain anatomy of meditation practitioners: alterations in cortical gyrification. *Front Hum Neurosci, 6*, 34. doi:10.3389/fnhum.2012.00034

Lundstrom, B. N., Ingvar, M., & Petersson, K. M. (2005). The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *Neuroimage, 27*(4), 824-834. doi:10.1016/j.neuroimage.2005.05.008

McNab, F., Zeidman, P., Rutledge, R. B., Smittenaar, P., Brown, H. R., Adams, R. A., & Dolan, R. J. (2015). Age-related changes in working memory and the ability to ignore distraction. *Proceedings of the National Academy of Sciences of the United States of America, 112*(20), 6515-6518. doi:10.1073/pnas.1504162112

Mechelli, A., Friston, K. J., Frackowiak, R. S., & Price, C. J. (2005). Structural covariance in the human cortex. *J Neurosci, 25*(36), 8303-8310. doi:10.1523/JNEUROSCI.0357-05.2005

Mechelli, A., Price, C., Friston, K., & Ashburner, J. (2005). *Voxel-Based Morphometry of the Human Brain: Methods and Applications* (Vol. 1).

Melby-Lervag, M., Redick, T. S., & Hulme, C. (2016). Working Memory Training Does Not Improve Performance on Measures of Intelligence or Other Measures of "Far

Transfer": Evidence From a Meta-Analytic Review. *Perspectives on Psychological Science, 11*(4), 512-534. doi:10.1177/1745691616635612

Mercadante, A. A., & Tadi, P. (2021). Neuroanatomy, Gray Matter *StatPearls*. Treasure Island (FL).

Metzler-Baddeley, C., Caeyenberghs, K., Foley, S., & Jones, D. K. (2016a). Longitudinal data on cortical thickness before and after working memory training. *Data Brief, 7*, 1143-1147. doi:10.1016/j.dib.2016.03.090

Metzler-Baddeley, C., Caeyenberghs, K., Foley, S., & Jones, D. K. (2016b). Task complexity and location specific changes of cortical thickness in executive and salience networks after working memory training. *Neuroimage, 130*, 48-62. doi:10.1016/j.neuroimage.2016.01.007

Meule, A. (2017). Reporting and Interpreting Working Memory Performance in n-back Tasks. *Front Psychol, 8*(352). doi:10.3389/fpsyg.2017.00352

Miro-Padilla, A., Bueicheku, E., Ventura-Campos, N., Flores-Compan, M. J., Parcet, M. A., & Avila, C. (2019). Long-term brain effects of N-back training: an fMRI study. *Brain Imaging Behav, 13*(4), 1115-1127. doi:10.1007/s11682-018-9925-x

Montal, V., Vilaplana, E., Alcolea, D., Pegueroles, J., Pasternak, O., Gonzalez-Ortiz, S., Clarimon, J., Carmona-Iragui, M., Illan-Gala, I., Morenas-Rodriguez, E., Ribosa-Nogue, R., Sala, I., Sanchez-Saudinos, M. B., Garcia-Sebastian, M., Villanua, J., Izagirre, A., Estanga, A., Ecay-Torres, M., Iriondo, A., Clerigue, M., Tainta, M., Pozueta, A., Gonzalez, A., Martinez-Heras, E., Llufriu, S., Blesa, R., Sanchez-Juan, P., Martinez-Lage, P., Lleo, A., & Fortea, J. (2018). Cortical microstructural changes along the Alzheimer's disease continuum. *Alzheimers Dement, 14*(3), 340-351. doi:10.1016/j.jalz.2017.09.013

Moore, A. B., Li, Z., Tyner, C. E., Hu, X., & Crosson, B. (2013). Bilateral basal ganglia activity in verbal working memory. *Brain Lang, 125*(3), 316-323. doi:10.1016/j.bandl.2012.05.003

Mukherjee, P., Berman, J. I., Chung, S. W., Hess, C. P., & Henry, R. G. (2008). Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. *AJNR Am J Neuroradiol, 29*(4), 632-641. doi:10.3174/ajnr.A1051

Reference

Nissim, N. R., O'Shea, A. M., Bryant, V., Porges, E. C., Cohen, R., & Woods, A. J. (2016). Frontal Structural Neural Correlates of Working Memory Performance in Older Adults. *Front Aging Neurosci, 8*, 328. doi:10.3389/fnagi.2016.00328

Oberauer, K. (2005). The Measurement of Working Memory Capacity *Handbook of understanding and measuring intelligence.* (pp. 393-407). Thousand Oaks, CA, US: Sage Publications, Inc.

Osaka, M., Osaka, N., Kondo, H., Morishita, M., Fukuyama, H., Aso, T., & Shibasaki, H. (2003). The neural basis of individual differences in working memory capacity: an fMRI study. *Neuroimage, 18*(3), 789-797. doi:10.1016/s1053-8119(02)00032-0

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., Jacobson, K., Lyons, M. J., Grant, M. D., Franz, C. E., Xian, H., Tsuang, M., Fischl, B., Seidman, L., Dale, A., & Kremen, W. S. (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex, 19*(11), 2728-2735. doi:10.1093/cercor/bhp026

Park, D. C., & Bischof, G. N. (2013). The aging mind: neuroplasticity in response to cognitive training. *Dialogues Clin Neurosci, 15*(1), 109-119.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol Aging, 17*(2), 299-320.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol, 60*, 173-196. doi:10.1146/annurev.psych.59.103006.093656

Peters, R. (2006). Ageing and the brain. *Postgraduate medical journal, 82*(964), 84-88. doi:10.1136/pgmj.2005.036665

Pichet Binette, A., Gonneaud, J., Vogel, J. W., La Joie, R., Rosa-Neto, P., Collins, D. L., Poirier, J., Breitner, J. C. S., Villeneuve, S., Vachon-Presseau, E., Alzheimer's Disease Neuroimaging, I., & Group, P.-A. R. (2020). Morphometric network differences in ageing versus Alzheimer's disease dementia. *Brain, 143*(2), 635-649. doi:10.1093/brain/awz414

Reference

Qing, Z., Chen, F., Lu, J., Lv, P., Li, W., Liang, X., Wang, M., Wang, Z., Zhang, X., Zhang, B., & Alzheimer's Disease Neuroimaging, I. (2021). Causal structural covariance network revealing atrophy progression in Alzheimer's disease continuum. *Hum Brain Mapp, 42*(12), 3950-3962. doi:10.1002/hbm.25531

Reuter, M., & Fischl, B. (2011). Avoiding asymmetry-induced bias in longitudinal image processing. *Neuroimage, 57*(1), 19-21. doi:10.1016/j.neuroimage.2011.02.076

Reuter, M., Rosas, H. D., & Fischl, B. (2010). Highly accurate inverse consistent registration: a robust approach. *Neuroimage, 53*(4), 1181-1196. doi:10.1016/j.neuroimage.2010.07.020

Reuter, M., Schmansky, N. J., Rosas, H. D., & Fischl, B. (2012). Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage, 61*(4), 1402-1418. doi:10.1016/j.neuroimage.2012.02.084

Richter-Levin, G., & Akirav, I. (2000). Amygdala-hippocampus dynamic interaction in relation to memory. *Mol Neurobiol, 22*(1-3), 11-20. doi:10.1385/MN:22:1-3:011

Ripp, I., Wu, Q., Wallenwein, L., Emch, M., Yakushev, I., & Koch, K. (2022). Neuronal efficiency following n-back training task is accompanied by a higher cerebral glucose metabolism. *Neuroimage, 253*, 119095. doi:https://doi.org/10.1016/j.neuroimage.2022.119095

Rogers, J., Kochunov, P., Zilles, K., Shelledy, W., Lancaster, J., Thompson, P., Duggirala, R., Blangero, J., Fox, P. T., & Glahn, D. C. (2010). On the genetic architecture of cortical folding and brain volume in primates. *Neuroimage, 53*(3), 1103-1108. doi:10.1016/j.neuroimage.2010.02.020

Roman, F. J., Lewis, L. B., Chen, C. H., Karama, S., Burgaleta, M., Martinez, K., Lepage, C., Jaeggi, S. M., Evans, A. C., Kremen, W. S., & Colom, R. (2016). Gray matter responsiveness to adaptive working memory training: a surface-based morphometry study. *Brain Struct Funct, 221*(9), 4369-4382. doi:10.1007/s00429-015-1168-7

Romero-Garcia, R., Whitaker, K. J., Vasa, F., Seidlitz, J., Shinn, M., Fonagy, P., Dolan, R. J., Jones, P. B., Goodyer, I. M., Consortium, N., Bullmore, E. T., & Vertes, P. E. (2018). Structural covariance networks are coupled to expression of genes

enriched in supragranular layers of the human cortex. *Neuroimage, 171*, 256-267. doi:10.1016/j.neuroimage.2017.12.060

Süß, H.-M., Oberauer, K., Wittmann, W. W., Wilhelm, O., & Schulze, R. (2002). Working-memory capacity explains reasoning ability--and a little bit more. *Intelligence, 30*(3), 261-288. doi:10.1016/S0160-2896(01)00100-3

Sala, G., Aksayli, N. D., Tatlidil, K. S., Gondo, Y., & Gobet, F. (2019). Working memory training does not enhance older adults' cognitive skills: A comprehensive meta-analysis. *Intelligence, 77*, 101386. doi:https://doi.org/10.1016/j.intell.2019.101386

Salmi, J., Nyberg, L., & Laine, M. (2018). Working memory training mostly engages general-purpose large-scale networks for learning. *Neurosci Biobehav Rev, 93*, 108-122. doi:10.1016/j.neubiorev.2018.03.019

Schaer, M., Cuadra, M. B., Schmansky, N., Fischl, B., Thiran, J. P., & Eliez, S. (2012). How to measure cortical folding from MR images: a step-by-step tutorial to compute local gyrification index. *J Vis Exp*(59), e3417. doi:10.3791/3417

Schaer, M., Cuadra, M. B., Tamarit, L., Lazeyras, F., Eliez, S., & Thiran, J. P. (2008). A surface-based approach to quantify local cortical gyrification. *IEEE Trans Med Imaging, 27*(2), 161-170. doi:10.1109/TMI.2007.903576

Schneiders, J. A., Opitz, B., Krick, C. M., & Mecklinger, A. (2011). Separating intra-modal and across-modal training effects in visual working memory: an fMRI investigation. *Cereb Cortex, 21*(11), 2555-2564. doi:10.1093/cercor/bhr037

Schneiders, J. A., Opitz, B., Tang, H., Deng, Y., Xie, C., Li, H., & Mecklinger, A. (2012). The impact of auditory working memory training on the fronto-parietal working memory network. *Front Hum Neurosci, 6*, 173. doi:10.3389/fnhum.2012.00173

Schott, B. H., Wustenberg, T., Lucke, E., Pohl, I. M., Richter, A., Seidenbecher, C. I., Pollmann, S., Kizilirmak, J. M., & Richardson-Klavehn, A. (2019). Gradual acquisition of visuospatial associative memory representations via the dorsal precuneus. *Hum Brain Mapp, 40*(5), 1554-1570. doi:10.1002/hbm.24467

Schroll, H., Vitay, J., & Hamker, F. H. (2012). Working memory and response selection: a computational account of interactions among cortico-basalganglio-thalamic loops. *Neural Netw, 26*, 59-74. doi:10.1016/j.neunet.2011.10.008

Reference

Schultz, S. K. (2001). Principles of neural science, 4th edition. *American Journal of Psychiatry, 158*(4), 662-662.

Schweizer, S., Grahn, J., Hampshire, A., Mobbs, D., & Dalgleish, T. (2013). Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. *Journal of Neuroscience, 33*(12), 5301-+. doi:10.1523/Jneurosci.2593-12.2013

Sciubba, J. D. (2020). Population Aging as a Global Issue: Oxford University Press.

Sereno, M. I., Dale, A. M., Reppas, J. B., Kwong, K. K., Belliveau, J. W., Brady, T. J., Rosen, B. R., & Tootell, R. B. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science, 268*(5212), 889-893. doi:10.1126/science.7754376

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

Shipstead, Z., Redick, T. S., & Engle, R. W. (2010). Does working memory training generalize? *Psychologica Belgica, 50*(3-4), 245-276. doi:10.5334/pb-50-3-4-245

Shock, N. W. (2020). Human aging. *Encyclopedia Britannica*.

Silk, T. J., Rinehart, N., Bradshaw, J. L., Tonge, B., Egan, G., O'Boyle, M. W., & Cunnington, R. (2006). Visuospatial processing and the function of prefrontal-parietal networks in autism spectrum disorders: a functional MRI study. *Am J Psychiatry, 163*(8), 1440-1443. doi:10.1176/ajp.2006.163.8.1440

Simon, J. R., & Berbaum, K. (1990). Effect of conflicting cues on information processing: the 'Stroop effect' vs. the 'Simon effect'. *Acta Psychol (Amst), 73*(2), 159-170. doi:10.1016/0001-6918(90)90077-s

Soveri, A., Antfolk, J., Karlsson, L., Salo, B., & Laine, M. (2017). Working memory training revisited: A multi-level meta-analysis of n-back training studies. *Psychon Bull Rev*. doi:10.3758/s13423-016-1217-0

Reference

Storsve, A. B., Fjell, A. M., Tamnes, C. K., Westlye, L. T., Overbye, K., Aasland, H. W., & Walhovd, K. B. (2014). Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: regions of accelerating and decelerating change. *J Neurosci, 34*(25), 8488-8498. doi:10.1523/JNEUROSCI.0391-14.2014

Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., & Kawashima, R. (2011). Working Memory Training Using Mental Calculation Impacts Regional Gray Matter of the Frontal and Parietal Regions. *PLoS ONE, 6*(8). doi:ARTN e23175

10.1371/journal.pone.0023175

Tewes, U. (1994). *HAWIE-R: Hamburg-Wechsler-Intelligenztest für Erwachsene, Revision 1991 ; Handbuch und Testanweisung*: Huber.

Torkzad, M. R., Ahlstrom, H., & Karlbom, U. (2014). Comparison of different magnetic resonance imaging sequences for assessment of fistula-in-ano. *World J Radiol, 6*(5), 203-209. doi:10.4329/wjr.v6.i5.203

Tusch, E. S., Alperin, B. R., Ryan, E., Holcomb, P. J., Mohammed, A. H., & Daffner, K. R. (2016). Changes in Neural Activity Underlying Working Memory after Computerized Cognitive Training in Older Adults. *Front Aging Neurosci, 8*, 255-255. doi:10.3389/fnagi.2016.00255

Ungerleider, L. G., Courtney, S. M., & Haxby, J. V. (1998). A neural system for human visual working memory. *Proceedings of the National Academy of Sciences of the United States of America, 95*(3), 883-890. doi:10.1073/pnas.95.3.883

Uttl, B., & Graf, P. (1997). Color-Word Stroop test performance across the adult life span. *J Clin Exp Neuropsychol, 19*(3), 405-420. doi:10.1080/01688639708403869

Veale, J. F. (2014). Edinburgh Handedness Inventory - Short Form: a revised version based on confirmatory factor analysis. *Laterality, 19*(2), 164-177. doi:10.1080/1357650X.2013.783045

von Bastian, C. C., & Oberauer, K. (2014). Effects and mechanisms of working memory training: a review. *Psychol Res, 78*(6), 803-820. doi:10.1007/s00426-013-0524-6

Reference

Wannan, C. M. J., Cropley, V. L., Chakravarty, M. M., Bousman, C., Ganella, E. P., Bruggemann, J. M., Weickert, T. W., Weickert, C. S., Everall, I., McGorry, P., Velakoulis, D., Wood, S. J., Bartholomeusz, C. F., Pantelis, C., & Zalesky, A. (2019). Evidence for Network-Based Cortical Thickness Reductions in Schizophrenia. *Am J Psychiatry, 176*(7), 552-563. doi:10.1176/appi.ajp.2019.18040380

Weishaupt, D., Köchli, V. D., Marincek, B., & Kim, E. E. (2007). How Does MRI Work? An Introduction to the Physics and Function of Magnetic Resonance Imaging. *Journal of Nuclear Medicine, 48*(11), 1910-1910. doi:10.2967/jnumed.107.045104

White, T., Andreasen, N. C., & Nopoulos, P. (2002). Brain volumes and surface morphology in monozygotic twins. *Cereb Cortex, 12*(5), 486-493. doi:10.1093/cercor/12.5.486

Wierenga, L. M., Langen, M., Oranje, B., & Durston, S. (2014). Unique developmental trajectories of cortical thickness and surface area. *Neuroimage, 87*, 120-126. doi:10.1016/j.neuroimage.2013.11.010

Wilhelm, O., Hildebrandt, A., & Oberauer, K. (2013). What is working memory capacity, and how can we measure it? *Front Psychol, 4*(433). doi:10.3389/fpsyg.2013.00433

Winkler, A. M., Sabuncu, M. R., Yeo, B. T., Fischl, B., Greve, D. N., Kochunov, P., Nichols, T. E., Blangero, J., & Glahn, D. C. (2012). Measuring and comparing brain cortical surface area and other areal quantities. *Neuroimage, 61*(4), 1428-1443. doi:10.1016/j.neuroimage.2012.03.026

Wu, Q., Ripp, I., Emch, M., & Koch, K. (2021). Cortical and subcortical responsiveness to intensive adaptive working memory training: An MRI surface-based analysis. *Hum Brain Mapp, 42*(9), 2907-2920. doi:10.1002/hbm.25412

Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in gray and white: neuroimaging changes in brain structure during learning. *Nat Neurosci, 15*(4), 528-536. doi:10.1038/nn.3045

Reference

Zilles, K., Palomero-Gallagher, N., & Amunts, K. (2013). Development of cortical folding during evolution and ontogeny. *Trends Neurosci, 36*(5), 275-284. doi:10.1016/j.tins.2013.01.006

Acknowledgements

First of all, I would like to express my deep gratitude to my supervisors: professor Ernst Pöppel and professor Kathrin Koch. Prof. Pöppel, thank you for being my doctor father. I am truly grateful for that. I really enjoyed every inspiring conversation and scientific discussion we had, which benefited me greatly. As you said before, age-wise you certainly belong to my grandfather generation. In fact, to some extent, you do play a role of grandfather to bring care and warmth. Thanks for organizing 'lab lunch' to provide the opportunity to bring lab members together, on a personal level also. It's my great honor to be a part of your lab.

Dear Kathrin, my supervisor, I would like to give special thanks and appreciation to you. I'm grateful that you gave me the opportunity to do my PhD project in such an awesome team. Thanks for your openness to all questions and new research ideas, as well as your always positive energy. Thanks for giving me confidence and encouragement whenever I encountered difficulties. Thanks for your empathy and patience. To me you are not only my supervisor, but also a friend – we also had a lot topics to talk about other than research and work. I really enjoyed that and will miss that. I appreciate all that you have done to supervise, inspire, help and encourage me during my PhD study. I've learnt a lot from you, especially your research enthusiasm and desire to explore. My role model, I feel extremely fortunate to be your PhD student.

I would like to thank my TAC member Prof. Karin Meißner. Thank you for being supportive as well as your feedback on my presentation in every TAC meeting.

I also want to thank all awesome colleagues I met here in 'TUM-NIC' as well as 'Cellar group', I love these international research teams. Big thanks to 'international dinner' group, I enjoyed every moment we spent together – various events like movie nights, dinner, Octoberfest, etc. Thank you for making my time in Munich even more memorable.

Here I would especially thank my colleague, my good friend, Isabelle, thank you so much for all your encouraging words, your empathy and your company whenever I needed, all these meant a lot to me. I miss every brainstorm and inspirations collide we had. I am grateful to have such an awesome colleague and friend. I must say that you are outstanding on many levels. Thanks Alyssa, Deniz, Daniela, Monica, and Maria, thank you so much for being such amazing colleagues and friends. Without you, our research group would not have such a friendly, positive, and mutually helpful working atmosphere.

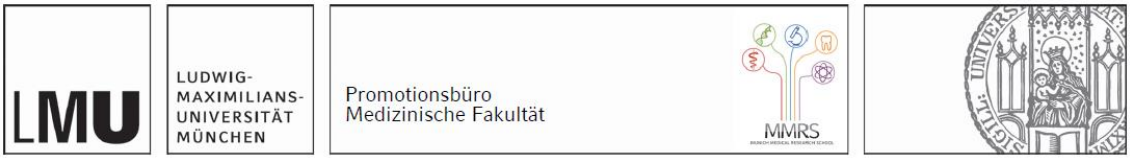
Acknowledgements

I want to thank all my friends, from ‘Bogenhasuen group’ to ‘Girl’s party’, thank you for being my ‘Munich family’, thank you for making my life full of variety in the past four years.

I want to thank my family, thank them for their unconditional and endless love, thank them for always being supportive and being there for me whenever I need them.

I also would like to thank myself, the version of me fours ago, thank you for being brave enough to make such a good decision – to pursue a PhD abroad. It was a really good adventure, a great experience, and a really good gift for me.

Affidavit



Affidavit

Wu, Qiong

Surname, first name

Street

Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Morphometric reorganization induced by working memory training:

perspective from vertex & network levels

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

A part of the work of current thesis has been published in Human Brain Mapping (2021).

Leipzig, 18.01.2023 — Qiong Wu 吴琼

place, date — Signature doctoral candidate

List of publications

1. **Wu, Q.**, Ripp, I., Emch, M., & Koch, K. (2021). Cortical and subcortical responsiveness to long-term adaptive working memory training: A MRI surface-based analysis. Human Brain Mapping;1-14. doi: 10.1002/hbm.25412

2. Ripp, I., Wallenwein, L., **Wu, Q.**, Emch, M., Koch, K., Cumming P., Yakushev, I. (2021). Working memory task induced neural activation: a simultaneous PET/fMRI study. Neuroimage, 2021 May 2; 237:118131. doi: 10.1016/j.neuroimage.2021.118131

3. Ripp, I.*, **Wu, Q.***, Wallenwein, L., Emch, M., Yakushev, I., & Koch, K. (2022). Neuronal efficiency following n-back training task is accompanied by a higher cerebral glucose metabolism. Neuroimage, 253, 119095. doi: https://doi.org/10.1016/j.neuroimage.2022.119095 *(Equally contributed first author & corresponding author)*

4. Ripp, I., Emch, M., **Wu, Q.**, Lizarraga, A., von Bastian, C. C., Koch, K., & Yakushev, I. (2022) Absence of transfer effects due to working memory training: a comprehensive cognitive and neuroimaging study. Translational Psychiatry *(major revision, under review)*

5. Bremer B.*, **Wu Q.***, Mora Álvarez M.G., Hölzel B., Wilhelm M., Hell E., Tavacıoğlu E. E., Torske A., Koch K. (2021) Mindfulness meditation increases default mode, salience, and central executive network connectivity. Scientific Reports, *(major revision, under review) (Equally contributed first author)*

6. **Wu, Q.**, Zhang, X., Dong, D., Wang, X., & Yao, S. (2017). Altered spontaneous brain activi-ty in adolescent boys with pure conduct disorder revealed by regional homogeneity analysis. Eur Child Adolesc Psychiatry, 26(7), 827-837. doi:10.1007/s00787-017-0953-7

7. 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. Front Aging Neurosci, 11, 300. doi:10.3389/fnagi.2019.00300

8. Gao, Y., Jiang, Y., Ming, Q., Zhang, J., Ma, R., **Wu, Q.**, . . . Yao, S. (2021). Neuroanatomical changes associated with conduct disorder in boys: influence of childhood maltreatment. Eur Child Adolesc Psychiatry. doi:10.1007/s00787-020-01697-z

9. Gao, Y., Jiang, Y., Ming, Q., Zhang, J., Ma, R., **Wu, Q.**, . . . Yao, S. (2020). Gray Matter Changes in the Orbitofrontal-Paralimbic Cortex in Male Youths with Non-comorbid Con-duct Disorder. Front Psychol, 11, 843. doi:10.3389/fpsyg.2020.00843

10. Zhang, J., Liu, W., Zhang, J., **Wu, Q.**, Gao, Y., Jiang, Y., . . . Huang, B. (2018). Distinguish-ing Adolescents With Conduct Disorder From Typically Developing Youngsters Based on Pattern Classification of Brain Structural MRI. Front Hum Neurosci, 12, 152. doi:10.3389/fnhum.2018.00152

11. Sun, X., Ma, R., Jiang, Y., Gao, Y., Ming, Q., **Wu, Q.**, . . . Yao, S. (2018). MAOA genotype influences neural response during an inhibitory task in adolescents with conduct disorder. Eur Child Adolesc Psychiatry, 27(9), 1159-1169. doi:10.1007/s00787-018-1170-8

12. Dong, D., Ming, Q., Wang, X., Yu, W., Jiang, Y., **Wu, Q.**, . . . Yao, S. (2016). Tem-poroparie-tal Junction Hypoactivity during Pain-Related Empathy Processing in Ad-olescents with Conduct Disorder. Front Psychol, 7, 2085. doi:10.3389/fpsyg.2016.02085