Working Memory Updating Training and the Rehabilitation of Goal Management After Brain Injury

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Submitted in fulfilment of the requirements of the Degree of Doctor of Philosophy.

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June 2022

Abstract

This thesis follows an interdisciplinary research approach employing methods from the fields of clinical neuropsychology and cognitive neuroscience to investigate the plastic changes following cognitive training. Disentangling the mechanism behind the training-induced cognitive and neural plastic changes can have a direct impact on the cognitive rehabilitation of individuals with long term cognitive impairments.

Chapter one provides a brief overview of the executive function difficulties associated with acquired brain injury (ABI) and a description of the clinically evaluated goal management strategy-based training (Levine, Manly and Robertson, 2012). Process-based training paradigms and their implication for generalisation of learning are subsequently discussed together with the theoretical framework of adult plasticity proposed by Lövdén et al., (2010). The chapter discusses working memory processes, their relationship with executive functions and provides a description of the WM neural network involving fronto-parietal and striatal areas. At the end of this chapter, the development of a multidisciplinary intervention integrating goal management strategies and working memory process-based training in adults with ABI is described.

Chapters two, three and four primarily focus on research in healthy adult populations and investigate the cognitive and neural changes following working memory updating (WMU) training. Chapter two is a meta-analysis of the training and transfer effects conducted together with a systematic review of the functional activity changes following WMU training. Existing work focuses mainly on healthy adults together with a small number of studies involving neurological populations. Chapters three and four investigate the grey matter volumetric changes and the task-based functional connectivity changes following adaptive working memory updating training in healthy young adults. These analyses are complementary to a previous fMRI analysis conducted by Flegal, Ragland and Ranganath (2019).

Chapters five, six and seven focus on the transition from research with healthy adults to individuals with ABI and describes the development of an

integrated goal management strategy and WMU process-based training protocol targeting executive dysfunction ABI. Chapter five is a critical review discussing key issues in the field of cognitive training with emphasis on WM protocols and highlights the importance of employing interdisciplinary methods from the field of cognitive neuroscience and clinical neuropsychology. Chapter six involves the detailed description of the integrated processes and strategies (iPRESS) training protocol combining the goal management training (GMT) (Levine, Manly and Robertson, 2012) with the adaptive WMU training protocol employed in Flegal, Ragland and Ranganath (2019). This chapter further describes the amendments put in place to allow for remote delivery of the iPRESS protocol due to COVID-19 constraints and disruptions. Chapter seven investigates the feasibility of running the remote version of iPRESS and to test the fMRI task protocol adapted for an individual with ABI.

Chapter eight discusses the implications of the research conducted in this thesis involving a better understanding of the training-induced plastic changes as well as the development of interdisciplinary cognitive interventions. Finally, the chapter posits research questions to be addressed in the future.

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Pappa, K., Biswas, V., Flegal, K. E., Evans, J. J. and Baylan, S. (2020). 'Working memory updating training promotes plasticity & behavioural gains: A systematic review & meta-analysis'. *Neuroscience & Biobehavioral Reviews*, 118, pp. 209–235. doi: 10.1016/j.neubiorev.2020.07.027.

Pappa, K., Flegal, K. E., Baylan, S. and Evans, J. J. (2021). *Working memory training: Taking a step back to retool and create a bridge between clinical and neuroimaging research methods*. Applied Neuropsychology: Adult. doi: 10.1080/23279095.2021.1904243.

Acknowledgements

My PhD journey has been long, tiresome, and quite emotional but I made it to the end. I am grateful and forever in debt to my amazing supervisory team who helped me through it. Jon, Kristin and Satu, I really could not have done it without you. Thank you for giving me the opportunity to work on a research project I truly believe in and produce high quality research; for giving me the time and space to grow and flourish as an independent researcher, for being patient with my indecisiveness, and for giving me the courage to finally feel confident in myself. More importantly, thank you for allowing me to be unapologetically myself through it all. A few words for each one.

Jon Evans, you are genuinely one of the kindest, nicest, most gentle people I have ever met, and despite your brilliance, so humble and modest. Having the privilege to flourish and grow as a researcher under your supervision is something I will cherish forever. You always challenged me by asking the hard scientific questions, a truly valuable learning experience. You would always ask for my opinion, always made me feel like I have something important to say and take my suggestions into consideration. Thank you, Jon.

Kristin Flegal, you taught me everything I know about neuroimaging analysis, literally sitting by my desk explaining things step by step, making the most complex concepts seem tangible. Kristin, you truly went above and beyond your standard supervisory duties to cheer me on when I was down, looking after me after a breakdown, offer moral support and give friendly advice throughout. I was fortunate to have a supervisor and friend in one, you always had my back and looked out for me both professionally and personally. Thank you, Kristin.

Satu Baylan you always provided concrete solutions to a challenging issue; you were a problem-solver. Even though you moved on to complete your DClin training during the remainder of my PhD, you were still actively involved in my supervision, making sure you were on top of your supervisory duties even though in full-time training. You have always been so supportive, encouraging, and compassionate. Thank you, Satu.

I am grateful to all the participants for making this research possible and for sticking with iPRESS with all its COVID glitches and delays. Thank you to our collaborators in the NHS, and specifically to Dr Nicola Goudie, for your ongoing support and involvement in the project, as well as Meghann Richardson and the rest of the CTCBI team, NHS GG&C. Likewise, thank you to both brain injury and stroke teams at NHS Lanarkshire and particularly Dr Jane Moir, Dr Jane-Marie Stobie, Dr Louise Roach, and Dr Susan Kennedy. I would also like to thank everyone who assisted with fMRI data collection and in particular Tracey Hopkins, Rosie Woodward, Dr John McLean and Dr Natasha Fullerton. A big thank you to the ICE family for creating a warm and friendly atmosphere at our workplace. Finally, many thanks to the Neurosciences Foundation, the Mortimer and Theresa Sackler foundation and the Margaret Murdoch charitable trust that supported this research.

I obviously could not leave my support network out of this long acknowledgement section and so I need to thank my most previous friends Evi, Stephanie, Dafni, Viveka, Sophie. Each of your friendships individually made this a sunnier, warmer, and more colourful journey. I am grateful to Debbie; I really would not be writing this if it were not for your unconditional help and support.

Thank you, Matt, simply for being there, loving me and telling me you got me. Noted.

Thank you, mum, dad, for turning me into that independent young woman moving to London at 21 years of age. Thank you for supporting me and providing a safe space at my most vulnerable. Thank you to the most amazing big sister; Marita, you always have my back, defend, and protect me and truly believe in me. Thank you to both you and Panagiotis for providing a safety net for me and taking care of me at my darkest. Thank you to my family for always being there and supporting me one way or another.

I will finish this long acknowledgement section quoting Stephen Hawking to say I am truly grateful for finding my way out of my black hole and into a universe where I persevered, and I made it to the end. I am truly proud of this work; I am content, I am ready for my PhD. Thank you.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Aikaterini Pappa

1 Introduction

1.1 Acquired Brain Injury (ABI)

Acquired brain injury (ABI) refers to any brain injury occurring after birth, i.e., an injury that is not developmental, hereditary or congenital in nature. Such injuries could be caused due to stroke, traumatic brain injury (TBI), aneurysm, tumour, or infection with the first two being the most common. Stroke and head injuries are leading causes of disability in the UK (Thornhill et al., 2000) and according to a report published in 2018 by Headway[1], ABI hospital admissions in the UK increased by 10% since 2005; a 1% increase for TBIs and a 10% increase for strokes. The long-term effects following ABI fall under three main categories:

1. Physical such as hemiparesis or hemiplegia, fatigue, mobility issues, ataxia, and epilepsy.
2. Emotional and behavioural involving personality changes, mood swings, depression, anxiety, disinhibition, and impulsiveness.
3. Cognitive including difficulties with memory, attention, executive functions, language, and perception.

Physical, emotional and/or cognitive deficits can occur in any combination and are usually comorbid. Cognitive deficits are common in ABI, including impairment in frontal-lobe 'executive' functions such as working memory (WM) and the ability to solve problems, plan, and regulate actions to achieve intended goals (Krasny-Pacini, Chevignard and Evans, 2014; Tate et al., 2014). These impairments affect peoples' ability to live independently, work, and maintain social relationships (Krasny-Pacini, Chevignard and Evans, 2014; Tate et al., 2014).

[1] https://www.headway.org.uk/media/7865/acquired-brain-injury-the-numbers-behind-the-hidden-disability-2018.pdf

1.1.1 Executive function and the frontal lobes

> "Executive functioning is the term used to encompass a range of cognitive skills including problem solving, planning and organisation, self-monitoring, initiation, error correction and behavioural regulation. Executive functions enable us to deal with problems that arise in everyday life and to cope with new situations" (Evans, 2008, pp.193).

Essentially, executive functions enable us to solve complex problems, understand abstract concepts, adapt to novel situations, and in general go about our day. So, it is perhaps unsurprising that impairments in executive functioning (EF) can have such devastating long-term effects on people's lives. EF has traditionally been linked to the frontal lobes; a link that traces back to the famous case of Phineas Gage in 1848. He suffered a tragic accident while at work when a large iron rod passed through his left frontal lobe. Remarkably, he survived the accident but nevertheless experienced the devastating consequences of his injury which dramatically changed his personality and behaviour. The case of Phineas Gage is the first documented account of the complexity of EF and its relationship with the frontal lobes. Further cases of patients exhibiting EF impairments following frontal lobe damage have been recorded over the years (Eslinger and Damasio, 1985; Shallice and Burgess, 1991). Nevertheless, the relationship between frontal lobes and EF has been difficult to define on the basis of neuropsychological case studies primarily due to the long-standing debate concerning the unity and diversity of frontal lobe function (Stuss and Alexander, 2000). For this reason, several theoretical accounts and models of EF have been proposed over the years, some of which are briefly discussed in the next section.

Luria was the first author who conceptualised EF and made a connection between EF, problem solving and the frontal lobes (Luria, 1976). Even though the term EF was not coined until later (Lezak, 1982), Luria developed a theoretical framework where he described anticipation (setting realistic expectations, understanding consequences), planning (organisation), execution (flexibility, maintaining set) and self-monitoring (emotional control, error recognition) as the main components of EF. A few years later, Lezak (1982) termed EF as those mental capacities essential for goal formulation, planning,

carrying out goal-directed plans and effective performance. She additionally made a connection between EF, the frontal lobes as well as involvement of subcortical regions. Duncan et al., (1996) subsequently argued the frontal lobes are involved in identifying goals and managing actions to achieve intended goals. According to this framework, frontal lobe damage leads to "goal neglect" where the individual may be able to identify a goal and even devise a plan of action. During the operation phase of the plan however, the main goals become neglected whilst the actions taken do not lead to goal achievement. Consequently, behaviour is no longer goal directed.

Another influential theory comes from Norman and Shallice's work (Norman and Shallice, 1986) where the existence of a supervisory attentional system (SAS) is attributed to the frontal lobes. The SAS comes into play when encountering novel situations that cannot be adequately resolved through well learned behaviours. The theory was later updated to include the notion of the frontal lobes containing a set of subsystems responsible for distinct processes which in turn contain a further set of sub-processes (Burgess and Simons, 2004; Shallice et al., 1996; Shallice and Burgess, 1991). The system follows a hierarchical organisation where novel problem solving follows a three-phase approach.

Phase 1: problem orientation including the sub-processes of goal setting, aspiration setting, spontaneous schema generation, progressing deepening phase and solution checking, i.e., a set of mental operations necessary for formulating a plan of action.

Phase 2: implementation of new schema including the sub-process of a special purpose WM required for carrying out the proposed plan.

Phase 3: assessment and verification of the new schema including the sub-processes of monitoring and rejection of the plan depending upon its success in solving the novel problem.

We will further consider the EF model proposed by Miyake et al. (2000). The authors tried to resolve the issue of unity and diversity of the EF by conducting an individual differences study focusing on the three most frequently posited executive functions (EFs); 1. shifting of tasks/ mental sets, 2. inhibition

of automatic responses. and 3. monitoring and updating WM representations. They selected various cognitive tasks targeting each of the EFs and examined their unity or diversity at the latent variable level, i.e., variables not directly observed but rather inferred from others. In more detail, Miyake and colleagues extracted the common characteristics across the selected tasks targeting each of the three EFs and then used that latent variable factor to investigate the relationship between them. The findings revealed that shifting, updating and inhibition are distinct yet related EFs sharing underlying commonalities. In reference to the diversity of EFs, the study findings are in line with clinical research suggesting dissociations in task performance as well as studies on individual differences exhibiting low inter-correlations between the different EFs. In relation to the unitary nature of EFs, Miyake et al. (2000) offered two possible explanations with the first relating to the selection of the various experimental tasks. In more detail, even though the tasks were chosen to tap into a specific EF, it is quite probable they also shared some task requirements and particularly maintaining goal related and other task relevant information in WM during processing (Miyake et al., 2000). The second explanation suggests the EFs of shifting, updating and inhibition, all require some level of inhibition of prepotent responses to operate smoothly and therefore, findings revealed moderate correlations amongst them.

Finally, Stuss (2007) proposed a model where the prefrontal cortex (PFC) of the frontal lobes has four different yet related functions; executive cognitive in the lateral PFC, behavioural-emotional self-regulatory in the ventral PFC, energisation regulating function in superior medial frontal region and meta-cognitive processes in the frontal polar region. Focusing on the first category; executive cognitive functions involve high-level cognitive functions, i.e., planning, monitoring, switching, inhibiting, and are directly involved in the control and regulation of lower-level automatic functions. Rather than a central executive component, there are different functions within the frontal lobes which receive input from and interact with one another (Stuss, 2011).

1.1.2 Executive function beyond the frontal lobes

Stuss and Alexander (2000) posit that conceptualising EF as synonymous to frontal lobe function is problematic. One of the reasons for the difficulty in

defining EF and its neural underpinning is the fact that executive impairments have also been documented following damage to brain regions other than the frontal lobes (Lezak, 2012; Elliott, 2003). There is also a well-documented cortico-striatal circuit (Alexander, DeLong and Strick, 1986; Haber, 2016) linking frontal regions to striatal structures (caudate nucleus, putamen and nucleus accumbens) via the thalamus and globus pallidus. The influential model originally proposed by Alexander, DeLong and Strick (1986) suggests a functional as well as anatomical relationship between the frontal cortex and striatum. Evidence to support striatal involvement in executive functions comes from studies of neurodegenerative disorders such as Huntington's (Lawrence et al., 1996; Robbins et al., 1994) and Parkinson's disease (Owen et al., 1992; Taylor, Saint-Cyr and Lang, 1986), where deficits in executive function are quite prominent. Individuals with Parkinson's disease in particular exhibit executive impairments quite early in the disease progression when pathology is still restricted in the basal ganglia regions (Elliott, 2003). Evidence from neurological disorders in combination with the established cortico-striatal model has led to the conclusion that executive function is not solely dependent upon the frontal lobes but rather on the intact functioning of the cortico-striatal circuitry which in turn is mediated by dopaminergic neurotransmission (Elliott, 2003).

Despite the complexity of defining EF and its neural signature, many of the proposed EF models are similar or share core characteristics. Even though choosing between the different theoretical accounts can be challenging, the classification under a specific EF framework can be helpful especially when attempting to understand the behavioural nuances of executive impairments. This can prove particularly useful for clinical neuropsychologists and neuroscience researchers alike in terms of developing and refining behavioural interventions targeting cognitive rehabilitation.

1.1.3 Cognitive rehabilitation and Goal Management Training (GMT)

> "Cognitive rehabilitation is defined as a systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioural deficits." (Keith D Cicerone et al., 2000, pp. 1596–1597).

In neuropsychological rehabilitation, interventions are classified as restorative, i.e., restoration of underlying core cognitive processes including executive functions, or compensatory, i.e., compensation of function using external aids or instructed strategies. Clinical guidelines recommend the use of meta-cognitive compensatory strategy training for the treatment of deficits in frontal-lobe executive functions (Cicerone et al., 2011; Tate et al., 2014). Goal Management Training (GMT) is one such validated meta-cognitive strategy rehabilitation program targeting executive functions and training compensatory mental strategies to manage attention during multi-step tasks (Levine et al., 2000, 2011; Levine and Stamenova, 2018). GMT can take place both in a group setting and a one-to-one format and is comprised of 9 modules and contains approximately 20h of training; it includes psychoeducation, mindfulness practice as well as assignments to complete within and between sessions (Levine and Stamenova, 2018).

GMT was originally conceived by Robertson (1996) with the first published report involving a brief one-hour trial in patients with ABI (Levine et al., 2000); whilst the multi-session GMT version was implemented in a subsequent study with older adults (Levine et al., 2007). A few years later, Levine and colleagues expanded GMT by introducing a mindfulness meditation component which was evaluated in individuals with frontal lobe damage (Levine et al., 2011). This GMT version is offered as a commercially available package published by Baycrest (Levine, Manly and Roberton, 2012). The latest development coinciding with the increasing needs for remote rehabilitation due to COVID-19, involves developing a digital version of the GMT tools[2].

The theoretical framework for developing GMT was based upon different EF theories. Originally, it was influenced from Duncan's theory of disorganised behaviour, "goal neglect", where individuals with EF impairments might be able to devise a plan to achieve intended goals but have difficulty employing the appropriate actions as well as monitor their progress towards (sub) goal achievement. GMT subsequently drew from the theory of sustained or vigilant attention (Robertson and Garavan, 2004). Sustained attention denotes the ability to remain vigilant over time in specific goal-directed behaviours; it is highly

[2] https://gmt.learnworlds.com/course/digital-gmt-tools

sensitive to repetitive, highly practiced and dull tasks where the ability to maintain alertness diminishes. Sustained attention is particularly impaired in individuals with brain injury either due to the pathology itself or secondary factors such as fatigue, depression etc. (Cristofori and Levin, 2015). Even though slightly different, the SAS model also makes the distinction between conscious control of action and automatic function and proposes a hierarchical phased approach to achieve novel problem solving (Shallice et al., 1996; Shallice and Burgess, 1991). The sustained attention system is associated with the right hemisphere and specifically the dorsolateral prefrontal and inferior parietal cortices (Robertson and Garavan, 2004) and also links with subcortical networks, i.e., thalamic and midbrain circuits (Robertson and Garavan, 2004). Higher order goals are maintained in this right fronto-thalamic-parietal sustained attention system (Petersen and Posner, 2012), and therefore when the system gets damaged, either through focal or diffuse lesions, it can manifest behavioural effects similar to those following prefrontal damage.

Sustained or vigilant attention can be enhanced both short- and longer-term through exogenous and endogenous meta-cognitive strategies respectively (Robertson and Garavan, 2004). One such endogenous meta-cognitive strategy technique became the basis for developing GMT as a structured rehabilitation program, in combination with Duncan's theory of goal neglect and the SAS model. Central concepts to the training involve absentmindedness, i.e., forgetfulness, and its opposite, i.e., present-mindedness, which means an enhanced state of awareness that can be practiced through mindfulness techniques. The act of being absentminded is explained with the notion of being on automatic pilot, i.e., our attention wanders off when performing routine automatic tasks which in turn leads to errors. Another central GMT concept is the idea of WM functioning as a mental blackboard where goals and tasks can roll off with distractions. GMT encourages people to practice using endogenous meta-cognitive self-instructed strategies where they periodically need to:

STOP! to interrupt the automatic pilot

Take a moment to focus by using brief mindfulness exercises and **STATE** what the goal is

CHECK the mental blackboard and purposefully bring attention back to the goal/task at hand

SPLIT complex tasks into smaller sub-tasks and finally repeat the cycle as described in Figure 1.1.1.

GMT has been evaluated behaviourally in randomised controlled trials with positive, albeit modest, outcomes in individuals with ABI (Tornås et al., 2016). According to a recent systematic review on the efficacy of GMT however, it is suggested that it is more beneficial when combined with other approaches (Krasny-Pacini, Chevignard and Evans, 2014). These could involve a form of external alert, such as text messaging (Fish et al., 2007), auditory alerts (Manly et al., 2002; Sweeney et al., 2009); training planning and problem solving, i.e., problem solving therapy (PST) (Miotto et al., 2009; Novakovic-Agopian et al., 2018; Spikman et al., 2009); as well as combined GMT with WM strategy training (Emmanouel et al., 2018).

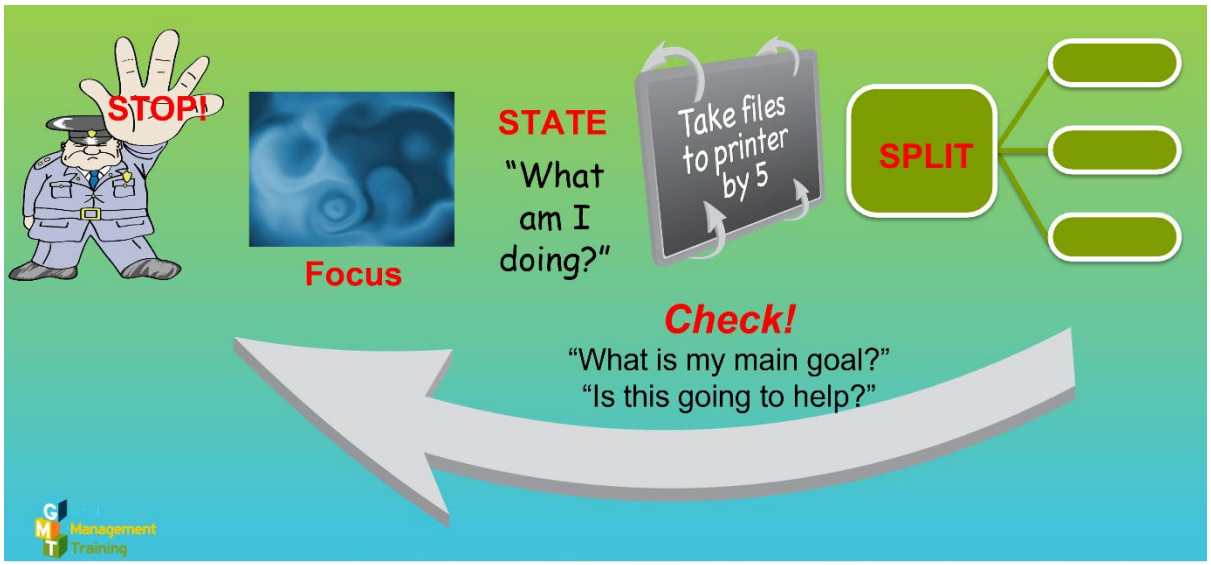

Figure 1.1.1: STOP! - STATE - SPLIT cycle. Adapted from Levine et al., (2012).

1.2 Experience-induced plasticity

> "Adult cognitive plasticity is driven by a prolonged mismatch between functional organismic supplies and environmental demands and denotes the brain's capacity for anatomically implementing reactive changes in behavioural flexibility (i.e., the possible range of performance and function)", (Lövdén et al., 2010, pp. 659).

In contrast to compensatory strategy interventions, researchers in the field of cognitive neuroscience have been particularly interested in process-based interventions, often termed restorative, i.e., aiming to restore or otherwise enhance underlying cognitive function including EFs. The preference for process-based training, over strategy-based interventions such as GMT, is directly linked to the hypothesis that protocols targeting a specific cognitive process could potentially produce cognitive improvements directly related to the trained tasks but furthermore induce broader learning effects and facilitate generalisation to other non-trained tasks, i.e., transfer of learning (Schmiedek, Lövdén and Lindenberger, 2010, 2014; Bergman Nutley et al., 2011; Strobach, Frensch and Schubert, 2012). A traditional strategy-based training approach, on the other hand, is viewed as task-specific: emphasising the trained tasks' procedures and strategies without the potential for transferring any training gains to untrained tasks. The promise for broader transfer of learning has given rise to a plethora of training protocols targeting core cognitive processes such as attention, working memory, speed of processing to name a few, which theorise a broad improvement in cognitive function and generalisation of learning due to process-based training. Studies using such protocols have reported training-related improvements in performance, as well as transfer effects, across the lifespan from young to older adults (Brehmer *et al.*, 2008; Hertzog *et al.*, 2008; Diamond, 2012).

An emerging research area using non-invasive neuroimaging methods to measure outcomes from training interventions, commonly referred to as neural plasticity, concerns experience-induced changes in brain structure and function. Plasticity has traditionally been termed as the neural system's secondary reaction following a primary change (Lövdén et al., 2010). Following a brain injury or insult, plasticity is seen as the restoring and compensation of the neural system following the injury. In cases of reactions induced by experience,

e.g. training, rather than injury, plasticity is seen as the improved performance (behavioural plasticity) and neural changes (functional and structural plasticity) that occur following task practice. In the context of experience-induced plasticity, we could then differentiate between behavioural, structural, and functional measures of plasticity.

Behavioural plasticity is viewed as the potential for change in behaviour as measured through task performance, such as in accuracy, response time, etc. These training-related behavioural changes could be further categorised based upon the nature of the task, i.e. criterion and transfer. The first involves training-related performance changes on a task that participants have trained on whilst the second involves performance changes on an untrained task which is different to the criterion task and may either make demands on the same cognitive domain as the criterion task (near transfer) or may make demands on other cognitive domains (far transfer).

Structural plasticity involves brain changes in the macro-structural level, i.e. gray matter and white matter measures. According to a review by Zatorre, Fields and Johansen-Berg (2012), potential candidate mechanisms resulting in gray matter volume changes are the following: 1. neurogenesis, with evidence for adult neuronal growth primarily involving the hippocampus, 2. gliogenesis, i.e. increases in the number of non-neuronal cells. Examples include astrocytes and oligodendrocytes progenitor cells which retain the ability to divide in the adult brain, 3. synaptogenesis and other alterations in neuronal morphology such as changes in dendritic spine morphology, 4. vasculature, with increases in vascular volume observed following physical activity training regimes. White matter structural changes involve alterations in axon diameter, the number of myelinated axons in a tract, the thickness of myelin, or other morphological features such as internodal distance. In their review, Zatorre, Fields and Johansen-Berg (2012) suggest the following potential mechanisms for changes in white matter volume: 1. myelination changes, with evidence from rodent studies suggesting physical activity can influence myelin formation as well as maintenance and morphology of myelin sheath, 2. activity-dependent axonal sprouting, pruning, or re-routing after induction of long-term potentiation, and 3. inter-relations between neuron and glial changes.

Functional plasticity involves changes in functional activity between task-relevant brain areas most commonly measured through alterations in the blood oxygen level dependent (BOLD) signal using functional Magnetic Resonance Imaging (fMRI) methods. Experience-induced functional activity changes could involve BOLD decreases, BOLD increases, BOLD reorganisation, i.e., redistribution of functional activity or functional reorganisation of activity, as well as a mixture of increases and decreases (Kelly, Foxe and Garavan, 2006). The mechanisms underlying functional activity changes in animal studies have been associated with alterations in synaptic connections between neurons i.e., long-term potentiation (LTP) and long-term depression (LTD) changes (Tardif et al., 2016). Defining the mechanism of functional plasticity in humans is more complex due to the difficulty in drawing a distinction between the mechanisms underlying functional and structural changes as well as the changes potentially taking place at the network level (Tardif et al., 2016). Experience-induced functional plasticity could then also involve functional connectivity changes between networks of functionally coupled brain regions (Constantinidis & Klingberg, 2016; Tardif et al., 2016). These primarily involve changes in resting-state or intrinsic connectivity as measured through alterations in BOLD signal in the absence of a specific task (Tardif et al., 2016).

Lövdén et al. (2010) introduced the term *flexibility* to define the neural system's existing ability to adapt effectively to environmental demands and utilise the necessary neural processes for a given task. In contrast, the term of *plasticity* is viewed as the reaction after meeting changes in environmental demands through acquisition of new knowledge which subsequently produces a change in the pre-existing adaptive ability. The authors explained this by theorising that a mismatch between functional "supply" (i.e., neural resources) and environmental "demands" (e.g., a continuously challenging training task) is a necessary condition for neural plasticity to occur. If training task difficulty is not challenging enough then there is no mismatch between supply and demand, thus no capacity for plastic change. However, if challenge is progressively increased (as under conditions of adaptive difficulty), then more neural resources will become available through plastic change by the constant mismatch between the neural resources and the environmental demands, i.e., there is a need to ensure an optimal degree of difficulty.

1.2.1 Working Memory (WM) executive functions

> "Working Memory is the ensemble of components of the mind that hold information temporarily in a heightened state of availability for use in ongoing information processing." (Cowan, 2017).

There is evidence to suggest that training cognitive processes, including WM, produces neural changes and behavioural plasticity (Hsu, Novick and Jaeggi, 2014; Klingberg, 2010). WM is a concept that has been increasingly used in the past 40 years; originating from cognitive psychology, extending to the research fields of cognitive science and neuroscience with further applications on a wide range of areas such as education and psychiatry (Baddeley, 2010). The term WM was first used by Miller, Galanter and Pribram (1960); later mentioned by Atkinson and Shiffrin (1968) in their seminal paper; and subsequently became the title for the influential multi-component theoretical framework proposed by Baddeley and Hitch (1974). Originally, the WM multi-component model was comprised of two slave systems: 1. the *phonological loop* for maintaining verbal information, and 2. the *visuospatial sketch pad* for maintaining visuo-spatial information; and 3) a *central executive* system which controls and regulates the slave sub-systems (Figure 1.2.1). These three components were thought to be separable yet interacting sub-systems. The multi-component model was proposed as a broad theoretical framework accounting for patient cases exhibiting dissociations between impaired long-term and intact short-term memory, as well as placing emphasis on the interactive and dynamic role of WM rather than simply considering it a storage place (Baddeley, 2010). The WM multi-component theory has stood the test of time and has been updated over the years to include a fourth component, the episodic buffer, serving as a passive temporary store of various WM components (Baddeley et al., 2009). Naturally, the multi-component model hasn't been the only effort to provide a theoretical framework and/or definition of WM; and in fact, in a recent article, Cowan (2017) summarises nine definitions of WM drawn from their respective theoretical frameworks.

In this research, however, we are focusing on the WM multi-component theory and its link to the EF model proposed by Miyake et al. (2000) suggesting the WM central executive comprises three main independent yet moderately correlated executive functions:

1. Shifting, i.e., cognitive flexibility to switch between different tasks
2. Inhibition, i.e., ability to control prepotent responses and
3. Updating, i.e., continuously modifying the content of working memory according to newer incoming information.

Shifting is assessed with paradigms measuring the time it takes for participants to switch between two or more simple task sets (Hofmann et al., 2012; Monsell, 2003); whilst inhibition is typically measured with tasks where participants need to inhibit an automatic response, such as versions of the Stroop (Stroop, 1935) or stop signal tasks (Logan, Schachar and Tannock, 1997). The high demands of maintaining and updating task-relevant information involved in updating are usually measured with the operation span and n-back tasks (Hofmann et al., 2012; Miyake et al., 2000). The view that WM functions exhibit both unity and diversity led to a subsequent study investigating the relationship between EFs and intelligence (Friedman et al., 2006), suggesting WM updating as the only function exhibiting strong correlations with intelligence.

In an interesting review, Hofmann et al., (2012) posited the involvement of EFs in supporting self-regulatory mechanisms as well as the potential for improvement of self-regulation based upon four propositions:

1. The EFs updating, inhibiting, and shifting, are involved in several processes; the active representation of self-regulatory goals, top-down control of attention towards goal-related information, active inhibition of impulsive and habitual behaviour, and switching between different goals, to name a few.

2. The additional involvement of WM in regulating emotional processes such as suppression of ruminative thoughts, unwanted desires, and cravings.

3. Temporary impairments in self-regulation resulting from various factors, such as environmental stressors, cognitive load etc., can in fact be explained by reductions in EF as the underlying mechanism.

4. Improving EFs through training might subsequently lead to additionally enhancing self-regulation processes.

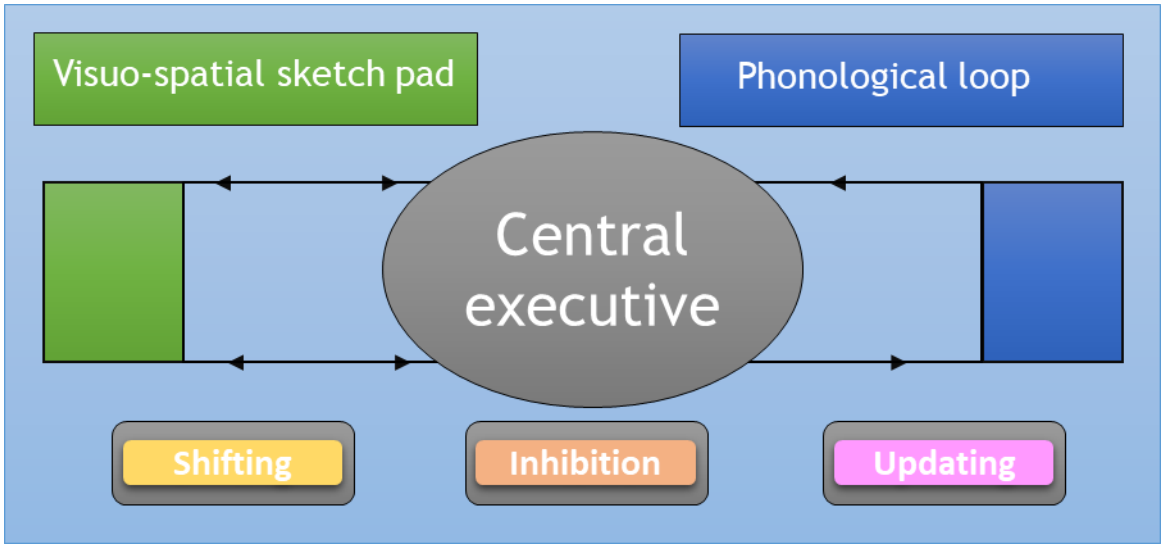

Figure 1.2.1: The original WM multi-component model adapted from Baddeley and Hitch (1974), with the addition of the EFs shifting, inhibition, updating, proposed by Miyake et al. (2000).

1.2.2 WM executive functions: neural underpinnings

There is converging evidence from both neuropsychology (Burgess and Stuss, 2017; Diamond, 2013; Shallice and Burgess, 1991) and neuroimaging work (Collette and van der Linden, 2002; Emch, von Bastian and Koch, 2019a; Frank, Loughry and O'Reilly, 2001; Nee et al., 2013; Salmi, Nyberg and Laine, 2018; Wager and Smith, 2003) of an established WM fronto-parietal network involving the areas of mid-ventrolateral PFC (VLPFC), including inferior frontal gyrus (IFG), dorsolateral PFC (DLPFC); precentral gyrus (preCG) (Nee et al., 2013; Salmi, Nyberg and Laine, 2018); the posterior parietal cortex (PPC) including the superior and inferior parietal lobules, i.e., SPL and IPL respectively, (Nee et al., 2013; Salmi, Nyberg and Laine, 2018); in addition to PFC interactions with subcortical areas, such as basal ganglia (caudate nucleus and putamen) (Emch, von Bastian and Koch, 2019a; Frank, Loughry and O'Reilly, 2001; Salmi, Nyberg and Laine, 2018; Wager and Smith, 2003).

Let's now consider the neural basis for each WM executive function separately. A meta-analysis on the executive components of WM (Nee et al., 2013) sorted the data by function, i.e., shifting, inhibition, and updating, and content, i.e., verbal, spatial. When examining the data by function, the authors reported strong convergence in the left temporoparietal junction across studies investigating the shifting function. Similarly, inhibition, which was further

subdivided in distractor resistance and intrusions resistance, revealed convergent activations in the right caudal superior frontal sulcus (SFS), posterior preCG, left SPL, left intra parietal sulcus (IPS); whilst the updating function was strongly associated with bilateral caudal SFS, left midlateral PFC, bilateral inferior preCG, bilateral IPS and pre supplemental motor area (SMA). Interestingly, conjunction analyses revealed the most consistent activation across all three executive functions for both verbal and spatial content located in the caudal SFS which was additionally found to be particularly sensitive to spatial content.

1.2.3 WM processes training

Due to the WM system's involvement in complex cognitive tasks and goal-oriented behaviour, as well as its role in the regulation of executive process and association with other cognitive constructs such as language comprehension and fluid intelligence (Wiemers, Redick and Morrison, 2019), WM training protocols have been the most popular form of cognitive training paradigm to date (Brehmer et al., 2014; Wiemers, Redick and Morrison, 2019). A plethora of training protocols with variable features have been employed across research studies assessing WM training-related changes in cognitive performance. A few examples of key training features include: 1. the trained WM process, e.g., maintenance, updating, 2. the training task, e.g., n-back, 3. task modality, e.g., visuo-spatial, verbal as well as single or dual, 4. task difficulty, e.g., fixed or adaptive, 5. type of control group (CG), e.g., passive, active or both. Consequently, the possibilities to mix and match across the different training features are countless, and as expected, this variability has made comparisons across studies extremely challenging (Pergher et al., 2020).

One of the key issues in cognitive training studies concerns how best to measure the effect of training or in other words improved performance following training. Researchers employ various outcome measures such as experimental tasks, psychometric tools measuring cognitive constructs of interest, questionnaires etc. In most cases, research outcomes involve measuring performance change on the trained task, otherwise referred to as *criterion* task. Typically, one would expect post-training performance on the criterion task to

show improvements compared to pre-training scores. Training-related performance patterns, however, has prompted fruitful discussions on whether improvements on the criterion task are in fact meaningful especially in relation to real-life situations. This brings us to one of the most highly debated issues in the WM training literature, the existence of transfer to untrained tasks. The reason for considering transfer an issue of high interest is because its existence has become equated with training efficacy. There are two broadly defined types of transfer: 1) *near transfer*, i.e., improving performance on a task similar to the trained or criterion task, also called task specific and 2) *far transfer*, i.e., improving on a task less comparable to the criterion, also referred as generalisation to other cognitive domains. There are conflicting conclusions across different meta-analytic reviews with some authors supporting the evidence of far transfer to more general cognitive domains (Au et al., 2015) and others suggesting there is supporting data regarding short-term near transfer effects solely and no evidence favouring far transfer after WM training (Melby-Lervåg, Redick and Hulme, 2016; Melby-Lervåg and Hulme, 2013).

In terms of the neural changes accompanying cognitive outcomes after training, these may involve: 1. functional activation pattern changes, i.e., BOLD activity increases, decreases, or reorganisation, 2. structural changes, i,e, grey matter and white matter volume changes (Brehmer et al., 2014), 3. functional connectivity changes, i.e., changes in connectivity between brain regions that are recruited for a mental procedure as well as changes in the strength and magnitude (Constantinidis and Klingberg, 2016).

Functional activation increases in practice-related studies is explained as the added recruitment of brain regions or as response strengthening within a cortical region (Kelly, Foxe and Garavan, 2006). Increase in functional activation is seen after practice on motor or sensory tasks, while activation decreases are explained as increased efficiency, i.e., fewer neurons need to fire when responding to the stimulus (Kelly, Foxe and Garavan, 2006). Decreased activation is viewed as a robust and efficient neural representation and is usually observed after higher cognitive training such as WM (Kelly, Foxe and Garavan, 2006). Reorganisation of activation is commonly observed after practice and is

distinguished between two types: 1. redistribution of functional activations and 2. functional reorganisation of activation (Kelly, Foxe and Garavan, 2006).

In the WM literature, training-related functional activity changes involving fronto-parietal and subcortical regions have been reported across studies. However, the direction of the fronto-parietal changes has been inconsistent (Brehmer et al., 2014; Dahlin et al., 2009) with three types of patterns reported following training, i.e., increases (Jolles et al., 2010; Westerberg and Klingberg, 2007), decreases (Brehmer et al., 2011), and a mixture of both increases and decreases (Olesen, Westerberg and Klingberg, 2004), i.e., reorganisation. Changes in subcortical patterns of activation have also been discrepant (Dahlin et al., 2009) with studies reporting both increases (Olesen, Westerberg and Klingberg, 2004) and decreases after training (Landau et al., 2004; Tomasi et al., 2004). Interestingly, the neural basis of transfer to untrained tasks has not been examined extensively. There is a consensus however, that the trained criterion task and the untrained transfer task need to share some underlying cognitive and neural processes for transfer to occur (Constantinidis and Klingberg, 2016; Dahlin et al., 2008; Hsu, Novick and Jaeggi, 2014). Contrary to functional activity outcome measurements, a very small number of studies have explored changes in functional connectivity after WM training (Jolles et al., 2013; Takeuchi et al., 2013), making it difficult to draw confident conclusions, though the studies report increases in fronto-parietal networks. Similarly, there are only a handful of research studies investigating WM training-related structural changes (Caeyenberghs et al., 2016; Metzler-Baddeley et al., 2016; Takeuchi et al., 2010, 2011) despite the increasing interest of the research community.

After a brief summary of studies training working memory processes in healthy adults, we can conclude: 1. it is possible to improve performance after WM process-based training and thus, 2. there is evidence for behavioural plasticity albeit 3. with constraints as suggested by the difficulty to compare across studies and contradictory findings regarding the existence of transfer. However, the picture remains unclear regarding: 1. the direction of the functional activity changes both in fronto-parietal and subcortical regions, 2. the existence of changes in functional connectivity and the structure of the brain.

1.2.4 Cognitive process training: Individuals with ABI

The conclusions relating to improved performance drawn in the previous section refer specifically to studies including healthy adults and therefore do not necessarily relate to individuals with ABI. Nevertheless, cognitive training research in individuals with ABI is growing, with reviews concluding cognitive impairments can in fact be improved following computerised cognitive training (Bogdanova et al., 2016; Spreij et al., 2014). Investigating brain activation patterns following cognitive training in ABI, however, is still at its infancy with most fMRI studies conducted so far having: 1. small sample sizes, 2. large variability amongst the ABI sample and 3. a variety of cognitive processes being trained, i.e., WM, attention, language etc., 4. absence of control groups, thus making it difficult to draw any meaningful conclusions (Galetto and Sacco, 2017). Therefore, further neuroimaging studies are essential to advance and make progress in this field (Sigmundsdottir, Longley and Tate, 2016).

1.3 Integrated processes and strategies (iPRESS) training

> "… it is probable that in some instances, the greatest real-world generalization will occur when cognitive enhancing interventions are sequenced with other psychosocial or vocational treatments, or when lower-level cognitive training is followed by higher-level metacognitive interventions." (Shawn Green et al., 2019, pp.20)

One aim of the present research is to develop and evaluate the feasibility of a novel intervention program for individuals with ABI experiencing EF impairments. Building upon existing work in the fields of clinical neuropsychology and cognitive neuroscience, we consider the following points. Firstly, the theoretical framework proposed by Chen, Abrams and D'Esposito, (2006) suggests the following approaches to enhance prefrontal cortex (PFC) function in ABI individuals: 1. training WM processes, 2. training goal-oriented behaviour, and 3. adaptively increasing training challenge/difficulty. Secondly, the systematic review by Krasny-Pacini, Chevignard and Evans (2014) concludes GMT is more effective when used in combination with other approaches. Thirdly, a review on improving the methodological standards for behavioural interventions for enhancing cognition conducted by 48 scientists (Shawn Green et al., 2019), predicts the greatest benefit and/or generalisation when cognitive

training is combined with higher-level metacognitive interventions and places emphasis on the need for interdisciplinary collaboration.

Focusing on the latter, this research follows an interdisciplinary research approach and employs multi-disciplinary research methods. Therefore, we propose that the combination of a WM process-based adaptive training, specifically the WM updating (WMU) function, with a strategy-based GMT rehabilitation intervention may provide greater benefit than either of these interventions applied alone. This is evaluated in a novel training approach of integrated processes and strategies (iPRESS). The reasons for choosing WMU as the target for process-based training are its reported relationship with intelligence (Friedman et al., 2006), thus making transfer more likely to occur, as well as the rich literature of studies demonstrating improved performance after training with n-back task protocols thought to involve the updating process. We further employ an adaptive difficulty paradigm rather than fixed level across training sessions, in agreement with Lövdén and colleagues' (2010) plasticity framework suggesting a continuously challenging task is a necessary condition for plasticity to occur, and the framework by Chen, Abrams and D'Esposito (2006) for enhancing recovery following brain injury proposing adaptively increasing challenge. Finally, fMRI data will be acquired before and after the training period to measure changes in patterns of brain activity associated with tasks requiring WMU.

To do this we follow a stage-based approach where the first stage investigates training-related cognitive and neural changes in healthy individuals. This acts as the basis for developing and optimising the second stage, i.e., development and evaluation of the cognitive intervention for individuals with ABI. Stage one involves chapters two, three and four. More specifically, chapter two reviews neuroimaging studies training the process of WMU specifically, and the training-related cognitive and neural changes in healthy adults primarily, as well as a brief overview of studies with neurological samples. Chapters three and four investigate structural and functional connectivity outcomes respectively, following WMU training in healthy young adults. Stage two entails chapters five, six, and seven, with chapter five serving as the transition from research on healthy individuals to the population of interest, i.e., individuals with ABI. This

chapter is a critical review of the broader WM training literature in which the differences between the research fields of clinical neuropsychology and cognitive neuroscience are discussed and recommendations for advancing the field are put forward. Chapter six comprises the iPRESS study protocol as reviewed and approved by the NHS Greater Glasgow and Clyde Research Ethics Committee (REC); whilst chapter seven describes a small behavioural pilot of the remote iPRESS study version which was implemented to account for the challenges relating to COVID-19.

Understandably, the unprecedented occurrence of a global pandemic greatly impacted and delayed this research preventing us from running the iPRESS trial as originally planned. Therefore, substantial protocol changes were implemented to enable us to run a modified remote version of this study prioritising the behavioural component whilst fMRI data collection was unavoidably deferred until Covid restrictions allowed resumption of research scanning. Nevertheless, the modified remote iPRESS behavioural pilot provided valuable information on the feasibility of this trial in terms of recruitment, adherence to the protocol as well as participant feedback, before moving forward to a larger-scale finalised version. We strongly believe the purpose of research is to dynamically adjust and serve according to the needs of our times. So rather than viewing this development as a major limitation, we instead think of it as a positive advancement which has great potential for accommodating rehabilitation needs regardless of mobility, location, and funds in the future.

2 Working Memory Updating Training Promotes Plasticity and Behavioural Gains: A Systematic Review and Meta-Analysis

This chapter is a modified version of the article published in the journal of Neuroscience & Biobehavioral Reviews (Pappa et al. 2020).

Recent reviews yield contradictory findings regarding the efficacy of working memory training and transfer to untrained tasks. We reviewed working memory updating (WMU) training studies and examined cognitive and neural outcomes on training and transfer tasks. Database searches for adult brain imaging studies of WMU training were conducted. Training-induced neural changes were assessed qualitatively, and meta-analyses were performed on behavioural training and transfer effects. A large behavioural training effect was found for WMU training groups compared to control groups. There was a moderate near transfer effect on tasks in the same cognitive domain, and a non-significant effect for far transfer to other cognitive domains. Functional neuroimaging changes for WMU training tasks revealed consistent frontoparietal activity decreases while both decreases and increases were found for subcortical regions. WMU training promotes plasticity and has potential applications in optimizing interventions for neurological populations. Future research should focus on the mechanisms and factors underlying plasticity and generalisation of training gains.

Keywords: plasticity, learning, working memory updating, cognitive training, transfer, neuroimaging.

2.2 Introduction

In cognitive neuroscience, an emerging research area concerns experience-induced changes in brain structure and function, referred to as plasticity. Plasticity has traditionally been defined as the capacity of the brain to adjust in response to environmental changes and it is considered to mediate acquisition of knowledge, skill, and repair after injury (Kaas, 2001). For example, plasticity is seen as the restoration and compensation of the neural system following a brain injury. Similarly, following training on a cognitive task, the neural system's response to the training i.e., the improved cognitive performance and the structural changes in the brain's system are also considered indications of plasticity (Lövdén et al., 2010).

Structural changes can be direct, including neurogenesis (formation of new neurons), gliogenesis (formation of new glial cells), dendritic or axonal growth, as well as indirect changes to the system's function, such as angiogenesis (formation of new blood vessels). Both direct and indirect changes are considered structural changes in the overall neural system. Within Lövdén and colleagues' theoretical framework for plasticity (Lövdén et al., 2010), these structural changes can be measured in terms of: 1. the structure of the brain, e.g., changes in grey matter volume and white matter microstructure, 2. the molecular scale, e.g., changes in receptor density and 3. the function of the brain, e.g., changes in activation patterns. Therefore, signs of plasticity are measurable with neuroimaging methodologies such as structural and functional Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Arterial Spin Labelling (ASL), and Diffusion Tensor Imaging (DTI).

Lövdén et al. (2010) further defined the term flexibility as the neural system's existing ability to adapt effectively to environmental demands and utilise the neural processes necessary for performing a given task. This is in contrast to the concept of plasticity, defined as the system's response to meeting prolonged changes in environmental demands through learning, and structural alterations, which subsequently produces a change in the pre-existing adaptive ability. Lövdén et al. (2010) explained this by theorising that a mismatch between functional "supply" (i.e., neural resources) and environmental

"demands" (e.g., a continuously challenging cognitive task) is a necessary condition for plasticity to occur.

Working memory (WM) refers to a system that is essential for the maintenance and manipulation of information in order to successfully perform complex cognitive tasks such as learning and language comprehension (Baddeley, 1992). The classic WM model consists of three components: two slave systems (i.e., the phonological loop handling speech-based information and the visuospatial sketchpad manipulating visual images) and the central executive, an attentional control system responsible for the regulation of cognitive processes, i.e., executive functions (Baddeley, 1992; Miyake et al., 2000). It has been argued that executive functioning depends upon three processes: 1. shifting attention between tasks and active representations, 2. inhibition of automatic responses and irrelevant information; 3. working memory updating (WMU), i.e., modifying the content of WM according to incoming information (Nee et al., 2013). Miyake et al. (2000) proposed that these executive functions are correlated with each other but are also distinct from one another.

Neuropsychological and neuroimaging studies have established the reliance of these executive functions upon the prefrontal cortex (PFC) and parietal regions, in addition to PFC interactions with subcortical structures such as basal ganglia and thalamus (Nee et al., 2013; Collette et al., 2006; Wager and Smith, 2003; Burgess and Stuss, 2017; Diamond, 2013; Shallice and Burgess, 1991; Emch, von Bastian and Koch, 2019a; Salmi, Nyberg and Laine, 2018). Key regions forming the neural basis of WM comprise the mid-ventrolateral PFC (VLPFC) including the inferior frontal gyrus (IFG) pars triangularis, and IFG pars opercularis; dorsolateral PFC (DLPFC); precentral gyrus (preCG); posterior parietal cortex (PPC) including the superior parietal lobule (SPL) and inferior parietal lobule (IPL); temporo-parietal junction (TPJ) (Nee et al., 2013; Salmi, Nyberg and Laine, 2018); and subcortical regions such as the basal ganglia involving the striatum (caudate nucleus and putamen) (Wager and Smith, 2003; Emch, von Bastian and Koch, 2019a; Salmi, Nyberg and Laine, 2018).

There is evidence to suggest that training cognitive processes, including WM executive functions, produces plastic changes (Hsu, Novick and Jaeggi, 2014;

Klingberg, 2010) demonstrated by improved cognitive performance and neural changes. Cognitive training research, however, frequently faces criticisms that the cognitive improvement is limited to the task being trained, i.e., criterion task, and does not generalise (or transfer) to other untrained tasks (Dougherty, Hamovitz and Tidwell, 2016; Melby-Lervåg and Hulme, 2013; Melby-Lervåg, Redick and Hulme, 2016; Soveri et al., 2017). Similarly, in cognitive training studies including neuroimaging outcome measures, there is no consensus regarding the pattern of training-induced functional and structural changes (Brehmer et al., 2011; Dahlin et al., 2009). There have been a number of meta-analyses and systematic reviews of cognitive outcomes (Melby-Lervåg and Hulme, 2013, 2013; Melby-Lervåg, Redick and Hulme, 2016; Soveri et al., 2017; Au et al., 2015), including some examining both cognitive and neural outcomes, following WM training (Hsu, Novick and Jaeggi, 2014; Klingberg, 2010; Brehmer et al., 2011; Dahlin et al., 2009). Despite the increasing interest in WM training, different studies have presented contradictory findings concerning key issues (Soveri et al., 2017).

2.2.1 Cognitive Performance Changes following WM training

Previous meta-analyses evaluating the efficacy of WM training have concentrated on 1) transfer of training gains to untrained tasks, and degree of similarity to the trained criterion for untrained tasks in which this is observed (i.e., near or far transfer), 2) features of the training intervention, with the type of control group, age of the participants, training dose and specific training task most examined.

Different meta-analytic reviews have arrived at conflicting conclusions, with some authors (Au et al., 2015) finding evidence for far transfer (to more general cognitive domains) after WM n-back training and others concluding there are data to support near transfer effects (within the same cognitive domain) but very small or no evidence of far transfer (Melby-Lervåg and Hulme, 2013; Melby-Lervåg, Redick and Hulme, 2016; Soveri et al., 2017). Inconsistencies regarding the employment of an active or passive control group have also been reported, with some authors determining the type of control group does not affect the size of the transfer effect (Soveri et al., 2017; Au et al., 2015, 2020), and others

concluding there is no evidence of far transfer when comparing training groups against active control groups. The latter finding suggests that the transfer effect is overestimated when employing passive control groups (Dougherty, Hamovitz and Tidwell, 2016; Melby-Lervåg, Redick and Hulme, 2016). In a theoretical review, von Bastian and Oberauer (2014) state that more training sessions lead to a larger training effect while no consensus is reached regarding the most optimal spacing and scheduling of training sessions. The review concludes that the effect of training declines with age and suggests a lack of consistency in the evidence favouring training protocols with adaptive task difficulty.

2.2.2 Neural Changes following WM training

Functional activation increases in practice-related neuroimaging studies are explained as added recruitment of brain regions or as response strengthening within a cortical region (Kelly, Foxe and Garavan, 2006) and is usually seen after practice on motor or sensory tasks. Functional activation decreases, on the other hand, are explained as increased efficiency, indicating that fewer neurons needing to fire when responding to a stimulus (Kelly, Foxe and Garavan, 2006). This is interpreted as a robust and efficient neural representation and is usually observed after training higher cognitive processes such as WM (Kelly, Foxe and Garavan, 2006). Reorganisation of activation is commonly observed after practice and two types can be distinguished: 1) redistribution of functional activations and 2) functional reorganisation of activation (Kelly, Foxe and Garavan, 2006).

Neural changes induced by WM training have been observed in healthy young and older adults in fronto-parietal cortical regions and subcortical regions, e.g., the striatal system involving caudate nucleus and putamen; however, the direction of these changes after training is inconsistent (Dahlin et al., 2009). A comprehensive fMRI meta-analysis by Salmi, Nyberg and Laine (2018) examined the neural changes following all types of WM training and provided valuable insight into key issues including: 1. features of the neural networks exhibiting training-related modulations; 2. dynamic changes of the functional activity patterns when comparing training paradigms of shorter and longer duration and 3. patterns of training-related neural modulation in transfer tasks.

The meta-analysis concluded that activity decreases after WM training were more often reported and more consistent in the DLPFC area, while increases were reported less frequently and related to areas involved in the salience network and dorsal attention network as well as striatum and thalamus. The same review suggested that training-related neural changes are manifested in existing core WM networks including the dorsal attention and salience networks, the DLPFC and striatum, rather than recruitment of new networks following training (i.e., redistribution of functional activations within the same network) (Salmi, Nyberg and Laine, 2018). This observation proposes a direct relationship between a region's involvement in WM and training-related modulation in that region. Another interesting finding is the consistency of fronto-parietal activations and modulations in studies of any training duration, while activity modulations in the DLPFC and striatum were only evident in longer training protocols (i.e., more than two weeks). Overall, training-related activity pattern changes in transfer tasks have not been examined as extensively as for the trained criterion task. However, a meta-analysis of the training-related neural modulation for untrained transfer tasks revealed increases in the striatum and IFG and decreases in the DLPFC suggesting the fronto-striatal system mediates transfer of WM training (Salmi, Nyberg and Laine, 2018).

In contrast to functional activity outcome measurements, only a handful of studies to date have explored changes in functional connectivity after WM training, making it difficult to draw confident conclusions, though the studies report increases in fronto-parietal networks overall (Jolles et al., 2013; Takeuchi et al., 2013).

Alterations in brain structure as a result of training may involve changes in grey matter volume or cortical thickness in task-relevant regions and changes in white matter volume and microstructure, predominantly measured as fractional anisotropy (FA) using DTI (Lövdén et al., 2013; Zatorre, Fields and Johansen-Berg, 2012). FA is thought to be modulated by myelination and is considered an indication of structural connection strength, axon diameter and density (Zatorre, Fields and Johansen-Berg, 2012). Few studies to date have focused on structural changes after WM training. Nevertheless, one study reported reduced grey matter in frontal and parietal cortices (Takeuchi et al.,

2011) and another found both cortical thickness increases and decreases in frontal areas (Melby-Lervåg, Redick and Hulme, 2016; Metzler-Baddeley et al., 2016). Structural connectivity increases in the fronto-parietal network have also been reported following WM training (Caeyenberghs et al., 2016; Takeuchi et al., 2010).

2.2.3 The current review

The majority of published reviews to date are broad and include studies with a plethora of WM training tasks involving various processes and tapping into multiple executive functions such as shifting and inhibition as well as WMU (Miyake et al., 2000). Consequently, this variability has made it difficult to draw consistent conclusions on the efficacy of WM training (Soveri et al., 2017; Dahlin et al., 2009). In our review we focus solely on the updating process of WM to achieve greater homogeneity of the process being trained, regardless of modality and task parameters. For example, even though the recent fMRI meta-analysis by Salmi, Nyberg and Laine (2018) provides a comprehensive overview of the neural modulations following WM training, in addition to its basis on a large data sample, our review examines process-specific outcomes by focusing on the effects of WMU training exclusively.

In the cognitive training literature, the updating process of WM has been examined using different task paradigms such as memory updating and n-back. A working memory updating task paradigm requires participants to store and update incoming stimuli such as letters, digits or spatial locations, while performing a series of operations, e.g., spatial location changes, arithmetic operations (Schmiedek, Lövdén and Lindenberger, 2014). Another WMU paradigm involves the n-back task where participants are required to store and update the last n elements, e.g., numbers, letters, spatial locations; and then decide if the most recently presented item matches the one shown n steps back (Schmiedek, Lövdén and Lindenberger, 2014). The n-back task taxes various cognitive processes simultaneously, aside from updating, such as encoding, monitoring and maintenance (Jaeggi et al., 2010). It is a very frequently used paradigm in WM training studies (Linares et al., 2019) due to its usefulness in experimental research (Jaeggi et al., 2010).

A study by Schmiedek, Lövdén and Lindenberger (2014) reported high latent correlations of n-back and memory updating tasks and further concluded that both paradigms provide good measurements of WM. Linares et al. (2019) investigated the transfer effects following WM training comparing a memory updating training group and an n-back training group against an active control group. Both training groups improved their performance on their respective trained task, but none exhibited near or far transfer of learning. Furthermore, even though both paradigms in volved the WMU process; performance gains on the memory updating task did not lead to gains in the n-back task and vice versa, suggesting the tasks vary in other cognitive processes. Even though the memory updating and n-back tasks are not alike in every way, and each involves additional distinct cognitive processes, nonetheless they both tap into the WMU process (Linares et al., 2019). Consequently, the current re view includes studies using both training paradigms, especially since it is the first to focus on the process of updating exclusively.

The aim of this review is to examine the cognitive and neural outcomes of WMU training and transfer to untrained tasks. Meta-analyses on cognitive outcomes in the reviewed studies that assess task-based functional neuroimaging data is undertaken to further investigate the training-related effects in adults. The cognitive outcomes focus on the training and transfer effect sizes while the neural outcomes report on the changes following WMU training in terms of functional activation as well as functional connectivity and structural imaging measures for both training and transfer tasks.

2.3 Methods

This work was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and was registered on PROSPERO, the international prospective register of systematic reviews, (ID number: CRD42019120234).

2.3.1 Database Search and Study selection

A comprehensive search was conducted to identify studies that investigated cognitive and neuroimaging outcomes following WMU training in adults. Before proceeding with the final database searches, we repeatedly tested the sensitivity of a combination of key words and Medical Subject Headings (MeSH) to make sure our searches would be comprehensive and rigorous. We used the fMRI study by Dahlin et al. (2008) as an exemplar to inspect and confirm the search relevance in the different database searches. We further noted the keywords and MeSH terms listed for relevant studies in the different databases and tried to incorporate them in our search terms. When these didn't capture the exemplar study, the search terms were further refined. Once we were confident our search strategy was fitting, rigorous and that the exemplar study was identified in all databases, we then proceeded with the final search.

The studies were published up to and inclusive of 28th January 2019 in the first instance. An updated search was conducted for publications between January 2019 and 13th June 2020. The articles were sought from Ovid EMBASE, Ovid MEDLINE, PsycINFO, CINAHL, Scopus and Cochrane Library electronic databases consisting of the following MeSH and keyword search terms: 1. working memory OR executive function OR ("Working memory" adj5 train*) OR ("Working memory" adj5 updat*) OR (n-back adj5 train*), 2. training OR intervention OR remediation), 3. functional magnetic resonance imaging/ OR (FMRI OR PET OR MRI OR "resting state"). These search terms were then combined using a boolean operator "AND". Our search strategy was pre-registered on PROSPERO. Only peer-reviewed journals and articles written in English were included. Titles and abstracts were screened independently by two reviewers (KP and VB) while full texts were screened against inclusion criteria and when discrepancies occurred, a third reviewer was consulted (SB).

2.3.2 Eligibility Criteria

This systematic review included studies on adults over the age of 18. We included healthy participants as well as adults with neurological conditions, while psychiatric samples were excluded. Any type of experimental research

design, i.e., both non-randomised and randomised controlled trials, cross-over trials and single-case studies were included. The studies included any type of control group (CG), i.e., active CG, passive CG, and no CG. We included studies of any duration which trained the process specific to WMU regardless of training modality. Studies that used a WM training regime that was not specific to the WMU process were excluded, as well as other cognitive training unrelated to WM or multi-domain training. Our criteria in terms of the neuroimaging methodology were broad in that fMRI, PET, ASL, structural imaging and functional connectivity studies were all of interest. We only included studies that conducted more than one neuroimaging session, i.e., before and after WMU training, regardless of the total number of imaging sessions that took place after WMU training had commenced.

2.3.3 Outcomes

Our primary outcomes included cognitive and neural changes as a result of WMU training. In both cases we concentrated on the trained task, i.e., criterion task, to examine the training effect. If studies assessed the transfer of training to untrained tasks, then the transfer effect (cognitive and/or neural outcomes) was explored as a secondary outcome. The transfer effects were further subdivided into near transfer (within the same cognitive domain) and far transfer (to other more general cognitive domains).

2.3.4 Data Extraction and Synthesis

We created and piloted a list of data extraction items under three categories. The first included study characteristics, i.e., sample size and demographics, study design, number of scanning sessions, type of neuroimaging outcome, description of the tasks performed during brain imaging as well as independent to the scanning sessions. The second category listed information on the WMU training protocol followed by each study, i.e., training task, type and modality, training duration (total number of sessions and duration per session), total hours of training and information on the control group. The final category contained information on the cognitive and neural outcomes separated in terms of the specific neuroimaging methodology utilized. Data on the effect of training and/or transfer were extracted separately for tasks assessed inside or outside

the scanner. For both cognitive and neural outcomes, data on the group by time interaction together with significance level and F values were extracted if an ANOVA test was performed. Means and standard deviations (SDs) for each group pre and post training were also noted. We tried to extract data on the same statistical test across all studies to keep our data synthesis as homogeneous and unbiased as possible.

2.3.5 Quality Assessment

Methodological quality of studies was assessed using the Physiotherapy Evidence Database Rating Scale (PEDro-P) scale (Maher et al., 2003). This tool was chosen as it is the primary scale used in the NeuroRehab Evidence Resource (NeuroBITE, previously PsychBITE) to evaluate methodological quality for trials of cognitive, behavioural and other treatments. NeuroBITE offers an online extensive training program and scoring guidelines on the PEDro-P scale.1 The PEDro-P scale contains eleven items relating to the external and internal validity of the study. The first item is related to external validity and is not included in the overall score, the maximum quality assessment score on the scale is 10. A rating of 1 is awarded for each item if it is explicitly stated or deduced from the reported information that the criterion is satisfied. If the criterion is not fulfilled or the information is missing, a score of 0 is given instead. For our systematic review, the scores were divided into three categories: Good quality = score ≥ 6, Fair quality = score of 4–5 and Poor quality = score ≤ 3 as in Van Criekinge et al. (2019). The quality assessment on the PEDro-P scale was conducted by two reviewers independently (KP and SB). KP rated all the studies first and then SB assessed twenty percent of the total number of included studies to establish agreement between raters.

2.3.6 Meta-Analysis on Training and Transfer effects

Meta-analyses on the effects of WMU training on task performance in studies assessing task-based functional neuroimaging data were conducted using Review Manager 5.3 (RevMan, 2014). The training group (TG) and Control group (CG) outcome scores, i.e., means and SDs, were extracted for both pre and post training brain imaging sessions. If there were multiple difficulty levels or conditions expressing the primary outcome, the average means and SDs were

calculated. This is in accordance with the methodology from previous WM training meta-analyses (Melby-Lervåg and Hulme, 2013; Melby-Lervåg, Redick and Hulme, 2016) where, in studies that used multiple tests to assess the same construct, the average of means and SDs was calculated to produce a single measure for each study. If the outcome scores were not reported in tables or in text, they were extracted from figures using the Plot Digitizer Software version 2.6.8 (Huwaldt, 2015). In cases where the standard error (SE) was given, it was converted to SD using the RevMan calculator. If the range was provided for individual studies instead of the SD value, then an SD estimate was calculated as the quarter of the range (Higgins and Deeks, 2008). If it was not possible to extract the SD from other data, then the average SD was calculated as an approximation for that study (Higgins, Deeks and Altman, 2008). If the study had more than one control group, they were combined into a single control group where the overall means and SDs were calculated based on the formulae provided by Higgins and Deeks (2008). The difference between mean outcome score at pre and post training [Mean post - Mean pre] for each group was inserted into RevMan; a positive value suggesting performance was greater at post-test. The pooled SD at pre-test was calculated and inserted for both TG and CG as recommended by Morris (2008). This method has previously been used in other meta-analyses exploring the effects of cognitive training (Melby-Lervåg, Redick and Hulme, 2016; Zhang et al., 2019). A random effects analysis model calculating the standardized mean difference (SMD) was selected in RevMan, to obtain SMD using Hedge's adjusted g (Hedges and Olkin, 1985) which is corrected for small sample bias. Consistent with Cohen's d (Cohen, 2013), a Hedge's g was considered low at ≤0.20, moderate at ≥0.50, and large at ≥0.80. Heterogeneity was measured using the I^2 statistic and was considered low at 25 %, moderate at 50 % and large at 75 % (Higgins et al., 2003). Subgroup analyses based on the type of control group, training duration and type of transfer were conducted. Publication bias was examined using contour enhanced funnel plots created with the metafor package (Viechtbauer, 2010) within the RStudio environment (Team R. RStudio, 2019) in R (R Development Core Team, 2020). An Egger's regression test (Egger et al., 1997) was conducted to examine funnel plot asymmetry.

2.4 Results

2.4.1 Study Selection

Of the 3493 records identified, thirty-one were included in this systematic review (Figure 2.4.1). Twenty-three of those were conducted in Europe (Dahlin et al., 2008; Aguirre et al., 2019; Bäckman et al., 2011; Backman et al., 2017; Biel et al., 2020; Bonzano et al., 2020; Colom et al., 2016a;2016b; Emch et al., 2019b; Finc et al., 2020; Heinzel et al., 2014, 2016; Heinzel et al., 2017; Hempel et al., 2004; Miró-Padilla, Bueichekú and Ávila, 2020; Miró-Padilla et al., 2018; Opitz et al., 2014; Roman et al., 2017; 2016; Salminen et al., 2016; Schneiders et al., 2011; Schweizer et al., 2013; Kuhn et al., 2013) four took place in Canada (Clark, Lawlor-Savage and Goghari, 2017; Lawlor- Savage et al., 2019; Leung et al., 2014, 2016), three in the USA (Buschkuehl et al., 2014; Flegal, Ragland and Ranganath, 2019; Thompson, Waskom and Gabrieli, 2016) and one in China (Schneiders et al., 2012). Eleven studies employed a randomized controlled trial methodology (Dahlin et al., 2008; Aguirre et al., 2019; Bäckman et al., 2011; Backman et al., 2017; Biel et al., 2020; Finc et al., 2020; Miro-Padilla et al., 2018; Schweizer et al., 2013; Clark, Lawlor-Savage and Goghari, 2017; Lawlor-Savage, Clark and Goghari, 2019; Flegal, Ragland and Ranganath, 2019), while eighteen used a quasi-experimental design (Bonzano et al., 2020; Colom et al., 2016a;2016b; Emch et al., 2019b; Heinzel et al., 2014, 2016; Heinzel et al., 2017; Hempel et al., 2004; Opitz et al., 2014; Roman et al., 2017; 2016; Salminen et al., 2016; Schneiders et al., 2011; Kuhn et al., 2013; Buschkuehl et al., 2014; Thompson, Waskom and Gabrieli, 2016; Schneiders et al., 2012) and two were case studies (Leung et al., 2014, 2016). Twenty-seven of the studies included healthy adult participants, three included neurological populations (Bonzano et al., 2020; Leung et al., 2014, 2016) and one study included both (Aguirre et al., 2019).

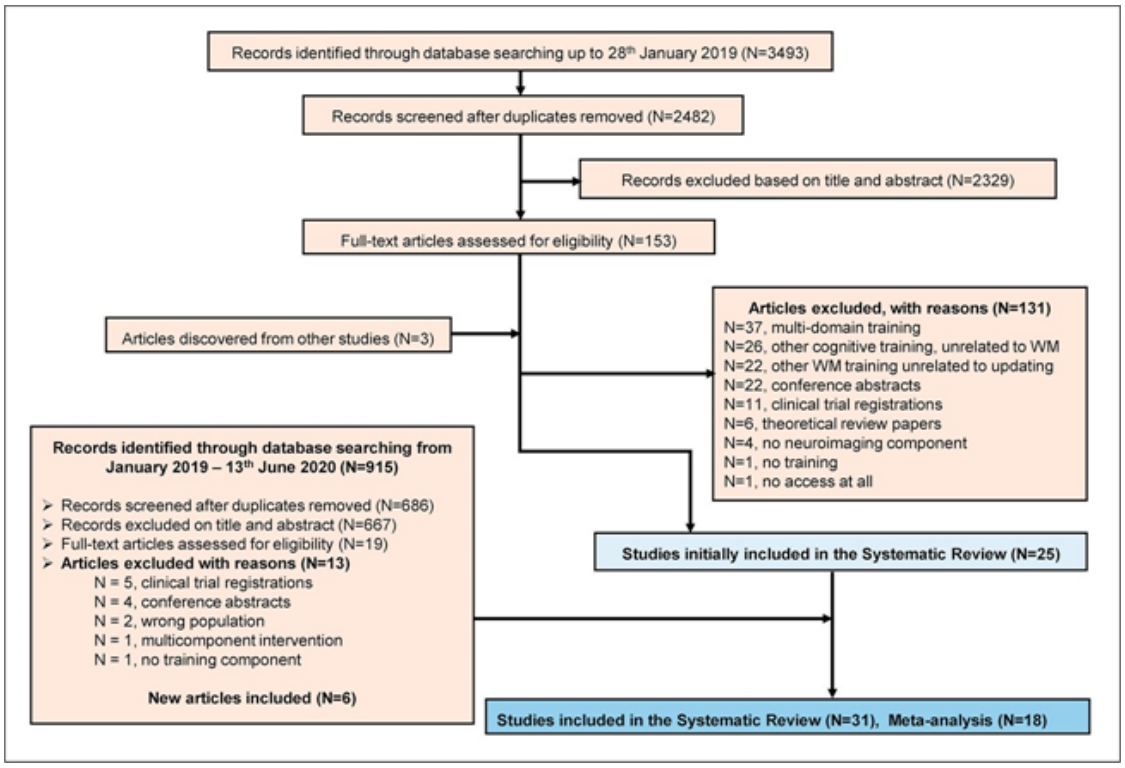

Figure 2.4.1: Summary of Study Identification and Selection.

2.4.2 Overview of healthy adult studies

The present review focuses primarily on studies with healthy adult samples, as this was the type of population investigated in most studies meeting the eligibility criteria. For this reason, information on the neurological samples is not presented in detail but summarized in Section 2.3.9. The total number of healthy adult participants across studies was 955 (weighted mean age = 31.94 (N = 900), pooled SD = 16.76 (N = 900)). The total number of training group participants was N = 464 (weighted mean age = 34.02 (N = 415), pooled SD = 18.35 (N = 415)), while those belonging to a control group were N = 486 (weighted mean age = 30.45, (N = 448), pooled SD = 15.21, (N = 448)). If different studies shared the same sample, the dataset was only used once to calculate the total numbers of participants, means and SDs of age. Twenty-five of the healthy adult studies included a CG in their design (Table 2.4.1). The CG was either passive (Dahlin et al., 2008; Aguirre et al., 2019; Bäckman et al., 2011; Backman et al., 2017; Biel et al., 2020; Colom et al., 2016a;2016b; Heinzel et al., 2016; Miró-Padilla, Bueichekú and Ávila, 2020; Miró-Padilla et al., 2018; Roman et al., 2017; 2016; Schneiders et al., 2011, 2012), active (Emch et al., 2019b; Finc et al., 2020; Schweizer et al., 2013; Kuhn et al., 2013;

Buschkuehl et al., 2014) or studies utilised both active and passive (Opitz et al., 2014; Salminen et al., 2016; Clark, Lawlor-Savage and Goghari, 2017; Lawlor-Savage, Clark and Goghari, 2019; Flegal, Ragland and Ranganath, 2019; Thompson, Waskom and Gabrieli, 2016) CGs. The remaining three studies had no CG (Heinzel et al., 2014, 2017; Hempel et al., 2004). Participants trained for a total of 199.96 h, ranging from 2.5 to 28 s (mean = 9.52, SD = 5.04) across studies. The total number of sessions varied between four and 55 (mean = 16.67, SD = 11.55), the training duration for each session ranged from 20 to 60 min per session (mean = 38.93, SD = 11.86) and total weeks of training ranged from one to 12 (mean = 4.29, SD = 2.65). Further study details and information on the training protocols are summarized in Table 2.4.1 below.

The neuroimaging measures used to evaluate the effect of WMU training are summarized in Table 2.4.2. Concentrating on the healthy adult studies, twenty-six used MRI (Dahlin et al., 2008; Aguirre et al., 2019; Biel et al., 2020; Colom et al., 2016a;2016b; Emch et al., 2019b; Finc et al., 2020; Heinzel et al., 2014, 2016; Heinzel et al., 2017; Hempel et al., 2004; Miró-Padilla, Bueichekú and Ávila, 2020; Miró-Padilla et al., 2018; Opitz et al., 2014; Roman et al., 2017; 2016; Salminen et al., 2016; Schneiders et al., 2011; Schweizer et al., 2013; Kuhn et al., 2013; Clark, Lawlor-Savage and Goghari, 2017; Lawlor-Savage, Clark and Goghari, 2019; Buschkuehl et al., 2014; Flegal, Ragland and Ranganath, 2019; Thompson, Waskom and Gabrieli, 2016; Schneiders et al., 2012) and only two used PET (Bäckman et al., 2011; Backman et al., 2017). In eleven studies only the trained task, i.e., the criterion task, was performed in the scanner (Aguirre et al., 2019; Bäckman et al., 2011; Emch et al., 2019b; Finc et al., 2020; Heinzel et al., 2014, 2017; Hempel et al., 2004; Miro-Padilla et al., 2018; Kuhn et al., 2013; Buschkuehl et al., 2014; Thompson, Waskom and Gabrieli, 2016), while seven studies scanned both the criterion task and at least one untrained task, i.e., transfer task (Dahlin et al., 2008; Backman et al., 2017; Heinzel et al., 2016; Salminen et al., 2016; Schweizer et al., 2013; Clark, Lawlor-Savage and Goghari, 2017; Flegal, Ragland and Ranganath, 2019). In four studies, a transfer but not the criterion task was performed in the scanner (Miró-Padilla, Bueichekú and Ávila, 2020; Opitz et al., 2014; Schneiders et al., 2011, 2012) and the remaining six studies did not assess task-based functional

neuroimaging data (Biel et al., 2020; Colom et al., 2016a;2016b; Roman et al., 2017; 2016; Lawlor-Savage et al., 2019).

2.4.3 Quality Assessment

Across studies on healthy adults, the PEDro-P score ranged from one to eight (table 1.1., Appendix 1). Five earned a good rating, thirteen were rated as fair and ten as poor. Most of the studies failed to meet or report information concerning the following items: allocation concealment (item 3), blinding of subjects (item 5), blinding of assessors (item 7) and whether participants with available outcome measures received the treatment or control condition allocated (item 9). On the contrary, items 10 (between-group statistical comparisons reported for at least one key outcome) and 11 (both point measures and measures of variability provided for at least one key outcome) were most frequently met.

2.4.4 Training Effect: Healthy Adult Studies

The TG showed greater improvement, as assessed in terms of criterion task accuracy compared to the CGs, across all included studies irrespective of training protocol (Table 2.4.3). Reaction times also improved after training in the studies additionally reporting this outcome measure (Biel et al., 2020; Heinzel et al., 2016; Miro-Padilla et al., 2018; Lawlor-Savage, Clark and Goghari, 2019; Thompson, Waskom and Gabrieli, 2016). For the studies employing criterion tasks with various difficulty levels, the training effect was greatest for higher levels of task difficulty. In addition, training duration as short as 2.5 (Buschkuehl et al., 2014) and 3 h (Miro-Padilla et al., 2018) produced a behavioural improvement.

Table 2.4.1: Study and training characteristics for reviewed studies

Reference	***Study Sample (N, Age mean ± SD years)***	***Study Design***	***Total Training Hours, no of sessions pw (Weeks total, Sessions total, Minutes per session)***	***Training (modality) (difficulty)***	***Control Group (control task)***
			Healthy Adults		
Aguirre et al. (2019)	Healthy Adults (N=29, 32.72±7.48)* TG (N=14, 31.21 ±8.72), PCG(N=15, 34.13±6.07)	Randomised controlled trial	4 hours, 4 sessions pw (1 week, 4 sessions, 60 min per session)	Single N-back (verbal, adaptive)	Passive
Backman et al. (2011)	Healthy Adults (N=20, 22.25±3.17*) TG (N=10, 22.8 ±3.9), PCG (N=10, 21.7 ±2.3	Randomised controlled trial	11.24 hours, 3 sessions pw (5 weeks,15 sessions, 45 min per session)	1. Letter Memory updating 2. Number updating 3. Letter updating 4. Colour updating 5. Spatial location updating 6. Verbal Keep Track (all adaptive)	Passive
Backman et al. (2017)	Healthy Adults (N = 27, 22.49 ± 1.61*) TG (N=14, 22.21, ±1.72),	Randomised controlled trial	11.24 hours, 3 sessions pw (5 weeks, 15 sessions, 45 min per session)	1. Letter Memory updating 2. Number updating 3. Letter updating 4. Colour updating	Passive

	PCG (N=13, 22.79 ±1.48)			5. Spatial location updating 6. Verbal Keep Track (all adaptive)	
Biel et al. (2020)	Healthy Adults (N = 83, 63.93±8.54*) TG (N=56, 64.24± 8.85)*, TG1 (N = 28, 64.29 ± 9.69) TG2 (N=28, 64.18 ± 8.10) PCG (N= 27, 63.30± 7.99)	Randomised controlled trial	7.2 hours, 3 sessions pw (4 weeks, 12 sessions, 36 min per session)	TG1: Single 2-back + Novel nature movies (NOV) (numerical, non-adaptive) TG2: Single 2-back + Familiarised Nature movies (FAM), (numerical, non-adaptive)	Passive
Buschkuehl et al. (2014)	Healthy adults (N= 55, 21.8 ±2.7) TG (N=27, 22.3± 3.1), ACG (N= 28 , 21.2 ±2.1)	Quasi-experimental	2.5 hours, 7 sessions a week (1 week,7 sessions, 20 min per session)	Single N-back (visuo-spatial, fixed)	Active (Vocabulary and General Knowledge Questions)
*Clark, Lawlor-Savage and Goghari (2017)***	Healthy Adults (N=76, 31.11±5.80) * TG (N=25, 30.68 ± 6.24), ACG (N=24, 31.33 ±5.78), PCG(N=27, 31.32 ±5.58) N=49 were scanned from TG and ACG	Randomised controlled trial	10 hours, 5 sessions pw (6 weeks, 30 sessions, 20 min per session)	Lumosity Training 1. Memory Match (Single 2-back, visual, fixed) 2. Memory Match overload (Single 3-back, visual, fixed) 3. Memory Lane (Dual N-back, adaptive)	I. Active Lumosity Training 1.Processing Speed Speed Match (speeded Single 1-back Task, visual) 2.Speed Match overdrive (like Speed Match including partial match option, visual)

					3.Spatial Speed Match (like the Speed match task but stimuli differ in spatial orientation) II. Passive
*Colom et al. (2016a) *** (Bx Data taken from Colom et al. (2013))*	Healthy Adults (N=56, 18.3±1.1) TG (N=28, 18.04±0.9) PCG (N=28, 18.2±1.2)	Quasi-experimental	12 hours, 2 sessions pw (12 weeks,24 sessions, 30 min per session)	Dual N-back (auditory and visual, adaptive)	Passive
*Colom et al. (2016b)***, Bx (Data taken from Colom et al.(2013)*	Healthy Adults (N=56, 18.12±1.05) * TG (N=28, 18.04±0.9), PCG (N=28, 18.2±1.2)	Quasi-experimental	12 hours, 2 sessions pw (12 weeks, 24 sessions, 30 min per session)	Dual N-back (auditory and visual, adaptive)	Passive
Dahlin et al. (2008)	Healthy Young Adults (N=22, 23.59±2.48) * TG (N= 15, 23.67±2.92), PCG (N=7, 23.43±1.27) Healthy Older Adults (N=19, 68.32±1.79) * TG (N=11, 68.27±1.79), PCG (N=8, 68.38 ± 1.92)	Randomised controlled trial	11.25 hours, 3 sessions pw (5 weeks,15 sessions, 45 min per session)	1. Letter Memory updating 2. Number updating 3. Letter updating 4. Colour updating 5. Spatial location updating 6. Verbal Keep Track (all adaptive)	Passive
Emch et al. (2019b)	Healthy Older Adults (N=57, 55.85±4.24)	Quasi-experimental	10.66 hours, 4 sessions pw (8	Single N-back (verbal, adaptive)	Active NA Single 1-back

	TG (N=30, 5.80±4.30), ACG (N=27, 55.92 ± 4.25)		weeks, 32 sessions, 20 min per session)		
Finc et al. (2020)	Healthy Adults (N=53, 21.17, age range 18 to 28 years, SD = 2.5*) N = 46 were scanned TG (N = 23) ACG (N = 23)	Randomised controlled trial (matched by sex)	9 hours, 3 sessions pw (6 weeks, 18 sessions, 30 min per session)	Dual N-back (auditory and visual, adaptive)	Active Single N-back (visual and auditory)
Flegal, Ragland and Ranganath (2019)	Healthy young adults (N=56, 20.8 ± 2.4) TG (N=19, 20.32±1.73) ACG (N=19, 20.79±2.92) PCG (N=18, 21.33±2.20) N=38 were scanned from TG and ACG	Randomised controlled trial	8.33 hours, 4 sessions pw (3 weeks, 10 sessions, 50 min per session)	1. Matrix updating (visuospatial) 2. Verbal Keep Track (all adaptive)	I. Active 1.NA Matrix updating (visuospatial) 2.NA Verbal Keep Track II. Passive
*Heinzel et al. (2014)***	Healthy Older Adults (N= 19, 65.95±3.73) N=15 were scanned	Quasi experimental Single group	9 hours, 3 sessions pw (4 weeks, 12 sessions, 45 min per session)	Single N-back (numerical, adaptive)	No CG
Heinzel et al. (2016) ****	Healthy Older Adults (N=29, 66.02±4.35) TG (N=15, 66.04±4.04), PCG (N=14, 66.00±4.82)	Quasi-experimental	9 hours, 3 sessions pw (4 weeks, 12 sessions, 45 min per session)	Single N-back (numerical, adaptive)	Passive

Heinzel et al. (2017) ****	Healthy Older adults (N=38), final sample N=34 (range 60-70 years) TG (N=18, 65,78±3.04) PCG (N=16, 65 ±3.67) N=15 were scanned	Quasi-experimental Single group	9 hours, 3 sessions pw (4 weeks, 12 sessions, 45 min per session)	Single N-back (numerical, adaptive)	No CG
Hempel et al. (2004)	Healthy Adults (N=9, age range 26 to 32, SD= 1.5) *	Quasi-experimental Single group	No information	Single N-back (visuospatial, no information)	No CG
Kuhn et al. (2013)	Healthy Adults (N=46, 25.0±2.7) TG (N=26, 24.7±2.3) ACG (N=20 (25.4 ±3.1)	Quasi-experimental	27.65 hours (no info, 55 sessions, 31.5 min per session)	1. Number Memory Updating 2. Single N-back (spatial) (all adaptive)	Active 1. NA Number Memory Updating 2. NA N-back (spatial)
*Lawlor-Savage, Clark and Goghari (2019)***	Healthy Adults (N=76, 31.11±5.80)* TG (N=25, 30.68 ± 6.24), ACG (N=24, 31.33 ±5.78), PCG(N=27, 31.32 ±5.58) N=49 were scanned	Randomised controlled trial	10 hours, 5 sessions pw (6 weeks, 30 sessions, 20 min per session)	Lumosity Training 1. Memory Match (Single 2-back, visual, fixed) 2. Memory Match overload (Single 3-back, visual, fixed) 3. Memory Lane (Dual N-back, adaptive)	Active Lumosity Training 1. Processing Speed Speed Match (speeded Single 1-back Task, visual) 2.Speed Match overdrive (like Speed Match including partial match option, visual) 3.Spatial Speed Match (like the Speed match task but stimuli differ in spatial orientation)

					II. Passive
Miro-Padilla et al. (2018,2020)†	Healthy Adults (N=52, 22.60±1.45) TG (N=25, 22.77± 1.5) PCG (N=27, 22.44±1.4)	Randomised controlled trial	3.33 hours, 4 sessions pw (1 week, 4 sessions, 50 min per session)	Single N-back (letter, adaptive)	Passive
Opitz et al. (2014)	Healthy Adults (N=48, 23.67±2.26*, range = 19-31) TG (N=16, 23.94±2*, range = 21-29), ACG (N=16, 23.54±2.4*, range= 20–28), PCG (N=16, 23.94±2.26*, range= 20–31)	Quasi-experimental	1.5 hours, 4 sessions pw (2 weeks, 9 sessions, 50 min per session)	1.Chinese Vocabulary Learning 2.Single N-back (visual, adaptive)	I. Active 1.Chinese Vocabulary Learning 2. Single N-back (auditory) II. Passive Chinese Vocabulary Learning, no WMU training
*Roman et al., (2016)*** *(Bx Data taken from Colom et al.(2013))*	Healthy Adults (N=56, 18.12±1.05)* TG (N=28, 18.04±0.9), PCG (N=28, 18.2±1.2)	Quasi-experimental	12 hours, 2 sessions pw (12 weeks, 24 sessions, 30 min per session)	Dual N-back (auditory and visual, adaptive)	Passive
*Roman et al. (2017) *** *(Bx Data taken from*	Healthy Adults (N=56, 18.12±1.05)* TG (N=28, 18.04±0.9), PCG (N=28, 18.2±1.2)	Quasi-experimental	12 hours, 2 sessions pw (12 weeks, 24 sessions, 30 min per session)	Dual N-back (auditory and visual, adaptive)	Passive

Colom et al.(2013))					
Salminen et al. (2016)	Healthy Adults (N=54, 24.5±3.67)* TG (N=18, 24.4±4), ACG (N=18, 24.1±3.1), PCG (N=18, 25±4.0)	Quasi-experimental (no info on randomization)	8 hours, 5 sessions pw (3 weeks, 16 sessions, 30 min per session)	Dual N-back (auditory and visual, adaptive)	I. Active Single N-back (auditory and visual at different sessions) II. Passive
Schneiders et al. (2011)	Healthy Adults (N= 48, 23.67± range= 19-31) TG1 (N= 16, 23.94± 2.4*, range=21-29), TG2 (N=16, 23.13±2*, range 20-28), PCG (N=16, 3.94±2.75*, age range 20-31)	Quasi-experimental	7.5 hours, 4 sessions pw (2 weeks, 9 sessions, 50 min per session)	TG1: Single N-back (visual) TG2: Single N-back (auditory) (all adaptive)	Passive
Schneiders et al. (2012)	Healthy Adults (N=32 21.31±1.27*, range=18-24) TG (N=16, 21.13±1.5, range=18–14), PCG (N=16, 21.50±1*, range = 19–23)	Quasi-experimental	6.66 hours, 4 sessions pw (2 weeks, 8 sessions, 50 min per session)	Single N-back (auditory, adaptive)	Passive
Schweizer et al. (2013)	Healthy Adults (N=34, 23± 2.4) TG (N=17, missing data, ACG (N=15, missing data)	Randomised controlled trial	8.33 hours, 5 sessions pw (4 weeks, 20 sessions, 25 min per session)	Dual N-back (affective, adaptive)	Active (Feature Matching)
Thompson, Waskom and	Healthy Adults (N=58, 21.86±2.69) *	Quasi-experimental	13.33 hours, 5 sessions pw (4	Dual N-back (auditory and visual, adaptive)	I. Active

Gabrieli (2016) (Bx data taken from Thompson et al., (2013)	TG (N=20, 21.3±2.3) ACG (N= 19, 21.2±2.0) PCG (N=19,23.1± 3.3)		weeks, 20 sessions, 40 min per session)		(Multiple Object Tracking) II. Passive
			Neurological Populations		
Aguirre et al. (2019)	Adults with MS (N=29, 32.72±7.48)* TG (N=15, 35.80 ±7.3), PCG(N=15, 36.14 ±5.97)	Randomised controlled trial	4 hours, 4 sessions pw (1 week, 4 sessions, 60 min per session)	Single N-back (verbal, adaptive)	Passive
Bonzano et al. (2020)	Adults with MS (N = 18, 45.3± 10.2)	Quasi-experimental Single group	20 hours, 5 sessions pw (40 Sessions, 30 min per session	Dual N-back (numerical and spatial) Single N-back (visuospatial) Operation N-back All adaptive	No CG
Leung et al. (2014)	Stroke Participant (N=1, Age = 39 years)	Case study	11.6 hours, 5 sessions pw (7 weeks, 35 sessions, 20 min per session)	Single N-back (auditory, increased difficulty be default but non adaptive to performance)	No CG
Leung et al. (2016)	Stroke participants (N= 2, Age = 37 years)	Case study	20 hours, 5 sessions pw (6 weeks, 30 sessions, 40 min per session)	Single N-back (auditory, increased difficulty be default but non adaptive to performance)	No CG

* The means and SDs to combine groups were calculated based on the formulae provided by Higgins and Deeks (2008), p. 177. When the range was reported for individual studies instead of the SD value, then an SD estimate was calculated as the quarter of the range (Higgins and Deeks, 2008, p.176). In two cases the SD was either missing or could not be calculated based on other measures of dispersion (Hempel et al., 2004; Schweizer et al., 2013). If studies included more than one control group in their design, then the data were collapsed across them. ** These studies shared the same dataset, *** These studies shared the same dataset,**** These studies shared the same dataset. †These studies share the same dataset; the neuroimaging data on the training effect are described in Miro-Padilla et al. (2018) and the neuroimaging data on the transfer effect are described in Miró-Padilla, Bueichekú and Ávila, (2020) ACG: Active Control Group, Bx: Behavioural, DAT-AR: Differential Aptitude Test – abstract reasoning, DAT-NR: Differential Aptitude Test – numerical reasoning subtest, DAT-VR: Differential Aptitude Test – verbal reasoning subtest, EF: Executive Function, eWM: emotional working memory, HVLT: Hopkins Verbal Learning Test, MS: Multiple Sclerosis, NA: Non-Adaptive, PMA-R: Primary Mental Abilities – Inductive reasoning subtest, PMA-V: Primary Mental Abilities – Vocabulary subtest, PCG: Passive Control Group, RAPM: Raven's Advanced Progressive Matrices, STM: Short Term Memory, TG: Training Group, TG1: Training Group 1, TG2: Training Group 2, WM: working memory, WMU: WM updating.

Table 2.4.2: Neuroimaging protocol details for reviewed studies

Reference	*Neuroimaging Method No of Sites*	*No of scanning sessions*	*Neuroimaging Outcome (Analysis, software)*	*Cognitive Outcome*	
				Changes in performance Criterion Task (modality)	*Changes in performance Transfer Task, near or far transfer (modality)*
			Healthy Adults		
Aguirre et al. (2019)	3T MRI 1	3	Changes in BOLD activity *(task-based fMRI, Whole-brain, SPM12)*	Single N-back *(numerical)*	-
Backman et al. (2011)	PET 1	2	Changes in raclopride binding to striatal D2 receptors *(PET, N/A, SPM8)*	Letter memory updating	-
Backman et al. (2017)	PET 1	2	Changes in raclopride binding to striatal D2 receptors *(PET, N/A, SPM8)*	Letter memory updating	N-back task, *near (numerical)*
Biel et al. (2020)	3T, MRI 1	2	Changes in Grey Matter Volume *(VBM, VBQ, N/A, SPM12)*	-	-
Buschkuehl et al. (2014)	No info, fMRI 1	2	Changes in Cerebral Perfusion *(ASL, N/A, MCFLIRT)*	Single N-back *(visuospatial)*	-
Clark, Lawlor-Savage and	3T fMRI 1	2	Changes in BOLD activity	Dual N-back *(visual and auditory)*	1.Raven's Standard Progressive Matrices, *far*

*Goghari (2017)***			*(task-based Fmri, Whole-brain, FSL 5.09)*		2.Lexical Decision, *far*
*Colom et al. (2016a) ****	3T MRI 1	2	Changes in Jacobian determinants *(TBM, N/A, SPM5)*	-	-
*Colom et al. (2016b)****	3T MRI 1	2	Changes in Grey Matter Volume *(VBM, N/A, SPM8)*	-	-
Dahlin et al. (2008)	1.5 fMRI 1	2	Changes in BOLD activity *(task-based fMRI, Whole-brain, SPM2)*	Letter Memory updating (*verbal)*	1.Single N-back, *near (numerical)* 2.Stroop, *far*
Emch et al. (2019b)	3T, MRI 1	2	Changes in BOLD activity *(task-based fMRI, whole-brain, SPM12)*	Single N-back (*verbal)*	-
Finc et al. (2020)	3T, MRI 1	4	Changes functional modularity (*task-based fMRI, ROI, fMRIPrep, Nipype*)	Dual N-back *(audio and visual)*	-
Flegal, Ragland and Ranganath (2019)	3T fMRI 1	2	Changes in BOLD activity *(task-based fMRI, ROI, SPM8)*	Matrix Updating *(visuospatial)*	1.Single N-back, *near (visuospatial)* 2.Object Location – Episodic Memory, *far*
*Heinzel et al. (2014)*****	3T fMRI, MRI 2	2	Changes in BOLD activity, Functional Connectivity and Grey Matter Volume, *(task-based fMRI and VBM, ROI, SPM8)*	Single N-back *(numerical)*	-
*Heinzel et al. (2016) *****	3T fMRI 2	2	Changes in BOLD activity, *(task-based fMRI, Whole-brain and ROI, SPM8)*	Single N-back *(numerical)*	DMS – Maintain and Update Condition, *near*

*Heinzel et al. (2017)*****	3T fMRI 2	2	Changes in BOLD activity, *(task-based fMRI, ROI, SPM8)*	Single N-back *(numerical)*	-
Hempel et al. (2004)	1.5T fMRI 1	3	Changes in BOLD activity, *(task-based fMRI, VOI, SPM99)*	Single N-back *(spatial)*	-
Kuhn et al. (2013)	3T fMRI 1	3	Changes in BOLD activity *(task-based fMRI, Whole-Brain and ROI, SPM5)*	Number Memory Updating *(numerical)*	-
*Lawlor-Savage, Clark and Goghari (2019)***	3T MRI 1	2	Changes in GM Surface Area, Thickness and Volume, *(MRI surface-based analysis, N/A, FSL, Freesurfer 5.3.0)*	-	-
Miro-Padilla et al. (2018, 2020)†	1.5T fMRI 1	3	Changes in BOLD activity *(task-based fMRI, Whole-brain, SPM12)*	Single N-back *(letter)* †	PASAT, *far* †
Opitz et al. (2014)	1.5 fMRI 1	2	Changes in BOLD activity *(task-based fMRI, VOI, Brain Voyager QX)*	-	Chinese Orthographic Task, *far*
*Roman et al. (2016)****	3T MRI 1	2	Changes in Cortical Thickness and Surface Area, *(surface-based Morphometry, N/A (FSL, FMRIB Diffusion toolbox, FDT)*	-	-
*Roman et al. (2017)****	No info, MRI 1	2	Changes in Structural Connectivity and Fractional Anisotropy, *(DWI, N/A (CIVET pipeline 2.0)*	-	-

Salminen et al. (2016)	3T fMRI 1	2	Changes in BOLD activity, *(task-based fMRI, Whole brain and ROI, SPM8)*	1.Dual N-back *(audio and visual)* 2.Single N-back	1.Dual Letter Memory, *near* 2.Single Letter Memory, *near, (verbal)*
Schneiders et al. (2011)	1.5T fMRI 1	2	Changes in BOLD activity, *(task-based fMRI,* VOI, Brain voyager QX*)*	-	Visual 2-back: *near* for Visual Training Group *far* for Auditory Training Group
Schneiders et al. (2012)	3T fMRI 1	2	Changes in BOLD activity, *(task-based fMRI, Whole-brain and ROI, Brain voyager QX)*	-	Single N-back, *near (auditory)* Single N-back, *far (visual)*
Schweizer et al. (2013)	3T fMRI 1	2	Changes in BOLD activity, *(task-based fMRI, ROI, SPM5)*	Dual N-back *(affective)*	Emotion Regulation task, *far*
Thompson, Waskom and Gabrieli (2016)	3T fMRI 1	2	Changes in BOLD activity and Functional Connectivity, *(task-based fMRI, ROI (FSL, Freesurfer)*	Dual N-back *(auditory and visual)*	-
			Neurological Populations		
Aguirre et al. (2019)	3T MRI 1	3	Changes in BOLD activity *(task-based fMRI, Whole-brain, SPM12)*	Single N-back *(numerical)*	-
Bonzano et al. (2020)	1.5 MRI 1	2	Changes in BOLD activity *(task-based fMRI, Whole-brain, SPM12)*	-	PVSAT, *far*
Leung et al. (2014)	1.5T fMRI 1	2	Changes in BOLD activity	Single N-back*(auditory)*	-

			(task-based fMRI, Whole-brain, SPM8)		
Leung et al. (2016)	1.5T fMRI 1	2	Changes in BOLD activity *(task-based fMRI, Whole-brain, SPM8)*	Single N-back*(auditory)*	-

These studies shared the same Bx dataset., * These studies shared the same Bx dataset., **** These studies shared the same Bx dataset. †These studies share the same dataset; the neuroimaging data on the training effect are described in Miro-Padilla et al. (2018) and the neuroimaging data on the transfer effect are described in Miró-Padilla, Bueichekú and Ávila (2020) **ASL:** Arterial Spin Labelling, **Bx:** Behavioural, **D2:** Dopamine 2, **DMS**: Delayed Match-to-Sample **DWI:** Diffusion Weighted Imaging, **fMRI:** functional Magnetic Resonance Imaging, **FSL:** FMRIB Software Library, **GM:** Grey Matter, **HAWIE-R**: Hamburg–Wechsler Adult Intelligence Scale–Revised, **N/A:** Non-Applicable, **Nipype:** Neuroimaging in Python Pipelines and Interfaces, **PASAT:** Paced Auditory Serial Addition Test, **PVSAT:** Paced Visual Serial Addition Test, **ROI:** Region of Interest, **SPM:** Statistical Parametric Mapping, **TBM:** Tensor Based Morphometry, **VBM:** Voxel-Based Morphometry, **VBQ:** Voxel-Based Quantification, **VOI:** Volume of Interest.

Table 2.4.3: Cognitive Performance Changes after WMU training for training and transfer tasks.

Reference	*Training*	*Transfer*
	Healthy Adults	
Aguirre et al. (2019)≠	*Training (both Healthy and Multiple Sclerosis training groups collapsed) by Time comparison* 2-back accuracy: non significant. 3-back accuracy: Both TGs significantly improved accuracy on the 3-back level after training compared to the CGs, ($F(2,51) = 10.18$, $p<0.001$, $\eta^2 = 0.29$). *Training (TG vs CG) by Group (Healthy vs Multiple Sclerosis) comparison, ns* *Training by Group by Session, ns*	-
Backman et al. (2011)	Updating training significantly improved letter-memory performance ($p<0.001$, $d=1.7$). The training group ($p < 0.001$), but not the controls ($p> 0.20$) improved after training.	Near transfer (n-back task)‡ significant transfer effect ($P < 0.01$, $d = 0.98$)
Backman et al. (2017)	*Session by Group comparison* TG showed larger performance gains after training than the CG, ($F (1, 23) = 24.579$, $p < 0.001$, η^2partial $= 0.52$; $d = 2.07$)	*Session by Group comparison* There were no time effects as a function of group ($p > 0.05$; $d = 0.00$). No behavioural transfer effects were observed.
Biel et al. (2020)	Both TG1 and TG2 improved their performance over time‡ *Main effect of time*	*Session by group comparison* ‡

	- Correct Hit Rates (cHR): F(1,53) = 227.293, p < .001, partial η^2 = .811, higher cHR post-test - Reaction Times (RTs): F(1,53) = 51.830, p < .001, partial η^2 = .494, faster RTs post-test	- *Far transfer, Processing speed* (d2-R working speed: F(2,80) = 3.588, p =0.032, partial η^2 = .082) - *Near transfer, Verbal memory* (VLMT learning: F(2,80)= 3.254, p=0.044, partial η^2 = .075). Comparisons did not survive Bonferroni corrections so there is no evidence of transfer.
Buschkuehl et al. (2014)	*Session by group by load comparison* TG improved more from pre to post than the CG in the 4-back load condition, (F(1,52)=12.41, p<.001, η^2partial =0.19).	Near transfer (auditory n-back task)‡ *Session by Group comparison* (p<0.001) TG improved on the auditory n-back task compared to the CG, specifically driven by the 3-back condition.
*Clark, Lawlor-Savage and Goghari (2017)***	*Group by time comparison* Better performance in the TG compared to the CG for the 3-back condition (F(1,47)=17.04, p < 0.001).	*Far transfer* *Group by time comparison* - *RSPM transfer task* Better performance in the TG compared to the CG for the hardest difficulty level (F (1,47)=5.88, p = 0.019). This effect was driven by worst performance in the CG post training. - *Lexical decision task* Better performance in the TG compared to the CG for the easy condition (F(1,47)=5.37, p = 0.019). This effect was driven by significantly different performance before training (t_{47}=2.0, p=0.043).
*Colom et al. (2016a)****	Participants improved for both single and dual versions of the training tasks. They engaged in	-

	the training protocol and reached the required performance levels by the end of the training. For the visual condition the improvement was 41%, for the auditory condition it was 39%, and for the dual condition it was 53% across the training sessions as reported in Colom et al. (2013) ‡ There were large individual differences in the level achieved ranging from 3- to 9-back.	
*Colom et al. (2016b)***	*Same as Colom et al. (2016a)*	-
Dahlin et al. (2008)	- Experiment 1 – Young adult Group *Group by session comparison* TG showed larger gains in letter memory compared to the CG, (F(1,20) =26.45, P < 0.001). - Experiment 2 – Older adult Group *Group by session comparison* TG showed larger gains in letter memory compared to the CG, (F(1,17) =20.56, P < 0.001).	- Experiment 1 - Young adult Group *Near Transfer* *Group by session comparison* TG performed better compared to the CG post training (F1.20 = 10.32, P < 0.01) for the 3-back condition, and the effect size for TG was significantly greater than for CG. *Far Transfer* No significant training-related changes in performance - Experiment 2 – Older adult Group *Near Transfer* No significant training-related changes in performance
Emch et al. (2019b)	*Group by Session Comparison for 3-back load,* (F(1,55)=18.07, p<0.001). Post hoc analyses revealed no significant improvement in the CG (p = 0.06), but a highly significant improvement in the TG (p< 0.001).	*Near transfer* (HAWIE-R forward and backward) ‡ - *HAWIE-R forward*

		Group by Session Comparison, ($F(1,55) = 17.248$, $p < 0.001$). Post hoc analyses revealed a performance decrease in the CG ($p = 0.045$) and a highly significant improvement in the TG ($p < 0.001$). - *HAWIE-R backward* Group by Session Comparison, ns.
Finc et al.(2020)	*Session by Condition by Group comparison* ($x^2(3)= 9.39$, $p= 0.02$) - *2-back:* TG exhibited significantly larger training gains post-training compared to the CG ($t(20)= -4.12$, $p=0.004$) - *1-back:* t-test comparison between groups, ns ($t(39.64) = -0.52$, $p = 0.47$)	-
Flegal, Ragland and Ranganath (2019)	*ANCOVA on post-training performance, controlling for pre-training performance* TG improved performance compared to the CG for the 7-updates condition $F(2,52)=4.50$, $p < .05$, η^2partial=0.15)	*ANCOVA on post-training performance, controlling for pre-training performance* - *Near Transfer* No significant differences between the groups. - *Far Transfer* TG improved performance compared to the CG for the 8-associates condition $F(2,52)=4.50$, $p < .05$, η^2partial=0.15)
Heinzel et al. (2014)	The older adult TG improved overall after training for all three difficulty levels, 1-,2- and 3-back while the strongest improvement was found for the 2-back condition.	-

Heinzel et al. (2016)	*Group by Time comparison* The TG showed stronger improvement in the n-back task compared to the CG in accuracy ($F(1,27)=24.07$, $p<0.001$, η^2 partial $=0.47$) and reaction times ($F(1,27) = 11.22$, $p =0.002$, η^2 partial$= 0.29$).	*Near transfer* (DMS task, maintain and update conditions) *Group by Time comparison* The TG showed stronger improvement for the maintain 5 condition only compared to the CG ($F(1,27)=4.92$, $p=0.035$)
Heinzel et al. (2017)	*Group by Time by Load comparison* The TG improved more compared to the CG in the 1-back, 2-back and 3-back load conditions.	*Near transfer (DMS* (single and dual versions, auditory and visual) ‡ - *Visual Single Task* General improvement in task performance but no significant differences between TG and CG post-training (Group by Time, ns; Main effect of group, ns; Main effect of Time, $p=0.025$). - *Auditory Single-Task* No significant differences between TG and CG post-training as well as no evidence for performance improvement over time. (Group by time, ns, Main effect of time, ns; Main effect of Group, ns). - *Dual Task (Accuracy)* Group by Time comparison, $p=0.038$ Training-related improvement for the TG compared to the CG. - *Transfer Dual Task* Absolute performance (%correct), Group by Time comparison TG improved dual-task performance compared to the CG

		Relative performance, Group by time by load by modality comparison The dual-task costs decreased in the TG compared to the CG for the auditory modality post-training in the 1-load condition.
Hempel et al. (2004)	The mean rate of relative errors improved significantly for the 2-back condition between the first and second sessions and remained stable in the third session. No significant changes for the 0-back and 1-back conditions.	-
Kuhn et al. (2013)	*Group by Time by load comparison* TG improved more compared to the CG post-training especially for the higher load condition.	*Near transfer (numerical N-back and spatial updating)* ‡ *Group by Time comparison* Significant linear and quadratic effects of time for both *n-back* and *spatial updating* tasks., ps<0.04. Only non-significant trends favouring the TG compared to the CG.
*Lawlor-Savage, Clark and Goghari (2019)***	*TG* Correct matches significantly increased in all training tasks (comparison of the average of the first five iterations of each game to the last five iterations of each game) ‡ *CG* Reaction times significantly decreased in all three training tasks (comparisons of the average of the first five to the last five games). ‡	-
Miro-Padilla et al. (2018, 2020) †	*Group by time by load comparison* TG performed better than CG in both sessions post-training in both accuracy and reaction times measures in the 2- and 3-back load levels.	*Far Transfer (PASAT)* *Group by Session comparison, ns.*

		TG did not perform the task significantly better than the CG after *n*-back training, no evidence of transfer.
Opitz et al. (2014)	*Time by Group comparison, ns* The visual TG as well as the active auditory CG improved their performance in the course of training as revealed by a significant main effect of session, ($F_{7,24}=11.58$, $p<0.001$, $\eta^2_{partial}=0.77$).	Far transfer (Chinese orthographic task) *Time by Group comparison, ns* Performance increased significantly from pre- to post-test only for visual TG [mean difference =.08, SD=0.13, t15=-2.68, $p<0.05$] but not for the ACG and PCG.
Roman et al. (2016) ***	*Same as Colom et al. (2016a)*	-
Roman et al. (2017) ***	*Same as Colom et al. (2016a)*	-
Salminen et al. (2016)	*Group by Session comparison* *Dual n-back* TG shows greater improvement compared to the ACG and PCG, $F(2,50)=25.06$, $p<0.001$, $\eta^2_{partial}=0.50$) *Single n-back* TG and ACG show equal improvement, $F(2,51)=15.40$, $p<0.001$, $\eta^2_{partial}=0.38$).	*Near transfer (dual and single WMU task)* *Group by Session comparison* - *Dual WM updating task* TG shows improved performance following training while the ACG and PCG showed no changes in performance. - *Single WM updating task* No significant interaction, all groups showed improved performance in both auditory and visual versions.
Schneiders et al. (2011)	-	*Visual n-back task* *Group by time comparison, F=2,45=3.52, p<0.05, ηp2=0.14* Group specific performance improvements. - *Near transfer for visual TG*

		The Visual TG significantly improved after training, [$F(1,15)=36.01$, $p<0.001$, η^2partial=0.71]. - *Far transfer for auditory TG* *Auditory TG* The auditory TG didn't exhibit significant improvement post training, $F(1,15)=3.73$, $p<0.10$, η^2partial=0.20, ns.
Schneiders et al. (2012)	-	*Auditory transfer task (near)* *Time by Group comparison,* [$F(1, 30) = 25.23$, $p < 0.001$, $\eta 2p= 0.46$] Post-test performance was significantly greater in the TG compared to no training ($t(30) = 4.23$, $p < 0.001$). *Visual transfer task (far)* No significant differences in the groups post-training.
Schweizer et al. (2013)	*Time by Group comparison* Significant pre to post training increase in performance for the TG while for the CG, no changes were evident.	*Far transfer (Emotion Regulation task)* *Time by Group comparison* The TG exhibited significantly greater reduction in emotional distress to negative films in the Regulate relative to the Attend condition compared to the CG. TG showed a decrease in emotional distress post-training (Regulate relative to attend condition) while the CG exhibited a non-significant
Thompson, Waskom and Gabrieli (2016)	*Session by Group comparison* TG improved more after training compared to the CG specifically for the highest load	-

	conditions, i.e., 2- and 3-back in both accuracy and reaction times.	
	Neurological Populations	
Aguirre et al. (2019) ≠	*Training (both Healthy and Multiple Sclerosis training groups collapsed) by Time comparison* *2-back:* ns 3-back: Both TGs significantly improved accuracy on the 3-back level after training compared to the CGs, ($F(2,51) = 10.18$, $p<0.001$, $\eta^2 = 0.29$). *Training (TG vs CG) by Group (Healthy vs Multiple Sclerosis) comparison, ns* *Training by Group by Session, ns*	-
Bonzano et al.(2020)	-	*Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-NT)* ‡ MS Patients improved significantly post-test in all BRB-NT subtests (all $p_s< 0.05$). *PVSAT* Performance data in this task is not reported.
Leung et al. (2014)	An average Cohen's d value of 4.11 for the pre-training and post-training assessments indicating a better than chance performance (1-back and 2-back conditions only).	-
Leung et al. (2016)	*Participant 1* exhibited longer reaction times for both 1-back and 2-back conditions in the post	-

	compared to the pre-training sessions, while the hit rate improved. *Participant 2* showed improvement in both hit rate and reaction times for the 1-back and 2-back conditions post-training.	

The group comparison tests and p values in this table were extracted directly from each study as reported by the authors. ≠ The data are collapsed across both training groups (Healthy adults and patients with MS); the F and p values cannot be reported for each group separately. ** These studies shared the same Bx dataset., *** These studies shared the same Bx dataset, †These studies share the same dataset; the neuroimaging data on the training effect are described in Miro-Padilla et al. (2018) and the neuroimaging data on the transfer effect are described in Miró-Padilla, Bueichekú and Ávila, 2020, ‡This data refers to cognitive tasks that were assessed outside of the scanner, Bx: Behavioural, MS: Multiple Sclerosis, ns: non significant, PASAT: Paced Auditory Serial Addition Test, PVSAT: Paced Visual Serial Addition Test, TG1:Training Group1, TG2: Training Group 2, VLMT: Verbal Learning Memory Test. The group comparison tests and p values in this table were extracted directly from each study as reported by the authors.

Meta-Analysis of Training effect in Healthy Adult Studies Assessing Task-Based Functional Neuroimaging data

Of the twenty-two healthy adult studies that assessed task-based functional neuroimaging data, 14 were included in a meta-analysis investigating training effects (Figure 2.4.2). One study was excluded as it did not report behavioural data on the scanned criterion task (Schweizer et al., 2013), three did not use a pretest-posttest control group design (Heinzel et al., 2014, 2017; Hempel et al., 2004); and four assessed scanned transfer tasks exclusively without including a criterion task in their protocol (Miró-Padilla, Bueichekú and Ávila, 2020; Opitz et al., 2014; Schneiders et al., 2011, 2012). Overall, the training effect following WMU training was large, Hedge's g = 1.29 (95 % CI 0.80–1.78, Z = 5.16, p < 0.00001), with large heterogeneity across studies (I^2 = 85 %). The training effect funnel plot exhibited signs of asymmetry indicating possible publication bias (Figure 1.1, Appendix 1); and the Egger's regression test yielded significant results (z = 9.36, p < .0001).

Control Group Sub-Group Analysis

Sub-group analyses were conducted to investigate whether heterogeneity across studies included in the meta-analysis was reduced by comparing the TG with the active control group (ACG) and passive control group (PCG) separately. The PCG sub-group analysis revealed a very large effect size of Hedge's g = 2.75 (95 % CI 1.48–4.02, Z = 4.25, p < 0.0001). In contrast, the ACG sub-group analysis showed a moderate to large effect size of Hedge's g = 0.67 (95 % CI 0.46 to 0.88, Z = 6.20, p < 0.00001). Heterogeneity remained large for the PCG analysis (I^2 = 92 %) while it reduced to zero for the ACG analysis (I^2 = 0 %). There was also a significant sub-group effect (x^2 = 10.02, p = 0.002) indicating that the type of control group significantly modifies the effect of training.

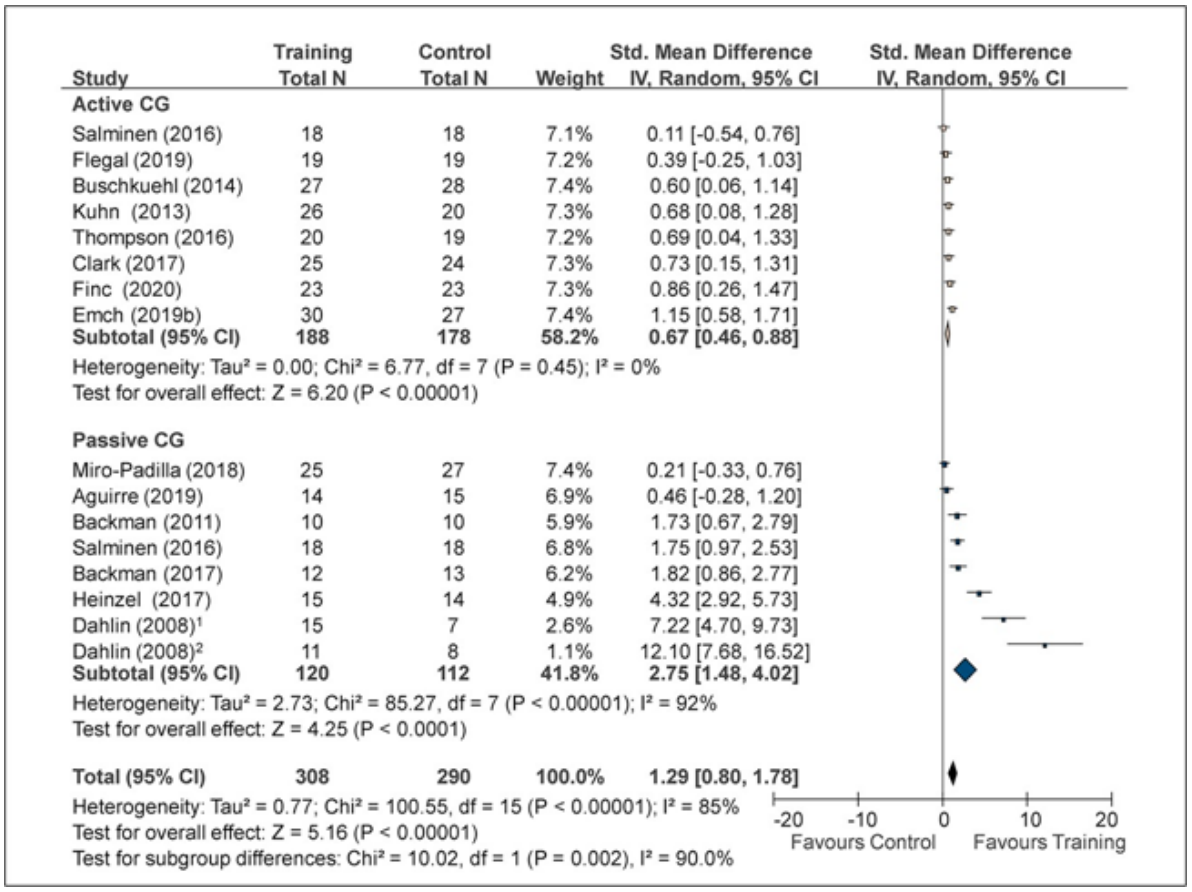

Figure 2.4.2: Training effect meta-analysis: Active and Passive CG sub-group analyses. One study (Salminen et al., 2016) involved both an ACG and a PCG, hence they were included in both sub-group analyses. 1 Experiment 1: young adults, 2 Experiment 2: older adults.

Training Duration Sub-Group Analysis

Further sub-group analyses were conducted to investigate if training duration impacted on the effect of WMU training. The median value for training hours across studies included in the meta-analysis was 10 (mean = 10.05, SD = 5.82) with those equal and below the median duration categorized as "shorter duration" and those above categorized as "longer duration". Both subgroups exhibited large training effect sizes: shorter duration group Hedge's g = 0.85 (95 % CI 0.37–1.33, Z = 3.45, p = 0.0006) and longer duration group Hedge's g = 2.22 (95 % CI 1.17–3.28, Z = 4.12, p < 0.0001) (Figure 2.4.3). There was a significant subgroup effect (x^2 = 5.39, p = 0.02), indicating that training duration significantly modified the effect of training, favouring training of longer duration. However, due to large heterogeneity within each group (shorter duration sub-group I^2 = 77 %; longer duration sub-group I^2 = 89 %), the overall effect sizes should be interpreted with caution.

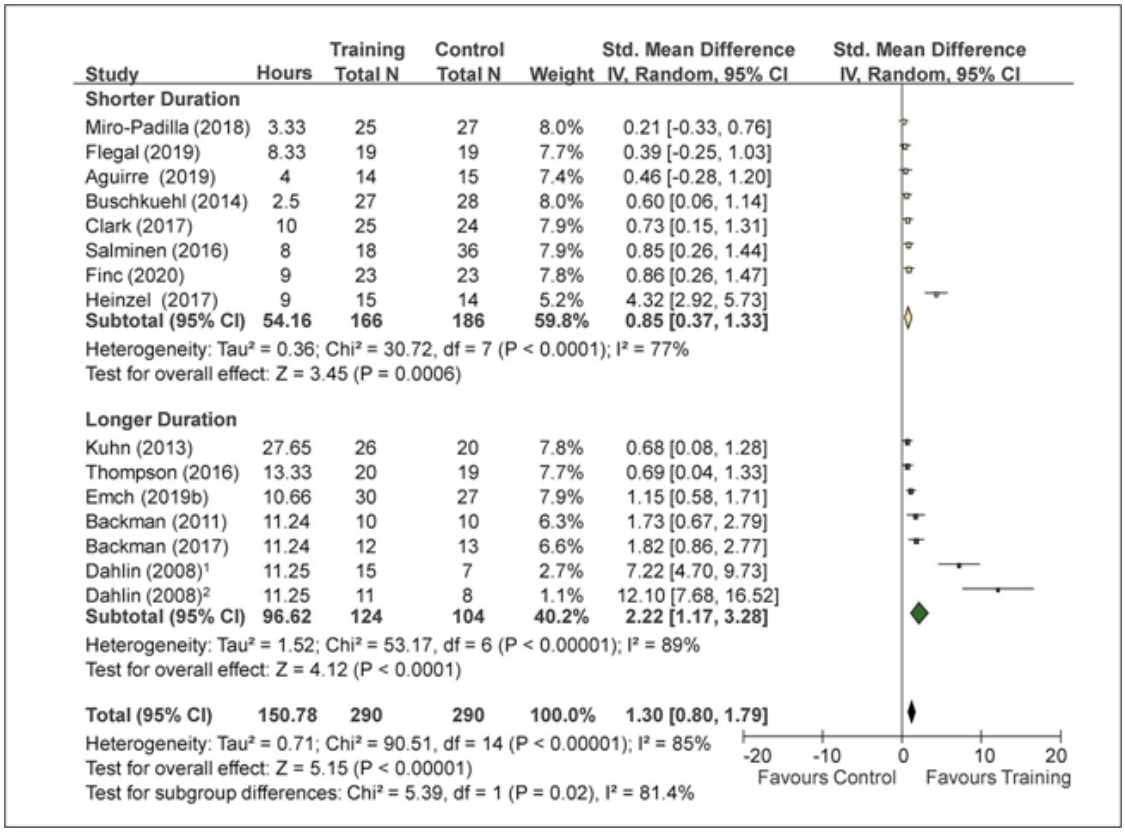

Figure 2.4.3: Training effect meta-analysis: shorter duration and longer duration sub-group analyses. In this analysis, the ACG and PCG for the study that involved both (Salminen et al., 2016) were combined into one CG, hence its training effect size is different to different to that reported in Figure 2.4.2. For the same reason, the total N value for the TG differs between Figures 2.4.2 and 2.4.3. Consequently, there is a very small difference in the total overall effect between these analyses. 1 Experiment 1: young adults, 2 Experiment 2: older adults.

Relationship between Control Group and Training Duration

We further plotted training duration against the effect of training for ACG and PCG sub-groups analyses (Figure 2.3.4). The training effect size for studies comparing the TG against ACG remains stable regardless of training duration while a linear upward trend is apparent in the training effect size for studies comparing the TG against PCG as the hours of training increase.

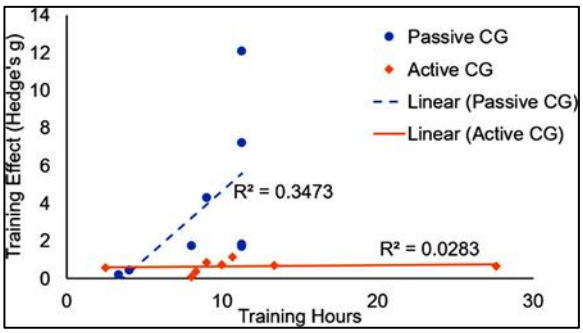

Figure 2.4.4: Relationship between training hours and training effect for Active and Passive CG sub-group comparisons.

2.4.5 Transfer effect: Healthy Adult Studies

Of the 13 included studies assessing near transfer effects following WMU training (Dahlin et al., 2008; Bäckman et al., 2011; Backman et al., 2017; Biel et al., 2020; Emch et al., 2019b; Heinzel et al., 2016, 2017; Salminen et al., 2016; Schneiders et al., 2011; Kuhn et al., 2013; Buschkuehl et al., 2014; Flegal, Ragland and Ranganath, 2019; Schneiders et al., 2012), mixed results were reported, (Table 2.4.3). The studies by Backman et al. (2017); Biel et al. (2020); Flegal, Ragland and Ranganath (2019); Kuhn et al. (2013) and the older adult training group in the study by Dahlin et al. (2008); did not find significant near transfer effects to untrained tasks in the same cognitive domain. On the contrary, the studies by Bäckman et al. (2011), Buschkuehl et al. (2014); Emch et al. (2019b); Heinzel et al. (2016); Schneiders et al. (2011), Schneiders et al. (2012) and the young adult training group in the study by Dahlin et al. (2008); all found evidence of a near transfer effect after WMU training. Finally, Heinzel et al. (2017) and Salminen et al. (2016) used single and dual versions of a delayed match to sample task and a WMU task, respectively, to assess near transfer. Both studies found significant effects only for the dual versions of the task and no effects for the single versions.

Far transfer following WMU training was assessed in nine of the included studies (Dahlin et al., 2008; Biel et al., 2020; Miró-Padilla, Bueichekú and Ávila, 2020; Opitz et al., 2014; Schneiders et al., 2011; Schweizer et al., 2013; Clark, Lawlor-Savage and Goghari, 2017; Flegal, Ragland and Ranganath, 2019; Schneiders et al., 2012), (Table 2.4.3). Biel et al. (2020); Schneiders et al. (2011), Schneiders et al. (2012), Miró-Padilla, Bueichekú and Ávila (2020) and

the young adult training group in the study by Dahlin et al. (2008) did not find significant far transfer effects following WMU training. On the contrary, Flegal, Ragland and Ranganath (2019) found evidence of far transfer for the highest difficulty level of an untrained episodic memory task; Opitz et al. (2014) reported improved performance in an untrained Chinese orthographic task assessing far transfer, while Schweizer et al. (2013) reported greater reduction in emotional distress exhibited by the TG compared to the CG following emotional WMU training. Clark, Lawlor-Savage and Goghari (2017) utilized two tasks to assess far transfer, the Raven's Standard Progressive Matrices (RSPM) and a lexical decision task and reported better performance for the TG compared to the CG on both tasks. However, the authors further explained that the RSPM task effect was driven by worse post-training performance in the CG compared to the TG, while significant differences between groups at baseline accounted for the far transfer effect for the lexical decision task.

Meta-Analysis of Transfer Effects in Healthy Adult Studies Assessing Task-Based Functional Neuroimaging data

Of the 22 healthy adult studies assessing task-based functional neuroimaging data a total of ten included transfer tasks in their protocol; with three investigating near transfer effects exclusively (Backman et al., 2017; Heinzel et al., 2016; Salminen et al., 2016), three assessing a far transfer task only (Miró-Padilla, Bueichekú and Ávila, 2020; Opitz et al., 2014; Clark, Lawlor-Savage and Goghari, 2017) and four examining both near and far transfer tasks (Dahlin et al., 2008; Schneiders et al., 2011; Flegal, Ragland and Ranganath, 2019; Schneiders et al., 2012).The near transfer effect after WMU training was moderate, Hedge's g = 0.63 (95 % CI 0.25–1.00, Z = 3.24, p = 0.001) with moderate heterogeneity across studies (I^2 = 49 %), (Figure 2.4.5A). On the contrary, the analysis of far transfer exhibited a small non-significant effect, Hedge's g = 0.15 (95 % CI −0.10 to 0.39, Z = 1.19, p = 0.23) and zero heterogeneity across studies (I^2 = 0 %), (Figure 2.4.5B). The Egger's test for funnel plot asymmetry yielded non-significant results for both near (z = 1.30, p = 0.19) and far transfer (z = 0.26, p = 0.79) (for further details please see Figures 1.2 and 1.3, Appendix 1).

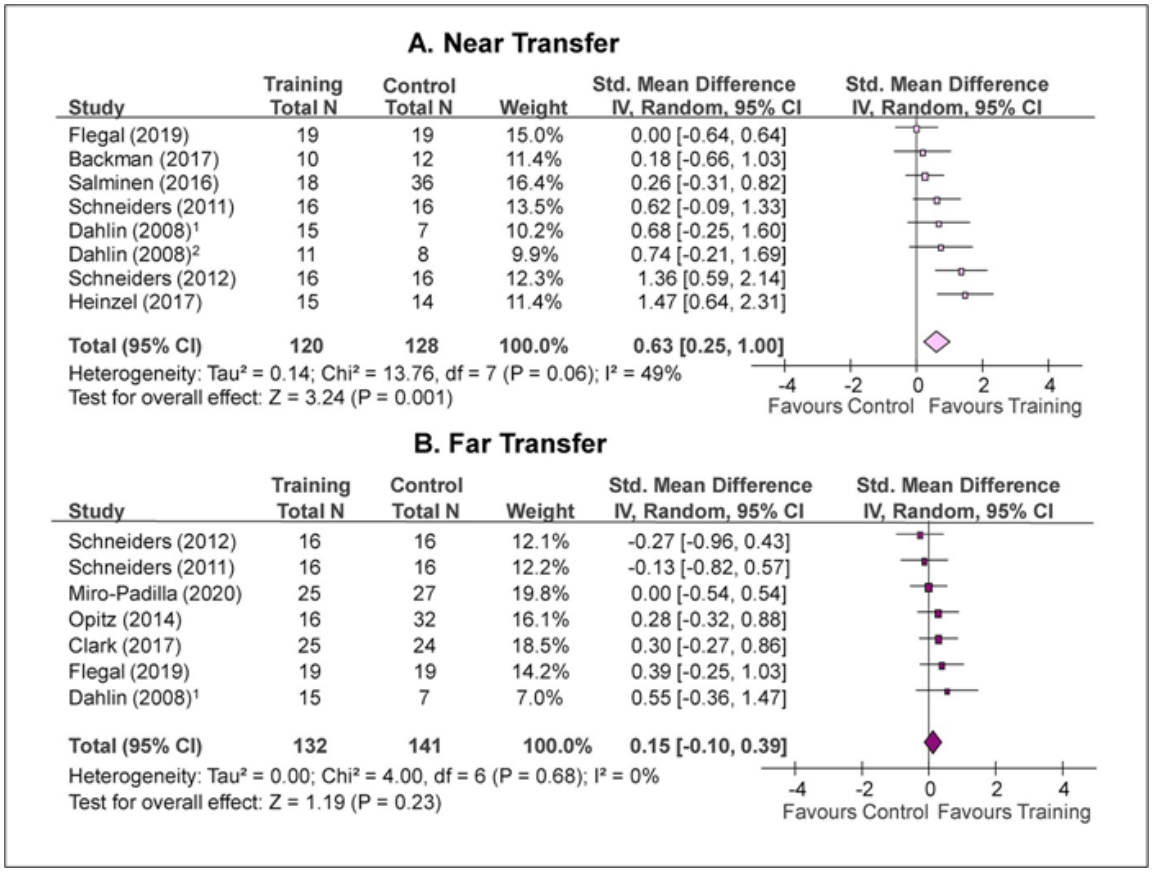

Figure 2.4.5: Transfer effect meta-analysis: A. Near transfer after WMU training, B. Far transfer after WMU training. 1 Experiment 1: young adults. 2 Experiment 2: older adults.

2.4.6 Training task: Functional Activity Changes in Healthy Adult Studies

Most of the reviewed fMRI studies found decreases in BOLD activity during the criterion task performance after WMU training (Aguirre et al., 2019; Emch et al., 2019b; Heinzel et al., 2014, 2016; Miro-Padilla et al., 2018; Schweizer et al., 2013; Clark, Lawlor-Savage and Goghari, 2017; Leung et al., 2014; Flegal, Ragland and Ranganath, 2019; Thompson, Waskom and Gabrieli, 2016), (Table 2.4.4). Despite varying in terms of training protocol, task type and modality, overall, these studies showed a similar pattern of results: decreases were detected primarily in: 1. frontal areas, i.e., frontal pole, superior frontal gyrus, DLPFC, the pre-motor and insular cortex, the cingulate gyrus, and 2. parietal areas, i.e., intraparietal sulcus, inferior parietal lobule. An exception to this

pattern was increased BOLD activity in fronto-parietal areas and striatum reported for the older adult training group in the study by Dahlin et al. (2008).

Backman et al. conducted two similar PET studies (Bäckman et al., 2011; Backman et al., 2017) and found decreases in raclopride binding to D2 receptors in the striatum, translating to increased dopamine (DA) release as a result of WMU training. Previous research has revealed a link between BOLD activity and DA release measures (Schott et al., 2008), and thus an increase in DA release is linked with an increase in striatal BOLD activity. Buschkuehl et al. (2014) conducted an ASL study and also found increases in signal magnitude indicative of increased perfusion, a surrogate for functional activity, on the criterion task in frontal and occipital areas after only 2.5 h of training.

Buschkuehl et al. (2014) additionally reported both increases and decreases in perfusion at rest. Increases were evident in the left pre-central gyrus and left parietal angular gyrus while a decrease was found in the right postcentral gyrus.

Salminen et al. (2016) found BOLD decreases in fronto-parietal regions, and an increase in the pre-central gyrus, on the criterion task after WMU training. For the young adult training group, Dahlin et al. (2008) reported decreases in fronto-parietal areas and increases in the striatum, temporal and occipital regions.

Studies employing more than two scanning sessions provide valuable insight into the dynamics of training-related activation increases and decreases elapsing over time. Hempel et al. (2004) and Kuhn et al. (2013) reported initial BOLD increases between sessions 1 and 2, i.e., pre training and early training fMRI session respectively, followed by decreases between sessions 2 and 3, i.e., from early training to post-training. More specifically, Kuhn et al. (2013) reported striatum increases at first followed by striatal and frontal decreases after several dozen intervening sessions of training, while Hempel et al. (2004) reported an initial BOLD increase at the right intraparietal sulcus and superior parietal lobe two weeks into a four-week training regimen, and a subsequent decrease in these areas post-training.

2.4.7 Transfer Task: Functional Activity Changes in Healthy Adult Studies

Near Transfer

Dahlin et al. (2008) found post-training BOLD increases in striatum and frontal, parietal and temporal cortex when assessing a near transfer task in a young adult training group, while no significant changes were reported in an older adult training group. Salminen et al. (2016) found increased BOLD activity in the striatum, cuneus and calcarine gyrus for a near transfer task. Schneiders et al. (2011) and Schneiders et al. (2012) reported decreases in BOLD activity as a result of n-back training in two different studies. The first involved decreases in the middle frontal gyrus for a visual n-back near transfer task (Schneiders et al., 2011), and the second found decreases in the IFG for an auditory n-back near transfer task (Schneiders et al., 2012). Heinzel et al. (2016) reported BOLD activity decreases in middle and superior frontal areas specifically for the combined 3 and 5 update condition of a near transfer task, in a study with older adults. The study by Flegal, Ragland and Ranganath (2019) interrogated a priori subcortical ROIs that revealed no significant differences in BOLD activity changes between the TG and ACG.

Finally, in a PET study, Backman et al. (2017) found increased striatal DA release, linked with an increase in striatal BOLD activity as explained above, for an n-back near transfer task.

Far Transfer

Clark, Lawlor-Savage and Goghari (2017) found increased activity post-training in frontal regions as well as the precentral and postcentral gyrus for the highest level of difficulty in a far transfer task. Schweizer et al. (2013) reported increased BOLD activity in the superior temporal gyrus associated with the emotional regulate condition in a far transfer task. On the other hand, Miró-Padilla, Bueichekú and Ávila (2020) reported activity decreases in the right DLPFC for a far transfer auditory attention task after 3.33 h of training. Opitz et al. (2014) found decreased BOLD activity in the fusiform gyrus for an untrained

Chinese orthographic task, only for the PCG, while no changes were reported for the TG or ACG. Lastly, Dahlin et al. (2008), Schneiders et al. (2011, 2012) and Flegal, Ragland and Ranganath (2019) did not report any significant BOLD changes when assessing far transfer tasks after WMU training.

2.4.8 Functional Connectivity Changes: Healthy Adult Studies

Only a handful of studies explored changes in functional connectivity as a result of WMU training (Table 1.2, Appendix 1). Thompson, Waskom and Gabrieli (2016) observed an increase in functional connectivity for all pairings of prefrontal and parietal ROIs, including lateral prefrontal and parietal cortex, for the 2-back load condition of the criterion task, whereas Heinzel et al. (2014) did not find any significant connectivity changes in the WM network as a result of training. Assessing training-induced changes in functional brain network modularity across four scanning sessions, Finc et al. (2020) reported increased recruitment of the fronto-parietal and default mode systems for the TG post-training, while the integration between these two systems decreased post-training. Integration changes between the subcortical and other systems was also explored with decreases reported at the early stages of training and increases post-training between the subcortical and default mode systems. The exact opposite pattern was revealed for the integration between the subcortical and dorsal attention, ventral attention, cingulo-opercular and auditory systems, in that increases were reported at first and decreases at the end of training.

2.4.9 Structural Changes: Healthy Adult Studies

The pattern of results regarding training-induced changes on structural imaging measures was not straightforward with most studies reporting null findings (Table 1.3, Appendix 1). The studies by Heinzel et al. (2014) and Biel et al. (2020) did not find significant GM volume changes, myelination, or iron levels Biel et al. (2020). Likewise, Lawlor-Savage, Clark and Goghari (2019) reported no changes in cortical surface, thickness, or volume after training. Colom et al. (2016a) found volume preservation for the TG and in the context of decreased grey matter volume for the CG in bilateral temporal lobe (Colom et al., 2016b). When carrying out further analyses on the same dataset as in Colom et al.,

(2016a,b), Roman et al. (2017) reported mean cortical thickness changes in the right ventral frontal and right middle temporal cortex, revealing minor thickening for the TG and minor thinning for the CG. They also found cortical surface area changes in the right pars opercularis and right posterolateral temporal cortex, revealing a small expanding effect for the TG and a small contracting effect for the CG. Finally, Roman et al. (2016) conducted network-based statistics in the same dataset as in (Colom et al., 2016a;2016b) and Roman et al. (2017) and identified a sub-network including frontal, parietal, temporal, subcortical regions and the insula where changes after training were more pronounced for the TG. The left middle temporal region was identified as the most highly interconnected area with connections to the bilateral basal forebrain, left parahippocampal area, left pallidum, left supramarginal and left parietal area, right insula, right accumbens, right postcentral gyrus, right pars opercularis and right pars triangularis. There was increase in structural connectivity for the TG post training in this network while no changes were observed for the CG. Furthermore, the authors reported increases in the connectome topological properties of global efficiency and strength in this sub-network for the TG while no changes were observed for the CG.

2.4.10 Neurological Populations: An overview of findings

Four studies included in this review assessed neurological samples; two of those were stroke case studies conducted in Canada (Leung et al., 2014, 2016), and the other two took place in Europe and included adults diagnosed with multiple sclerosis (Aguirre et al., 2019; Bonzano et al., 2020), (Table 2.4.1). Only one of the studies employed a pretest-posttest control group design (Aguirre et al., 2019) while the rest did not include a CG (Bonzano et al., 2020; Leung et al., 2014, 2016). All studies applied an n-back training protocol and the training duration ranged between four and 20 h. All studies included an fMRI task-based analysis while none explored changes in the brain's functional connectivity or structure changes following WMU training, (Table 2.4.1).

Participants improved their criterion task accuracy as a result of WMU training across studies (Aguirre et al., 2019; Leung et al., 2014, 2016), (Table 2.4.3). Aguirre et al. (2019) did not report data for the healthy controls (HC) and multiple sclerosis (MS) participants separately; thus, the exact training effect for each population could not be analysed. Bonzano et al. (2020) did not assess performance on the criterion task but examined transfer effects for tasks performed inside and outside the scanner. Improved performance was found on all tasks of the Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) post-training compared to pre-training, although it is important to note that this study did not include a CG.

As with the training-related behavioural data, Aguirre et al. (2019) did not report neural changes following WMU training for the different participant groups separately; nevertheless, fronto-parietal activity decreases were found for both HC and MS, (Table 2.4.4). Furthermore, Leung et al. (2014) and Leung et al. (2016) reported a mixture of BOLD increases and decreases in fronto-parietal and temporal areas after training. Finally, Bonzano et al. (2020) assessed fMRI performance on a far transfer task exclusively and reported decreases in fronto-parietal areas post-training compared to pre-training.

Table 2.4.4: Functional Activity Changes after WMU training for training and transfer tasks.

Reference	*Functional Activity Changes*	
	Training	*Transfer*
	Healthy Adults	
Aguirre et al. (2019) ≠	*Training (both Healthy and Multiple Sclerosis training groups collapsed) by Time comparison,* p<0.05 FEW corrected, p <0.001 and uncorrected. **2-back: ↓*Decreased* activity TG vs CG in:** i. R Angular gyrus ii. R Supramarginal gyrus iii. L/R Inferior parietal lobule iv. R middle frontal gyrus v. L Postcentral gyrus **3-back: ↓*Decreased* activity TG vs CG in:** i. R Superior medial frontal gyrus ii. L/R Middle frontal gyrus iii. L/R Superior frontal gyrus iv. L/R Supplementary motor area v. L Precentral gyrus vi. L Inferior frontal gyrus	-
Backman et al. (2011)	*Group by Time comparison, threshold at p<0.001*	-

	↓ ***Decreased raclopride binding to D2 receptors*** for the TG compared to the CG in the L caudate. Enhanced DA release after cognitive training is demonstrated. Suggestive of ↑ ***Increase in caudate BOLD activity***.	
Backman et al. (2017)	*Group by Time comparison* ↓ ***Decreased raclopride binding to D2 receptors*** for the TG compared to the CG in L/R Striatum. Enhanced DA release after cognitive training is demonstrated Suggestive of ↑ ***Increase in caudate BOLD activity***.	Group by Time comparison ↓ ***Decreased raclopride binding to D2 receptors*** for the TG compared to the CG in R Striatum.
Buschkuehl et al. (2014)	Group by Time comparison (4-back Vs 1-back) (threshold: z > 2.8; cluster size >= 19) ↑ ***Increase in magnitude of perfusion*** *for TG compared to the CG in:* i. R Frontal postcentral gyrus ii. L Superior frontal gyrus (BA6) iii. R superior occipital gyrus iv. R middle occipital gyrus Group by Time comparison (4-back Vs 1-back) ↑ ***Increase in perfusion changes at rest*** *for TG compared to the CG in:* i. L Frontal precentral gyrus (BA6)	-

	ii. L Parietal Angular Gyrus (BA39) ↑ ***Decrease in perfusion changes at rest*** *for TG compared to the CG in* R postcentral gyrus (BA5).	
Clark et al.(2017)	*Group by Time comparison* Z threshold of 2.3 and cluster threshold of 0.05 ↓ ***Decreased activity post-training*** for the TG compared to the ACG: i. L/R paracingulate gyrus ii. L/R anterior cingulate gyrus iii. L/R frontal pole iv. L/R superior frontal gyrus v. L/R cingulate gyrus vi. L/R insular cortex vii. L/R temporal pole viii. L/R parahippocampal gyrus ix. L/R posterior cingulate gyrus x. R middle temporal gyrus R angular gyrus xi. R supramarginal gyrus xii. L/R posterior cingulate gyrus xiii. L postcentral gyrus	***Transfer (far)*** Group by Time comparison ↑ ***Increased activity post-training*** for the TG compared to the ACG: i. L Inferior Frontal gyrus; ii. L Frontal pole iii. L Precentral gyrus; iv. L Postcentral gyrus; v. L Superior Frontal gyrus **Hard > Medium Condition**

	Brain regions combined from the following contrasts: 3-back > 2-back, 3-back > 1-back and 2-back > 1-back.	
Dahlin et al. (2008)	**Experiment 1: Young Adult Group** *Group by Session comparison* ↑ ***Increased activity*** for the TG post-training in: i. L/R striatum ii. R Temporal lobe iii. R Occipital lobe ↓ ***Decreased activity*** for the TG post-training in: i. L Frontal lobe ii. L Parietal lobe **Experiment 2: Older Adult Group** *Group by Session comparison* ↑ ***Increased activity*** for the TG post-training in: i. L Frontal lobe ii. L/R Parietal lobe iii. R Temporal lobe iv. L Cerebellum v. L Striatum	**Experiment 1: Young Adult Group** ***Transfer (near)*** Group by Session comparison ↑ ***Increased activity*** for the TG post-training in: i. L Frontal lobe ii. L Parietal lobe iii. L Temporal lobe iv. L Striatum v. Brain stem ***Transfer (far)*** No changes. **Experiment 2: Older Adult Group** No significant changes were found for the 3-back task
Emch et al. (2019b)	*Group by Time comparison FDR corrected p<0.05, k=6 voxels.*	-

	↓***Decreased activity for TG compared to CG post-training in:*** i. L middle temporal gyrus (BA20, BA39) ii. R superior frontal gyrus (BA9) iii. L/R supramarginal gyrus (BA40) iv. R anterior cingulate (BA32) v. R posterior cingulate (BA29) vi. L cuneus (BA7) vii. R middle frontal gyrus (BA9) viii. R angular gyrus (BA39) ix. R middle occipital gyrus (BA19) x. R occipital lobe (BA18) xi. L parahippocampal gyrus (BA30) xii. L/R cerebellum	
Flegal, Ragland and Ranganath (2019)	*Group x Time comparison all clusters above p<0.05.* Matrix Updating task ↓***Decreased activity*** greater for the TG compared to CG post-training in all ROIs: i. L/R Caudate ii. L/R Putamen iii. L/R Hippocampus **Whole brain analysis**	*Group by Time comparison* No significant differences between TG and CG for the near transfer and far transfer tasks in the ROIs.

	cluster corrected FWE threshold, p <.05. *Group by session interaction* ↓***Decreased activity for TG:*** xiii. L/R striatum, xiv. L/R prefrontal, xv. L/R temporal, xvi. L parietal regions xvii. L parietal regions.	
Heinzel et al. (2014)	*Time by Load comparison* p<0.05 FWE corrected for whole brain). ↓***Decreased activity*** for the TG post-training in the WM network: i. L/R Rostral Cingulate Zone (BA32/6) ii. L/R lateral premotor cortex (BA6) iii. L/R DLPFC (BA9/46) iv. L/R Intraparietal sulcus (BA40) Follow-up t-tests indicating the effect was driven by 1-back load.	-
Heinzel et al. (2016)	*Group x Time comparison*, all clusters above p<0.05. **Combined 1and2-back (k>90, alphasim-corr)** ↓ ***Decreased activity*** for the TG post-training in:	***Transfer (near)*** Group x Time comparison, all clusters above p<0.05. Sternberg Updating 3and5 **(k>57, alphasim-corr)** ↓ ***Decreased activity*** for the TG post-training in the R middle frontal gyrus/superior frontal gyrus (k=68)

	i. R/L Medial Frontal gyrus / Anterior Cingulate gyrus/ Supplementary Motor area (k=166) ii. R Middle and Superior Frontal gyrus (k=140) R supramarginal gyrus, Inferior Parietal lobule, and angular gyrus (k=112)	
Heinzel et al.(2017)	Same as in Heinzel et al., 2014.	-
Hempel et al. (2004)	Changes in mean effect sizes for 2-back and 1-back load levels for the TG. k=20 voxels; $p<0.05$, corrected for multiple comparisons) Significant Inverse U-Shape Quadratic Function for the mean effect size: ↑ ***Increased activity*** between sessions 1 and 2 in R Intraparietal sulcus/ superior parietal lobe for both 1 and 2-back load levels. ↓ ***Decreased activity*** between sessions 2 and 3 in R Intraparietal sulcus/ superior parietal lobe Non-significant quadratic trend for the mean effect size in the R inferior/medial frontal gyrus.	-

Kuhn et al.(2013)	Contrast of all load conditions against implicit baseline averaged over group and time point. (threshold p<0.01, cluster>22) ↑ ***Increased activity*** for the TG between sessions 1 and 2 in R/L striatum (putamen). ↓ ***Decreased activity*** for the TG between sessions 2 and 3 in: i. R striatum (putamen) ii. R inferior frontal gyrus	-
Miro-Padilla et al. (2018, 2020) †	*Group by Session* comparison separately for each load level (2-back and 3-back). p < 0.05 FWE cluster-corrected using a threshold of p < 0.001 at the uncorrected voxel level ↓ ***Decreased activity*** for the TG between sessions 1 and 2 in: i. R Frontal Superior (BA32/6) ii. L Frontal Middle (BA10) iii. R Frontal Middle (BA6) iv. L Parietal Inferior (BA40) v. R Parietal Inferior (BA40) vi. L Temporal Middle (BA21) vii. L Frontal Superior (BA6) viii. R Frontal Middle (BA46) ix. R Parietal Inferior (BA40) x. SMA (BA6)	***Transfer (far)***, *Group by session comparison, FDR threshold of p< 0.05* ↓***Decreased activity*** for the TG compared to the CG post-training in the R Dorsolateral Prefrontal Cortex (BA 46).

	xi. L Frontal Inferior (BA48) Brain regions combined from 3-back and 2-back levels.	
Opitz et al. (2014)	-	***Transfer (far)*** Time by Group comparison **PCG** ↓ ***Decreased activity*** in L fusiform gyrus. No significant changes for either of the TG or ACG.
Salminen et al. (2016)	AlphaSim correction p<0.001, cluster size>22. ↓ ***Decreased activity*** for the TG post-training in: i. R Inferior frontal gyrus ii. R Middle frontal gyrus iii. R Superior frontal gyrus iv. L Medial frontal gyrus v. L Superior frontal gyrus vi. R Inferior Parietal lobule vii. R Anterior cingulate gyrus viii. L Posterior cingulate gyrus ix. R Cerebellum x. L Cerebellum ↑ ***Increased activity*** for the TG post-training in L precentral gyrus.	***Transfer (near)*** ↑ ***Increased activity*** for the TG post-training in: i. L/R calcarine gyrus, cuneus ii. L/R Striatum ***No activation changes for the ACG or PCG for the transfer task.*** Group by Time comparison, for percentage signal changes (PSC), (AlphaSim p <0.001, cluster size >22) ↑ ***Increased activity*** for the TG pre to post-training in the striatum ↓ ***Decreased activity*** for the ACG and PCG pre to post-training in the striatum

	↓ ***Decreased activity*** for the ACG post-training in: i. R Middle Frontal gyrus ii. L Inferior Frontal gyrus iii. L Inferior Parietal lobule ***No training-related activation changes for the PCG.***	
Schneiders et al. (2011)	-	***Transfer (near)*** *Group by Time comparison* ↓ ***Decreased activity*** for the visual TG post-training in: i. R middle frontal gyrus (BA9) ii. R middle frontal gyrus (BA/46) ***Transfer (far)*** ***No significant changes post-training for the auditory TG.*** **Training (across modal training effects)** Group (collapsed across TGs vs CG) by Time comparison, ↓ ***Decreased activity*** for both TGs compared to the CG post training in: i. R Intraparietal sulcus (BA40) ii. R Superior Middle frontal gyrus
Schneiders et al. (2012)	-	***Transfer (near), auditory task and*** Group by Time comparison

		Percent signal change values of functional volumes of interests thresholded at p <0.005 (135 voxel extend ↓ ***Decreased activity*** for the TG post-training in: iii. R Inferior frontal gyrus (BA46) iv. R Inferior frontal gyrus (BA47) Decreased activity was larger in the near transfer task compared to the far transfer task. ***Transfer (far), visual task*** No significant group by time comparison
Schweizer et al. (2013)	Group by Time comparison, FDR, p<0.05 ↓ ***Decreased activity*** for the TG compared to the CG post-training across all n-back levels in: i. L ventrolateral to dorsolateral prefrontal cortex ii. L/R inferior parietal cortex iii. R precuneus iv. Inferior/middle temporal gyrus v. L/R middle and posterior cingulum vi. L ACC	**Transfer (far, ER task)** Whole-brain level, p uncorrected<0.001, Regulate relative to Attend condition, TG Vs CG ↑**Increased activity** for the TG compared to the CG post training in: R superior temporal gyrus
Thompson, Waskom and Gabrieli (2016)	*Time by Group comparison* ↓ ***Decreased activity*** for the TG compared to the CG post-training in: i. Prefrontal cortex	-

	ii. Parietal cortex iii. Insular cortex	
	Neurological Populations	
Aguirre et al. (2019) ≠	*Training (both Healthy and Multiple Sclerosis training groups collapsed) by Time comparison,* p<0.05 FWE corrected, and p <0.001 uncorrected. **2-back: ↓*Decreased* activity TG vs CG in:** i. R Angular gyrus ii. R Supramarginal gyrus iii. L/R Inferior parietal lobule iv. R middle frontal gyrus v. L Postcentral gyrus **3-back: ↓*Decreased* activity TG vs CG in:** *i.* R Superior medial frontal gyrus *ii.* L/R Middle frontal gyrus *iii.* L/R Superior frontal gyrus *iv.* L/R Supplementary motor area *v.* L Precentral gyrus *vi.* L Inferior frontal gyrus	-
Bonzano et al. (2020)	-	***Transfer (far)*** Paired t-test (p<0.001 uncorrected, k=30 voxels) ↓***Decreased*** activity found post-training compared to pre-training for the TG in:

		i. L Cingulate gyrus ii. R postcentral gyrus iii. L inferior parietal lobule
Leung et al. (2014)	All activations significant at p<0.005, cluster size>196ml **Main effect of time** (Pre> Post-training) ↓ **Decreased activity** in R Angular gyrus.	-
Leung et al. (2016)	All activations significant at p<0.005, cluster size>196ml - Participant 1 – 1-back level ↓ **Decreased activity** in R Middle temporal gyrus (BA37) ↑ **Increased activity** in L temporal gyrus (BA20) - Participant 1 – 2-back ↓ **Decreased activity** in i. R Middle temporal gyrus (BA37) ii. L Inferior parietal lobe (BA40) ↑ **Increased activity** in R Middle temporal gyrus (BA20) - Participant 2- 1-back level ↓ **Decreased activity** after training in: i. R Middle frontal lobe (BA6) ii. R Inferior frontal gyrus (BA45) iii. R Middle temporal gyrus (BA21)	-

		iv. L/R Inferior parietal lobe (BA7/BA40)			
		2-back level ↓ **Decreased activity** after training in L/R Middle frontal gyrus (BA45/47) ↑**Increased activity** after training in: i. L middle temporal gyrus (BA20) ii. L/R inferior parietal lobe (BA40) iii. R Cerebellum			

≠ The data are collapsed across both training groups (Healthy adults and patients with MS); the F and p values cannot be reported for each group separately, †These studies share the same dataset; the neuroimaging data on the training effect are described in Miro-Padilla et al. (2018) and the neuroimaging data on the transfer effect are described in Miró-Padilla, Bueichekú and Ávila (2020), **FDR:** False Discovery Rate, **FWE:** Family-Wise Error.

2.5 Discussion

This is the first systematic review assessing cognitive and neural outcomes following training of the WMU process specifically. We concentrated on neuroimaging studies in adults and further conducted meta-analyses to investigate the effect of training, and transfer to untrained tasks, in studies assessing task-based functional neuroimaging data. Cognitive outcomes across the included studies reveal a clear pattern consistent with previous meta-analyses in the wider field of WM training. The neural changes after WMU training were assessed qualitatively and examined for both training and transfer tasks. These data reveal interesting training-related patterns with greater consistency in fronto-parietal cortical regions than subcortical areas. We interpret our results in relation to previous theoretical models.

2.5.1 Training Effect: Healthy Adult Studies

A meta-analysis of published studies indicates that WMU training can significantly improve cognitive performance in adults. However, the funnel plot for the training effect exhibited significant asymmetry indicative of publication bias. The observed large overall training effect in the reviewed data could be overestimated and biased from studies with small sample sizes, considerable variability and large effect sizes. When conducting sub-group analyses according to the type of control group, the training effect size was very large for studies with a passive control group, while a moderate effect was revealed for studies with an active control group. There was a significant difference between the training effect sizes from the control group sub-group analyses. At the same time, the large heterogeneity value in the PCG comparison in contrast to no heterogeneity for the ACG comparison suggests that studies employing a PCG introduce greater heterogeneity or noise in the data which could be possibly overestimating the training effect sizes. Similar findings have been reported in previous meta-analyses examining the influence of type of control group on transfer effects (Dougherty, Hamovitz and Tidwell, 2016; Melby-Lervåg, Redick and Hulme, 2016). PCG designs do not control for a potential placebo effect thus making it difficult to discern whether the effect sizes stem from true training gains or perhaps mediated by non-specific factors such as increased effort

(Dougherty, Hamovitz and Tidwell, 2016). On the other hand, employing an ACG in which participants practice an alternative but similarly challenging task bears the risk of underestimating the effects of training (von Bastian and Oberauer, 2014). For this reason, there should be a dynamic balance between a no contact control group and a cognitively challenging control group such as employing a lower-level non-adaptive task paradigm (von Bastian and Oberauer, 2014).

We further inspected how training duration affects the WMU training effect and found some evidence for an association between training duration and training effect size, although heterogeneity within both shorter and longer duration sub-groups was large. Finally, there seems to be a linear upward trend for the training effect size as the total hours of training increase for studies with passive control groups, while the effect size is insensitive to training duration for studies with active control groups.

2.5.2 Training Task: Functional Activity Changes in Healthy Adult Studies

The most consistent pattern of training-related changes involved BOLD activity decreases in fronto-parietal regions. These include frontal areas such as the frontal pole, superior frontal gyrus, DLPFC, premotor and insular cortex, cingulate gyrus, and parietal areas such as the intraparietal sulcus, inferior parietal lobule. The locations are consistent with a WM fronto-parietal network already established in the neuroimaging literature (Nee et al., 2013; Wager and Smith, 2003; Salmi, Nyberg and Laine, 2018). Decreases in functional activation are thought to reflect neural efficiency, i.e., fewer resources needed to perform the same task after training than before training (Kelly, Foxe and Garavan, 2006). This interpretation is consistent with the concept of plasticity proposed by Lövdén et al. (2010) in which the neural system responds to a prolonged situation of environmental "demands" (e.g., a continuously challenging cognitive task) exceeding functional "supply" (i.e., neural resources) with plastic changes.

Increases in functional activation after WMU training were observed in an older adult group in fronto-parietal regions and striatal areas (Dahlin et al., 2008). This is in direct contrast to other studies which also included older adult

training groups but reported decreases in fronto-parietal activity instead (Emch et al., 2019b; Heinzel et al., 2016); a neural response pattern similar to that seen in young adults. Previous literature suggests that older adults often exhibit greater activation compared to young adults (Cabeza, 2002; Grady et al., 1994; Reuter-Lorenz et al., 2000) and one explanation for this is a compensatory use of neural circuits, known as the CRUNCH model (Reuter-Lorenz and Cappell, 2008). This model posits that older adults reach a peak in functional activity at lower difficulty levels than young adults, indicating that the point at which neural resources reach maximum capacity differs with age. Iordan et al. (2020) tested the CRUNCH hypothesis model on a within-subject intervention design with young adult and older adult groups and confirmed that, irrespective of age, WM training leads to functional activity decreases (i.e., fewer resources needed to perform the task after training), consistent with the studies by Heinzel et al. (2016) and Emch et al. (2019b). The results further suggest a shift in the peak activation as a result of training, i.e., neural resources reach maximum capacity at higher difficulty levels than before the intervention. However, the older adult training group in the study by Dahlin et al. (2008) was not found to exhibit overactivation compared to the young adult training group, and its reported increase in striatal activation resulted from significant post-training activation that was not present at the pre-test session. Additionally, the older adults' behavioural performance was quite poor at pre-training. These findings suggest the anomalous result of increased fronto-parietal activity post-training observed by Dahlin et al. (2008) could be explained by the older adult group experiencing the criterion task as markedly more difficult than the young adult group pre-training, for which a post-training shift in the peak activation via training-induced plasticity Iordan et al. (2020) would in fact produce relative increases in activity. A mixture of activity increases and decreases over time were reported in studies that employed three scanning sessions, i.e., pre- training, early-training and post-training. Initial striatal increases followed by striatal and frontal lobe decreases after training were reported by Kuhn et al. (2013), while Hempel et al. (2004) reported an initial BOLD increase and subsequent decrease at the right intraparietal sulcus and superior parietal lobe. Buschkuehl et al. (2014) also reported increases in ASL perfusion, a surrogate of BOLD activity, in superior frontal and postcentral gyrus together with superior and middle occipital gyrus after a brief 2.5 h of WMU training. Thus, it should be borne in

mind that some variability in the direction of activation changes across the other reviewed studies could be due to a dynamic process being captured at a single post-training timepoint for comparison to a pre-training baseline, defining an interval that ranges widely across studies.

Doyon and Benali (2005) proposed a fast-early and a slow-late stage model of motor learning in which the cortico-striatal and cortico-cerebellar systems contribute differentially to the learning process, where activity changes in the two systems are observed at different learning stages. Lustig et al. (2009) hypothesized that if this motor learning model is applied in cognitive training, then fronto-parietal increases should be observed at the beginning, followed by potential decreases or a mixture of increases and decreases in these networks. For WMU training, studies by Hempel et al. (2004) and Kuhn et al. (2013) support this hypothesis of early-stage activity increases and late stage decreases. The ASL study (Buschkuehl et al., 2014) further corroborates this model with evidence of increased perfusion after only 2.5 h of training.

Patterns of activation changes following WMU training appear less clear in subcortical regions. The two PET studies by Bäckman et al. (2011) and Backman et al. (2017) reported increased dopamine release specifically involving the striatal region which is consistent with training-induced functional activity increases in the striatum. Even though a link between DA release and BOLD activity has been previously established (Schott et al., 2008), this pattern of results should be interpreted with caution due to the different measures employed by the PET and fMRI methodologies, i.e., altered neurotransmitter synthesis and BOLD activation changes, respectively. Using fMRI, Flegal, Ragland and Ranganath (2019) and Kuhn et al. (2013) reported striatal activity decreases after WMU training, while Dahlin et al. (2008) found a striatal increase for a young adult training group. A commonality in these studies setting them apart from others that did not report subcortical activation changes is that all used memory updating task paradigms, rather than an n-back training task in which WM load varies along with WMU demand (perhaps accounting for the predominance of activity changes within the WM fronto-parietal network in studies that used n-back training tasks). One reason the direction of striatal activity change after training is inconsistent across studies could be that

decreases were observed for training groups compared to an active control group (Kuhn et al., 2013; Flegal, Ragland and Ranganath, 2019), while increases were observed in a passive control group comparison (Dahlin et al., 2008).

Our findings are consistent with those from reviews of the wider WM training literature in that the neural pattern of activation changes exhibited decreases, increases and mixture of decreases and increases post-training. A summary of these changes after WMU training suggests the following: 1. Robust evidence of BOLD decreases in fronto-parietal regions across studies, 2. Dynamics of activity changes differ at the fast-early and slow-late learning stages, showing an initial increase and a subsequent decrease in BOLD activity, 3. Training-related striatal activation changes are found when a memory updating task is employed rather than an n-back task; with some studies reporting increases and some reporting decreases.

Nyberg and Eriksson, (2016) proposed a subcortical dopaminergic updating system in which dopaminergic neurotransmission and striato-cortical interactions are involved in WMU and the striatum constitutes a major subcortical node for updating. Dopaminergic neurotransmission is also central to a model developed by Cools and D'Esposito (2011) which views cognitive control as a multifactorial phenomenon where a dynamic equilibrium between cognitive stability (manifested in the prefrontal cortex) and flexibility (manifested in the striatum) is essential. This model relies on the qualitatively different functional DA roles in the PFC and striatum. Recent findings propose that striatal DA plays a role in WM and cognitive control by serving as the gate mechanism crucial for flexibly updating the current goal representations in the PFC, while the PFC DA enhances stability of these representations by strengthening distractor resistance and attenuating the PFC networks (Cools and D'Esposito, 2011). The authors hypothesize that our behaviour needs to flexibly update according to relevant changes, e.g., switching between different tasks, but also remain stable when these are irrelevant, e.g., focussing on a task without getting distracted by external factors. Flexibility and stability are ascribed as two functionally distinct and opposing mechanisms that ultimately work together, complement each other and are manifested in the striatum and PFC respectively (Cools and D'Esposito, 2011).

We therefore suggest the striatum responds differentially to learning and/or cognitive training compared to the fronto-parietal network and that makes it a key factor to explain the pattern of results reported above. We propose that the hypothesized PFC involvement in cognitive stability is supported by the consistency in fronto-parietal BOLD decreases after WMU training across studies included in this review. Previous reviews have reported activity changes in fronto-parietal and subcortical areas after WM training (Hsu, Novick and Jaeggi, 2014; Klingberg, 2010; Brehmer et al., 2011; Dahlin et al., 2009) but the present review is the first to focus solely on the WMU process, finding a consistent pattern of decreased fronto-parietal activity post-training. In contrast, we view the inconsistencies in the striatal activity changes as a manifestation of cognitive flexibility. Based on the theoretical framework of adult cognitive plasticity by Lövdén et al. (2010) combined with models of the striatum as a major node for updating (Nyberg and Eriksson, 2016), we suggest that neural changes in the striatal region are a manifestation of Lövdén's concept of flexibility, i.e., the neural system's existing ability to adapt effectively to environmental demands and utilise the necessary neural processes for performing a given task. Our analyses suggest that significant changes in striatal activity are found only after training on studies employing a memory updating task paradigm. Even though both memory updating and n-back task paradigms tap into the WMU process, they also entail distinct cognitive processes. Memory updating tasks involve storage and updating, e.g., the WM load remains stable even though the updating demands vary across task difficulty levels. N-back tasks involve simultaneous storage, monitoring, maintenance and updating, e.g., the WM load also changes as a result of varying the updating demand. For this reason, we suggest that the memory updating paradigms are more likely to specifically target the WMU process and we will refer to them as "highly targeted" memory updating tasks, e.g., matrix updating or numerical memory updating. We further propose that these highly targeted WMU tasks can successfully "trigger" the neural system's flexibility which is manifested in the striatal changes after training. However, this is a speculative explanation of our findings and should be interpreted with caution due to the small sample of reviewed studies.

2.5.3 Transfer Effect: Healthy Adult Studies

For transfer of training gains to untrained tasks, WMU training was found to improve performance on near transfer tasks (same cognitive domain) but not far transfer tasks (different cognitive domain). Again, our findings are consistent with previous syntheses of cognitive outcomes from WM training (Melby-Lervåg, Redick and Hulme, 2016; Soveri et al., 2017) in reporting a medium-sized near transfer effect and a non-significant far transfer effect. Our transfer results seem consistent with the notion that overlapping cognitive processes are necessary for transfer to occur as previously suggested (Dahlin et al., 2009) and that would theoretically explain the lack of far transfer, i.e., when the criterion and transfer task do not share the underlying process of WMU.

However, it is important to point out there are discrepancies in what authors identify as near and far transfer across studies. These terms are not used consistently in the cognitive training literature, contributing to the difficulty of defining the concept of transfer adequately and ultimately reaching a consensus. In our review of WMU training studies, we categorised transfer tasks as near or far by following the authors' own classifications and we further collapsed across task difficulty levels and averaged performance across multiple tasks to minimise bias in our meta-analysis to the greatest extent possible. However, we acknowledge the complexity of this issue and would like to draw attention to the fact that our reported findings regarding transfer effects ultimately rely heavily upon the definitions of near and far transfer within each reviewed study.

Moreover, there were not enough reviewed studies with transfer task data to allow sub-group assessment for type of control group and therefore we are unable to make claims regarding the influence of active and passive control groups on WMU training interventions. We suggest that including sub-analyses to investigate the training duration, the training paradigm, and control group can potentially clarify the issue of near and far transfer further.

2.5.4 Transfer Task: Functional Activity Changes in Healthy Adult Studies

Most studies and previous literature reviews of WMU training have not focused on training-related neural changes on transfer tasks. We found activity increases and decreases, primarily in frontal and striatal regions, for scanned transfer tasks after WMU training. Overall, studies reported functional activation increases (Dahlin et al., 2008; Bäckman et al., 2011; Salminen et al., 2016; Schweizer et al., 2013; Clark, Lawlor-Savage and Goghari, 2017) consistent with the WM training meta-analysis by Salmi, Nyberg and Laine (2018) reporting IFG and striatum increases in transfer tasks. On the contrary, other studies observed no significant changes in activity (Dahlin et al., 2008; Opitz et al., 2014; Flegal, Ragland and Ranganath, 2019). A few studies reported transfer task activity decreases after WMU training, and a closer look reveals they are distinct from the rest. The study by Heinzel et al. (2016) involves older adults whose neural response is different compared to young adults (Cabeza, 2002; Grady et al., 1994; Reuter- Lorenz et al., 2000). Even though the study by Miró-Padilla, Bueichekú and Ávila, (2020) exhibited decreases in a far transfer task following n-back training, there were no significant behavioural transfer effects and thus we are unable to assign a meaningful interpretation to these neural findings. The remaining two studies by Schneiders et al. (2011) and Schneiders et al. (2012) differ in their categorization of transfer tasks; they use the definitions of intra-modal and across-modal general control task instead of near and far transfer task, respectively. We suggest that what the authors view as intra-modal transfer (performance on a visual 2-back task with novel stimuli following training with a visual adaptive n-back task) is what many cognitive training researchers would consider a measure of the criterion i.e., trained criterion task; while what they authors view as across-modal transfer (performance on a visual 2-back task following training with an auditory adaptive n-back task) is closer to a typical measure of near transfer. Following that logic, then frontal BOLD decreases for the intra-modal tasks are consistent with the fronto-parietal reductions for the training tasks in other reviewed studies, while the lack of activity changes for the across-modal tasks suggest no neural changes taking place for a near transfer task after WMU training.

Returning to the fast-early and slow-late stage model first applied to motor learning (Doyon and Benali, 2005), we propose this can be extended to account for the commonly observed activation increases for transfer tasks following WMU training. Similar to the dynamic activation increases and decreases elapsing over time for training tasks scanned early in training and then again later in training (Hempel et al., 2004; Kuhn et al., 2013), we suggest that activation profiles for transfer tasks also follow the same inverted U-shape pattern, but at a different rate reflecting their less frequent exposure to training study participants. Due to this, there is a hypothesized time-lag in the activation curve as a function of time for transfer tasks, compared to that of the training task. The post-training activity increases frequently reported for transfer tasks result from training on the criterion task, and although its post-training activation changes on the criterion task are most frequently reported as decreases, both profiles can be represented by the same schematic model of training-related neural changes (Figure 2.4.1). Repeated exposure to, and practice with, the training task is associated with functional changes observed as early-stage activity increases (on the scanned criterion task) followed by late-stage activity decreases that may represent neural efficiency resulting from plastic changes induced by WMU training. The most common experimental design for cognitive training studies assessing task-based functional neuroimaging data is to scan transfer tasks at one post-training session, and although participants have had repeated exposure to the training task at this point the post-training transfer task is still relatively novel and challenging, thus performance is still effortful—similar to a criterion task at the early stage of learning—and the activation change from baseline is observed as an increase. The dashed line following the post-training scanning session for the transfer task in Figure 2.4.1 represents a predicted functional activity decrease that would eventually occur if participants were repeatedly exposed to the transfer task, thereafter, consequently approaching the slow-late learning stage.

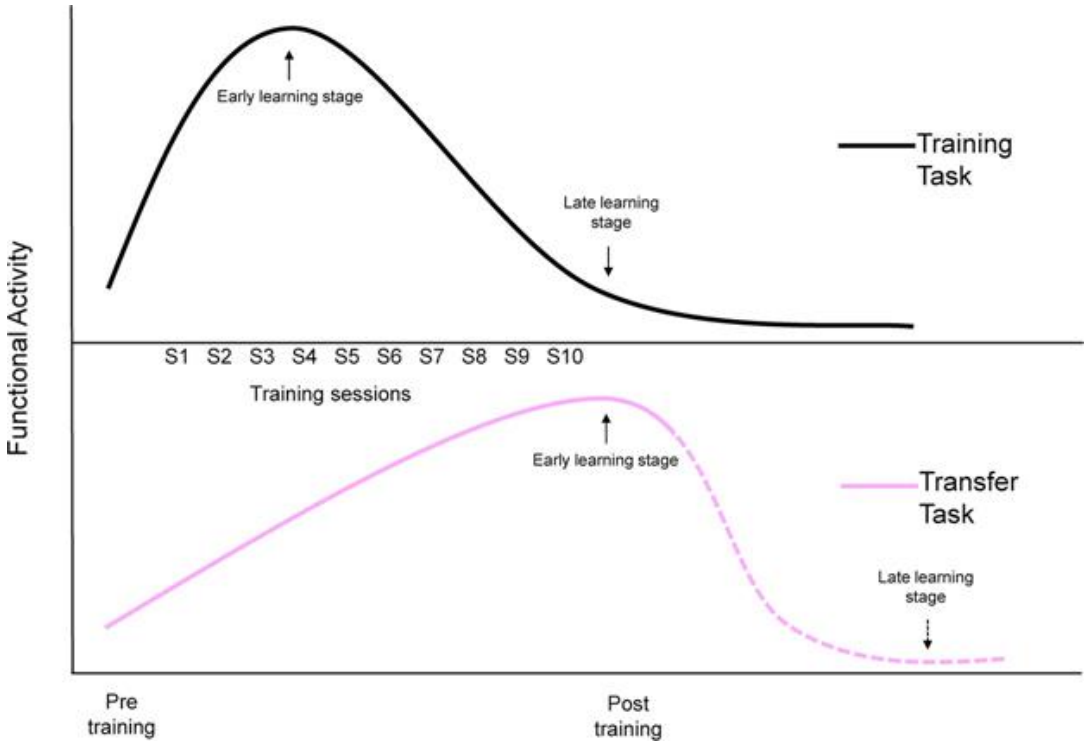

Figure 2.5.1: Schematic model for dynamic activity changes determined by repeated exposure to training and transfer tasks.

2.5.5 Other Neural Changes

Only three of the reviewed studies examined functional connectivity changes following WMU training, restricting the possibility of drawing definitive conclusions. Thompson, Waskom and Gabrieli (2016) reported connectivity increases within fronto-parietal ROIs for the training group, consistent with previous WM training literature (Jolles et al., 2013; Takeuchi et al., 2013). Finc et al. (2020) was the only study to conduct an extensive analysis on training-related functional connectivity modulations on large scale brain networks. Increased fronto-parietal and default mode system recruitment was reported post-training, while the integration between these two systems exhibited decreases post-training. Another interesting finding was a dynamic modulation of the integration between the subcortical and other systems. Decreases between the subcortical and default mode systems were reported at the early stages of training and increases post-training, while the exact opposite pattern was revealed for the integration between the subcortical and dorsal attention, ventral attention, cingulo-opercular and auditory systems, in that increases were reported at first and decreases at the end of training. Heinzel et al. (2014), on the other hand, did not find significant functional connectivity changes post-

training in the training group for any of the difficulty levels, however that null effect could be due to the lack of a training vs control group comparison.

We cannot draw conclusions on the structural changes taking place after WMU training, as from the seven relevant studies in this review, four constitute different analyses of the same dataset while the other three found no significant training-related changes in grey matter volume (Biel et al., 2020; Heinzel et al., 2014; Lawlor-Savage, Clark and Goghari, 2019), surface and thickness (Lawlor-Savage, Clark and Goghari, 2019). The studies by Colom et al. (2016a,b) and Roman et al. (2016) reveal an inconsistent pattern of grey matter changes where volume preservation in the training group was reported in bilateral temporal lobe in one study (Colom et al. 2016a) and an increase in volume in the right temporal lobe, left posterior cingulate cortex and right cerebellum in the other (Colom et al., 2016b). The only study examining structural connectivity reported an increase in a fronto-parietal network after WMU training (Roman et al., 2017), consistent with an earlier WM training study (Takeuchi et al., 2010).

2.5.6 Neurological Populations

Only a handful of the reviewed studies included neurological samples (Aguirre et al., 2019; Bonzano et al., 2020; Leung et al., 2014, 2016), thus making it difficult to draw solid conclusions. However, these studies provide promising results suggesting that adults who have sustained damage to the brain also seem to benefit from a WMU intervention and improve their cognitive performance on the criterion task. Furthermore, they exhibit training-related fronto-parietal decreases similar to those reported in healthy adult studies. Nevertheless, it is evident there is a need for additional neuroimaging studies with a pretest-posttest control group design examining the effects of WMU training in neurological disorders. The application of research findings in a clinical setting depends upon researchers designing and validating cognitive interventions with the objective to provide optimized and evidence-based training regimes for populations with cognitive impairments.

2.5.7 Summary

WMU training can significantly improve cognitive outcomes and produce moderate near transfer effects while there is currently no evidence for far transfer effects, consistent with previous reviews on WM training. The data included in this systematic review are indicative of publication bias, suggesting that studies with smaller samples exhibiting large training effects were more likely to have been published, which could potentially overestimate the overall effect size. Furthermore, WMU training effect sizes are significantly larger in studies comparing the training group to a passive control group than to an active control group. When comparing shorter versus longer training durations, there was a significant sub-group effect suggesting that longer duration produces a larger training effect, as suggested by von Bastian and Oberauer (2014). However, our results indicate that this is true only for passive control group comparisons, while the training effect size in active control group comparisons remains unchanged as the training hours increase.

Our review reveals a fairly homogeneous pattern in neural outcomes regarding the training-related changes in functional activity. We hypothesized that the consistency in fronto-parietal activity decreases is a sign of the prefrontal cognitive stability while the discrepancy in striatal changes is an indication of cognitive flexibility. We further propose that employing a highly targeted WMU task training protocol with adaptive difficulty can successfully trigger training-related changes in the brain's system, which is an indication of plasticity. Our results also support a fast-early and slow-late stage model of learning in cognitive training, following an initial increase and a subsequent decrease in fronto-parietal activity as hypothesized by Lustig et al. (2009). We further applied this learning model to explain the functional activity increases exhibited for transfer tasks post-training, suggesting the transfer activation profile is similar to that of the training task but slower, i.e., the response is lagged. This is the first review reporting consistent neural patterns of activation post-training and we attribute this to our inclusion of studies training the updating process of WM specifically.

2.5.8 Limitations

The reviewed studies are not standard randomized clinical trials, rather the majority are quasi-experimental cognitive training neuroimaging studies. Nevertheless, such experimental designs are standard practice in human neuroimaging research due to practical limitations involving costs, limited personnel and time constraints. Consequently, the methodological quality of the included studies based on the PEDro- P Scale was generally modest and thus the results should be interpreted with caution. At the same time, the neuroimaging methodological quality could not be similarly assessed due to the lack of a standard quality scale comparable to the PEDro-P.

Overall, there was a small number of included studies, due to our specific focus on neuroimaging studies with a pretest-posttest design targeting the WMU process exclusively in order to limit heterogeneity across studies. For the same reason, the small number of reviewed studies with transfer task data precluded a control group sub-group analysis on the transfer effect sizes. This would have the potential to reveal a significant difference between the active and passive control sub-groups and therefore clarify the mediators of far transfer. Similarly, our proposed interpretation of the functional activity changes in the transfer tasks following WMU training relies on a small number of studies and thus should only be considered speculative at this point and in need of testing with additional data. For the same reason, specific conclusions for studies assessing functional connectivity and structural imaging changes after WMU training could not be drawn.

There was also an overall lack of assessment on measures of everyday function in the reviewed studies and therefore we cannot be certain of the WMU training impact on daily living. Finally, the limited number of studies involving neurological populations makes it difficult to draw conclusions on WMU training efficacy in adults with brain damage or the impact on their ability to improve everyday functioning.

2.5.9 Conclusions

We conclude that WMU training can successfully promote plasticity under Lövdén's theoretical framework as exhibited by improved cognitive performance, near transfer of training gains and indirect alterations in the structure of the brain's system evidenced by fronto-parietal and striatal functional activity changes post-training. Neural changes associated with WMU training follow a fronto-parietal fast-early activity increase and a late-slow decrease, while those associated with transfer of training appear to follow the same pattern albeit with a lag. A cognitive training protocol targeting the WMU process specifically can successfully trigger the neural system's flexibility manifested by the involvement of the striatum which is considered a major subcortical node for updating. Cognitive training studies are recommended to compare the training intervention against active control groups and employ a highly targeted WMU training protocol.

Future studies should additionally examine changes in measures of the brain's functional connectivity and structure as well as include a third scanning point when possible, to improve our understanding of the neural mechanisms behind plasticity as well as the dynamic patterns of learning. Even though adding a third time-point in a longitudinal neuroimaging study can be quite challenging in terms of resources needed, evidence shows this can shed light into the dynamic patterns of neural modulation at distinct stages of training. There is no single right answer to the question of when the additional time point should be placed, as this is directly related to the specific research question the researcher wishes to pose. For example, in order to explore the plausibility of predicted functional activity increases early in training followed by decreases at later stages, then one would theoretically add a scanning session very early in the training period, e.g., after only a few hours of training. On the contrary, to examine whether the activation profiles for transfer tasks follow the same hypothesized inverted U-shape pattern as the training task, then the additional time-point would need to be placed after the end of the training period.

Finally, even though our interests include the cognitive and neural effects of WMU training in adults with neurological disorders, the small number of

relevant studies conducted in that population to date precluded our ability to draw any meaningful conclusions. A brief examination of initial reports, however, suggests there is a potential benefit. We would like to emphasize the imperative for further neuroimaging studies with a pretest-posttest control group design involving adults with brain damage. There is an urgent need to develop and validate training interventions for neurological populations in order to establish an optimal training protocol and ultimately translate research findings into a clinical setting.

3 Adaptive working memory updating training does not promote changes in grey matter volume.

In recent years, the behavioural and neural effects of cognitive training have been a focus of interest in the field of cognitive neuroscience. Process-based working memory training has been studied extensively due to the importance of working memory in complex cognitive tasks and goal-directed behaviours. Disproportionately more studies, however, investigate the training-related changes in functional patterns of brain activity compared to changes in functional connectivity or brain structure. The present study extends the work of Flegal, Ragland and Ranganath (2019) by focusing on grey matter (GM) volume changes following ten sessions of working memory updating training in healthy young adults. Three scanning sessions at different time points enabled longitudinal analysis of structural changes. Both whole-brain and a-priori region of interest analyses did not show evidence of any training-related volumetric changes. Furthermore, there was no relationship between training gains in the experimental group and post-training GM volume. Future research on cognitive training should focus on employing complementary, multimodal analyses on the same dataset to investigate plastic changes in greater depth.

Keywords: cognitive training; grey matter changes; voxel-based morphometry; working memory training; plasticity

3.1 Introduction

Cognitive training research has expanded considerably in recent years with researchers focusing on various cognitive processes and employing a plethora of training protocols (Hill et al., 2017; Karbach and Schubert, 2013; Kelly et al., 2014; Lampit et al., 2014; Melby-Lervåg and Hulme, 2013; Nguyen et al., 2019; van Balkom et al., 2020). A number of studies have examined whether signs of neural plasticity can be detected non-invasively by measuring training-related changes in the human brain's structure and function (Bäckman et al., 2011; Buschkuehl et al., 2014; Dahlin et al., 2008; Kühn et al., 2013; Lampit et al., 2015). Signs of neural plasticity could involve changes in: 1. the structure of the brain e.g., tissue volume, cortical thickness, 2. the molecular scale, e.g., receptor density, and/or 3. the function of the brain, e.g., changes in activation and connectivity patterns. Cognitive neuroscientists employing neuroimaging methodologies have demonstrated that training programmes targeting core cognitive processes can successfully drive neural changes in healthy adults (Hsu, Novick and Jaeggi, 2014; Klingberg, 2010). The present work investigates effects of working memory (WM) training, which has been a highly popular target for process-based training (Brehmer et al., 2014; Wiemers, Redick and Morrison, 2019) due to the involvement of WM in complex cognitive tasks and goal-oriented behaviour, its role in the regulation of executive process and association with other cognitive constructs such as language comprehension and fluid intelligence (Wiemers, Redick and Morrison, 2019).

Most neuroimaging studies of WM training to date have employed functional MRI (fMRI) analysis to explore functional activity changes induced by WM training (Clark, Lawlor-Savage and Goghari, 2017; Dahlin et al., 2008; Finc et al., 2020; Flegal, Ragland and Ranganath, 2019; Heinzel et al., 2016; Kuhn et al., 2013; Miro-Padilla et al., 2018). Despite the plethora of WM training studies with fMRI outcome measures, the nature and direction of activity changes following training are not consistent (Pappa et al., 2020). However, by narrowing the meta-analytic focus solely to the core cognitive process of WM updating (WMU), a more homogeneous pattern of activity reductions following training has been identified (Pappa et al., 2020). Meanwhile, other neuroimaging analyses to evaluate training-related changes in functional connectivity or

structural anatomy (morphometry) measures are much less frequently used. For example, a recent review was unable to draw conclusions on changes in the brain's structure following WMU training due to the small number of studies eligible for inclusion and the differences in the methods employed (Pappa et al., 2020).

Various morphometry methods can be used to perform computational analyses of brain anatomy, including: 1. Voxel-based morphometry (VBM), i.e., voxel-wise estimation of tissue volume, 2. deformation-based morphometry (DBM), i.e., identification of macroscopic anatomical differences, 3. surface-based morphometry, i.e., estimation of cortical thickness and central surface area of both hemispheres, and 4. diffusion tensor imaging (DTI), estimation of overall magnitude of water diffusion and fractional anisotropy. Naturally, the choice of method primarily relies upon the specific research question; VBM, however, has been the most popular method of computing volumetric changes in brain tissues to date (Mills and Tamnes, 2014), i.e., grey, and white matter, (Ashburner and Friston, 2000); in longitudinal studies (Ashburner and Ridgway, 2013).

VBM has been extensively employed in the broader field of research on neural plasticity investigating the structural changes occurring as a result of skill expertise, e.g., musicians, dancers etc., or new skill acquisition through repeated practice. For example, Maguire et al. (2006) found enlarged regions in the posterior hippocampus of London taxi travers when compared against London bus drivers. Draganski et al. (2004) reported significant grey matter volumetric changes in a group of healthy adults after three months of practicing juggling, compared to a non-jugglers control group. Grey matter volumetric changes have also been identified after three-month intense language learning (Mårtensson et al., 2012) and a year of moderate intensity physical exercise (Erickson et al., 2011).

Focusing on the field of WM training, however, to our knowledge only six published studies have examined training-related grey matter (GM) volumetric changes in healthy adults (Biel et al., 2020; Colom et al., 2016a;2016b; Heinzel et al., 2014; Miró-Padilla, Bueichekú and Ávila 2020; Takeuchi et al., 2011).

Some reported null results (Biel et al., 2020; Colom et al., 2016a; Heinzel et al., 2014; Takeuchi et al., 2011) while one study found reduced GM in the temporal lobe after training (Colom et al., 2016a). Others have found increased GM volume in temporal lobe, cerebellum, and posterior cingulate cortex (Colom et al., 2016b), while the most recently published study found GM increase in the right superior parietal cortex and GM decrease in the right putamen (Miró-Padilla, Bueichekú and Ávila, 2020). It is important to note, however, that two of the studies reporting significant findings (Colom et al., 2016a;2016b) come from the same dataset (Colom et al., 2013). The small number of studies examining GM volumetric changes along with their mixed results makes interpreting the nature and direction of those changes extremely difficult; therefore, this unexplored and neglected training-related area is extremely relevant.

The present study focused on GM volume changes following ten sessions of WMU training in healthy young adults. During the three-week training period there were three scanning sessions (pre-training; after two days of training; post-training) enabling longitudinal analysis of structural brain changes. This analysis is an extension of the study by Flegal, Ragland and Ranganath (2019) which examined changes in cognitive performance and functional activity following a well-controlled WMU training protocol in which the difficulty of practiced tasks either adaptively increased in response to performance or was fixed. Flegal, Ragland and Ranganath (2019) reported significant performance improvements for the adaptive training group compared to fixed-difficulty controls, on a WMU criterion, i.e., trained, task and an untrained episodic memory task. The fMRI data analysis exhibited greater post-training reduction in functional activity for the adaptive training group in a-priori defined regions of interest (ROI) of bilateral caudate, bilateral hippocampus and bilateral putamen. At the whole-brain level, greater BOLD reductions were identified for the adaptive training group in bilateral prefrontal, bilateral temporal, left parietal regions and bilateral striatum, consistent with the ROI analysis.

Further to these findings of adaptivity-related effects of WMU training on functional activity, as a secondary analysis the present study examined whether structural changes in GM volume occurred following WMU training. We

hypothesized there would be greater GM volumetric changes for the adaptive training group compared to fixed-difficulty controls following training. We additionally explored the relationship between structural brain changes and changes in cognitive performance after training and predicted significant correlations for the adaptive training group.

3.2 Methods

3.2.1 Participants

Healthy young adults were randomly assigned to two groups: adaptive training (AT) group (N = 26) and non-adaptive (NA) active control group (N=19). Following initial enrolment, two participants from the AT group withdrew prior to study completion whilst another five participants in the AT group were excluded from analysis due to lack of training improvement. Participant training gain in this group was measured with the linear slope calculated from the maximum level of performance achieved at each training session. These five participants exhibited negative training slope either for one or both training tasks and, due to the adaptivity being the key manipulation in the present analysis, they were excluded from the analysis. The final sample included N=38 participants (mean age = 20.55, SD = 2.37), AT group (N =19) and NA active control group (N=19). Participants were native English speakers with no history of neurological or psychiatric disorders and no known MRI contraindications. All participants gave informed consent and received payment for their participation. Compensation was $10 for each training session, $20 for each MRI session and an additional $50 if all study visits were completed. This research was conducted at the University California at Davis (UCD) and was given UCD Institutional Review Board approval. The primary analysis of this dataset examined adaptivity-related fMRI activation changes (Flegal, Ragland and Ranganath, 2019); further study design and procedure details can be found in this report.

The primary analysis of this dataset examined adaptivity-related fMRI activation changes (Flegal, Ragland and Ranganath, 2019); further study design and procedure details can be found in this report.

3.2.2 Training tasks

Both AT and NT groups completed 10 training sessions with two different tasks involving the WMU process, presented in different modalities: 1. visuospatial Matrix Updating (MU) and 2. verbal Keep Track (KT). Task administration and response recording was conducted with Presentation software (Version 14.9, www.neurobs.com).

The MU task requires updating the location of four coloured dots presented on a 4 x 4 grid (Chen and Li, 2007). In each trial the four coloured dots first appear on the screen followed by coloured arrows (pointing up, down, left, or right). The participants had to mentally move the coloured dots around the grid in the direction indicated by the colour-corresponding arrows. After a variable number of arrows, a coloured pointer would appear at the centre and participants were probed to respond by moving the pointer to the current location of the dot of that same colour. During each training session, participants performed the MU task for approximately 25-30min with five trials in each task block.

The KT task involves updating the identity of the most recently presented word from a series belonging to four semantic categories (Yntema, 1963). In each trial, the four categories were presented in boxes at the bottom of the screen and words from these categories appeared one at a time. Participants had to mentally assign each word to one of these categories, and after a variable number of words one of the category boxes was highlighted to prompt the participant to respond by typing the last presented word belonging to that category box. Four novel categories and related word lists were created for each of the training sessions and task duration on each occasion was 20-25min.

The choice of tasks was specifically targeting the WMU process while ensuring WM load remained constant, i.e., always four dots for MU and four categories for KT. For the AT group, the difficulty level of both training tasks dynamically adjusted based on the participant's performance while in the NA control group, difficulty was set at a fixed low level. The update level was adaptively adjusted according to the individual's performance on the final block

of the previous training session. If participants answered at least four trials correctly, i.e., 80% accuracy criterion after every five trials; then the update level would increase by one in the next five trials, alternatively the update level would decrease. For an extended training task description and protocol details please see Flegal, Ragland and Ranganath (2019).

3.2.3 Design, Procedure and MRI acquisition

Study participation involved twelve visits in total over a three-week period (Figure 3.2.1). MRI scanning sessions were conducted with a 3T Siemens Skyra at the University of California Davis (UCD) MRI Facility for Integrative Neurosciences, at three time points over the training period: pre-training, early training, and post-training. Behavioural data from the scanned tasks were collected using Presentation (www. neurobs.com) and E-Prime (Psychology Software Tools, Pittsburgh, PA). High-resolution T1-weighted anatomical images were acquired using an MP-RAGE sequence (TR = 1800 ms; TE = 2.96 ms; flip angle = 7° ; FOV = 256 mm; 256 x 256 matrix) at the end of each scanning session. One participant did not have an anatomical image acquired at Time 2. Participants in both AT and NA groups completed ten sessions of WMU training (a total of 8.33 training hours, 45-55min per session). Please refer to the published report by Flegal, Ragland and Ranganath (2019) for further details.

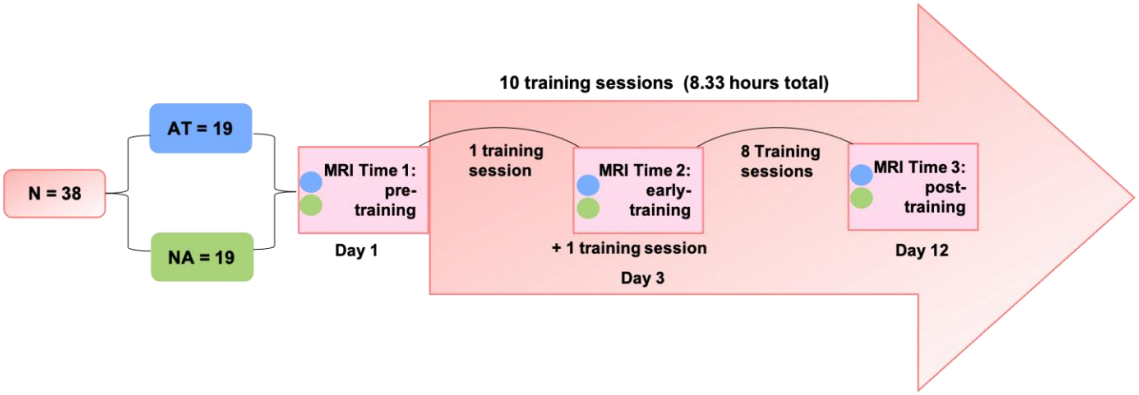

Figure 3.2.1: Twelve study days in total, including three MRI sessions and ten training sessions spaced out over a three-week period. AT: adaptive training (experimental group), NA = non-adaptive (active control group).

3.2.4 VBM pre-processing

Following a preregistered protocol published in open science framework (osf) (Pappa, 2020)[3], a voxel-based morphometry (VBM) analysis was conducted to test for longitudinal training-related GM volume changes between the two groups. The VBM analysis was performed using CAT12 (Gaser and Dahnke, 2016) for SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) in the MatLab environment (www.mathworks.com). The researcher conducting the analysis (KP) was blind to group allocation throughout the analysis process.

Before any processing took place, the T1-weighted anatomical images for all three time-points across participants were re-oriented to define the anterior commissure (AC) as the common point of origin in all images. A standard pre-processing procedure as per CAT12 manual guidelines was conducted using the longitudinal study design *segment mode* and selecting the optimised model to detect small changes, e.g., learning effects or brain plasticity, and applying default CAT12 parameters. The steps were: 1. inverse consistent rigid registration to the mean image for all participants' T1-weighted images across time-points including bias-correction between time points, 2. registration to a standard template taken from the International Consortium of Brain Mapping (ICBM) for European brains, 3. intra-subject realignment and segmentation into the different tissue types, i.e., grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) across time points, 4. estimate and average of deformation fields using non-linear spatial registration, employing the optimised Geodesic Shooting template, 5. application of mean deformation to the segmented tissues for each participant across time-points and modulated with Jacobian determinant. Additionally, the mean GM values inside six *a priori* Regions of Interest (ROI), described below, were estimated in their native space prior to normalisation and extracted for each participant across sessions using the Neuromorphometrics atlas[4] (Worth and Tourville, 2015). Following the segmentation process, the total intracranial volume (TIV) was estimated for all

[3] Pappa, K. (2020, November 13). Does working memory updating training induce grey matter changes? https://doi.org/10.17605/OSF.IO/8RJ75

[4] http://Neuromorphometrics.com/

participants across the three time-points and a data quality check was performed using CAT12 to inspect homogeneity of the segmented GM tissue across participants. Finally, the modulated segmented images were spatially smoothed using an 8-mm FWHM Gaussian kernel.

3.2.5 Analysis

For a primary whole-brain analysis, the significance threshold was set at $p < .05$ FWE corrected at the cluster level, with a voxel-level primary threshold of $p<.001$. Corrections based on the threshold-free cluster enhancement (TFCE) method (Smith and Nichols, 2009) were also estimated. This method is advantageous since the statistical analysis stems from a combination of local significance and spatial extent of the effect, thus making it more objective than an arbitrary cluster-forming threshold (Kurth and Luders, 2015). A flexible factorial model with the factors: *subject, group* (two levels: AT, NA), *time* (three levels: time 1, time 2, time 3) and co-variates of no interest, TIV and age, was estimated to examine differences in longitudinal changes between the two groups as per CAT12 manual guidelines. The main effect of subject, and time by group interaction were included in the model as per CAT12 manual.[5]

For an exploratory ROI-focused analysis, we inspected six a-priori structural ROIs: caudate, hippocampus and putamen all bilaterally, in which group differences were found in fMRI data as reported in Flegal, Ragland and Ranganath (2019). Mean GM volume for each ROI was entered as the dependent variable in an analysis of variance (ANOVA) model with group (AT, NA) as the between subject factor, time (time 1, time 2, time 3) as a within subject factor and an error term (model = aov (ROI ~ Group*Time + Error(Subject)). ANOVA analyses were conducted using the aov function in 'lme4' package (Bates et al., 2015) as implemented in R (R Development Core Team, 2020).

A training slope variable, indicating the relative amount of improvement on the trained tasks for each AT participant, was computed by averaging the linear slopes calculated from the maximum difficulty level achieved for each task at each training session. Pairwise partial correlations were then conducted

[5] http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf .

to investigate the relationship between the AT training slope and mean GM volume for each ROI while controlling for baseline GM volume in that ROI. This analysis was conducted in SPSS (IBM Corp., 2020).

3.3 Results

3.3.1 Whole brain

A *Group by Time* interaction analysis found no significant effects, for either the cluster-corrected results or the TFCE-corrected permutation test results. However, an exploratory non-parametric t-test revealed one significant cluster located in L cerebellum for an interaction effect contrast between time and group (Time 3 > Time 2 and NA > AT) (T=5.09; p = 0.014, FWE-cor; k = 9; x =-19.5, y = -37.5, z =-22.5). No significant main effects of group or time were found for either the cluster-corrected results or the TFCE-corrected permutation test results. A t-test comparing groups at the pre-training timepoint confirmed there were no significant GM baseline differences.

3.3.2 Region Of Interest (ROI)

Since no significant clusters were identified in the whole-brain VBM analysis, we additionally conducted an exploratory ROI-focused analysis to ensure the cluster-corrected threshold did not miss any smaller region-specific effects in bilateral caudate, hippocampus and putamen. However, no significant *Group by Time* interaction effects were found in mean GM volume for any of the selected ROIs, nor main effects of group or time. Finally, a pairwise partial correlation analysis did not reveal a significant relationship between training gains in the AT group and post-training GM volume, controlling for pre-training GM volume, in any of the selected ROIs.

3.4 Discussion

The primary aim of the present study was to investigate structural changes in GM volume from three structural brain scans across ten sessions of WMU training. We predicted greater GM volumetric changes for the adaptive training group compared to non-adaptive controls. Nevertheless, our VBM

analysis showed no evidence of training-related changes in GM volume between the two groups at a whole-brain level. An exploratory non-parametric t-test, however, revealed one significant cluster located in the left cerebellum exhibiting a greater increase in GM volume from early-training (i.e., time 2) to post-training (i.e., time 3) scanning sessions for the NA group than the AT group. Even though employing a TFCE method is considered advantageous due to the combination of local significance and spatial extent of the effect, compared to the traditional cluster-forming threshold (Kurth and Luders, 2015), this result should be interpreted with caution. This finding is not hypothesis driven since prior research in the area has not identified the left cerebellum as relevant to adaptivity-related WMU training effects and therefore, the observed effect may be spurious.

We further conducted an exploratory analysis focused on a-priori ROIs in the bilateral caudate, putamen and hippocampus regions in which significant group differences were previously found in an fMRI analysis (Flegal, Ragland and Ranganath, 2019). Once again, we did not find evidence of training-related changes in mean GM volume between the two groups in any of the pre-selected ROIs. We additionally investigated the relationship between post-training mean GM volume and behavioural training gains for the AT group whilst controlling for pre-training GM volume, and the results proved non-significant for all pre-selected ROIs. Overall, our findings suggest that ten sessions of adaptive WMU training do not promote changes in GM volume in a group of healthy young adults.

Even though the present findings are in line with other studies suggesting no evidence of WM training-related GM volumetric changes, there are a few limitations to consider. This analysis was conducted on a very well-controlled experimental study with both experimental and active control groups engaging in a challenging WMU training protocol. The only difference between groups was the manipulation of training task difficulty, which in the experimental group adaptively increased based on participants' performance, whilst in the control group it was fixed at a relatively low level throughout the training period. This experimental design was chosen in order to isolate adaptive task difficulty as a

factor predicted to influence efficiency of task-related brain activity, hence VBM analysis of structural brain images was not the intended study focus.

The present study had the advantage of collecting neuroimaging data at three time points, i.e., pre, early-, and post- training, for both groups. According to Strobach et al. (2016) complex study designs with a minimum of three measurement time-points are necessary to eventually gain deeper knowledge into the mechanisms of neural plasticity and its temporal dynamics in cognitive training. In fact, Lindenberger and Lövdén (2019) specifically suggest that multiple sessions of structural imaging should take place to capture the dynamic process of plasticity as well as adequately cover the early, middle and late phases of training related changes.

Wenger, Brozzoli, et al. (2017) describe how the *expansion-renormalisation* model for plastic changes established in animal model and human developmental research can facilitate our understanding of structural brain plasticity and its temporal dynamics. The model predicts an initial increase in GM, potentially reflecting an overall increase in neural resources, i.e., *expansion,* which is followed by a selection process resulting in complete or partial return to baseline in overall volume, i.e., *re-normalisation*. Potential mechanisms accounting for gray matter volume changes include neurogenesis, synaptogenesis and gliogenesis (Zatorre, Fields & Johansen-Berg, 2012). Building upon evidence from animal work, Wenger, Brozzoli, et al. (2017) describe how the underlying cellular changes hypothesised to accompany gray matter changes, take place throughout the learning period. In the case of neurogenesis, the neuronal progenitor cells are thought to initially proliferate with some cells subsequently undergoing apoptosis. Most of the new cells die during the neuronal differentiation, migration, and maturation and only some survive. It should be noted that evidence for adult neurogenesis in humans is restricted to the region of hippocampus (Zatorre, Fields & Johansen-Berg, 2012; Wenger et al., 2017). Similarly, in the case of synaptogenesis, the number of synapses increases during the early phases of learning through dendritic branching and axonal sprouting but then returns to baseline. Importantly, the process of pruning, i.e. the elimination of dendritic branches, axonal projections and synaptic connections, together with synapse stabilisation leads to effective

neural rewiring. Gliogenesis follows the same pattern where glial cells proliferate and shift from a resting to an activated state early on and subsequently return to a resting state at the late phase of learning.

Findings in support of this model in humans come from the motor learning literature and also seem to hold true across various spatial extensions and plasticity timescales (Wenger, Brozzoli, et al., 2017). It is based upon studies investigating changes in brain structure following balance training in dancers (Taubert et al., 2010, 2016) and left-hand writing and drawing skill acquisition (Wenger, Kühn, et al., 2017). If we assume that any potential structural plastic changes emerging from cognitive-process training can be explained using the *expansion-renormalisation* model, then in the current study we would anticipate an initial increase in grey matter volume between pre-training and early training and a subsequent (partial) return to baseline between early training and post-training. Therefore, we would not expect group differences between pre and post training. Instead, we would hypothesise any potential differences to be between the pre training and early time points and/or between early and post-training. However, even though significant training-related functional plastic changes were reported between pre and post training in a previous ROI analysis of fMRI data from the current study (Flegal, Ragland and Ranganath, 2019), no structural GM changes were detected in the present analysis. We suggest a few potential explanations taking into consideration the overall training protocol in other studies exploring training related structural plastic changes. These include the type of control group, and training features such as the training task itself, the task modality, the training duration, and the adaptivity of training task difficulty. Due to the variability in WM training protocols across studies (Pergher et al., 2020), drawing conclusions on an optimal training protocol most likely to produce plastic changes can be challenging.

The choice of control group (CG) in WM training studies – and its effect on the observed training-related changes in cognitive performance – is a longstanding debate, with some authors arguing that a passive CG overestimates the training-related effects (Dougherty, Hamovitz and Tidwell, 2016; Melby-Lervåg, Redick and Hulme, 2016), and others suggesting that choosing between an active and passive CG does not influence the results (Au et al., 2015; Soveri

et al., 2017). One could argue that in the present study employing an active CG engaging in a challenging WMU protocol may have influenced the detection of training-related structural brain changes. Consequently, when comparing the experimental group against an active control, any existing group effects are expected to be modest. This was not the case in the present study however, where group differences were not detected at all. On the contrary, previous WM training studies reporting significant volumetric differences between groups, employed a passive CG (Colom et al., 2016a;2016b; Miró-Padilla, Bueichekú and Ávila, 2020). Employing an adaptive non-WM training regime for an active CG might be a more suitable alternative to detect plastic structural changes resulting from WMU training specifically.

In the current study, participants received cross-modal WMU training (i.e., they trained on both visuo-spatial and verbal updating tasks) and they engaged in ten training sessions, roughly equal to eight hours of training, spaced over three weeks. One explanation for null results in VBM analysis could be the training duration is too short to produce structural changes in the brain. Most previous studies reporting volumetric changes following skills acquisition training, e.g., juggling training (Draganski et al., 2004); left-hand drawing and writing (Wenger, Kühn, et al., 2017) employed protocols with longer durations of more than 7 weeks. Another explanation could be that the specific WMU task protocol used by Flegal, Ragland and Ranganath (2019) simply does not promote volumetric plastic changes even though it does produce functional activity changes. In a study by Belleville et al. (2014), older adults were assigned into three groups, and each received distinct attention training task protocols. The functional activations post-training were notably different across the three training groups, where one type of training exhibited reduced functional activity post-training while another resulted in increased recruitment of regions in the right middle frontal gyrus. In our study, it could be that this specific WMU training program does not promote GM volumetric changes while employing a different protocol might have exhibited training-related structural brain changes as in previous studies (Colom et al., 2016a;2016b; Miró-Padilla, Bueichekú and Ávila, 2020).

This point illustrates the challenges of comparing across studies and research groups in the working memory training field (Pappa et al., 2020; Pergher et al., 2020). The variety of protocols makes it practically impossible to differentiate between the training protocol-specific effects and the training process-specific effects. Even though all three of the previous studies reporting GM volumetric differences employed an n-back training protocol (Colom et al., 2016a;2016b; Miró-Padilla, Bueichekú and Ávila, 2020), the tasks were presented in different modalities, i.e., auditory, visual, and verbal. In addition, one study used single n-back (Miró-Padilla, Bueichekú and Ávila, 2020), whilst the other two studies came from the same dataset using a dual n-back training paradigm (Colom et al., 2016a;2016b). Between these three studies, a mix of post-training GM volume increases and decreases were reported. Finally, it is notable that there is no consensus on the broader literature of training related structural brain changes, where mixed effects are reported across studies employing physical exercise (Hvid et al., 2021) and cognitive training (Nguyen et al., 2019; ten Brinke et al., 2017) paradigms.

Another explanation for the null findings in the present study could simply be the fact that VBM is not sensitive enough to detect microstructural changes following completion of a relatively short cognitive process-based training protocol. Some researchers have argued that the cognitive training literature has relied heavily on VBM methodology which has proven instrumental in advancing the field, but also comes with certain disadvantages (Bookstein, 2001; Davatzikos, 2004; Lövdén et al., 2013; Thomas and Baker, 2013). Lindenberger and Lövdén, (2019) further argued that VBM does not provide a deeper insight into the nature of training-related volumetric changes. On the contrary, myelinated cortical imaging techniques give information on the associated myelination changes taking place (Rowley et al., 2015; Waehnert et al., 2014), which in turn might prove more sensitive and thus yield a greater understanding of those training-related structural changes (Lindenberger and Lövdén, 2019).

The underlying cellular mechanism associated with training-related gray matter volume changes would most likely involve a complex mixture of changes across the different cell types (neurogenesis, changes in synapses, dendritic branching and axon sprouting, changes in glial number and morphology), thus

making it impossible to identify a specific cellular process with VBM. In addition, the interactions taking place between changes in neurons and glial cells during the learning period cannot be considered in isolation due to the tight link between these two cell types. Neurons and glial cells interact and communicate through various pathways in both gray and white matter tissue (Zatorre, Fields & Johansen-Berg, 2012). Therefore, a multimodal imaging approach in human studies would substantially increase the likelihood of discriminating between the specific cellular changes taking place throughout the learning period as well as their relationship with behavioural improvement.

Finally, investigating training-related volumetric changes is especially relevant for interventions aiming to remediate impaired cognitive function resulting from neurological injury or ageing-related decline. In these cases, preventing and/or delaying the brain's structural decline is especially relevant (Lindenberger and Lövdén, 2019), and therefore, longitudinal maintanance of brain volume could in fact be indicative of cognitive plasticity (Lövdén et al., 2013). A previous fMRI analysis on the dataset analysed in this study reported significant training-related functional activity changes accompanied by improved performance (Flegal, Ragland and Ranganath, 2019), although our volumetric analysis in the present study did not exhibit corresponding GM changes post-training. It may be that improved cognitive performance arises from more effective, or efficient, use of existing tissue overall rather than changes in the brain's volume per se. Consequently, improved cognitive function accompanied by changes in functional patterns of activation, in addition to preservation/maintenance of existing grey matter volume, could theoretically provide evidence for plasticity following brief cognitive training interventions.

However, the discrepancy between the existence of training related functional activity changes, and the absence of volumetric changes, in the same dataset, strengthens the argument that additional complementary analyses should be employed to further delineate the mechanisms of neural plasticity. Thus, a shift from exploring changes in the microstructure level to the functional and/or structural network level may shed further light on mechanisms of training-induced plasticity. Future neuroimaging research should focus on employing complementary, multimodal analyses on the same dataset to

investigate training-related plastic changes in greater detail. This could involve performing functional activity analyses and functional connectivity analyses, in addition to employing methods of analysing structural morphometry, connectivity and cortical myelination.

4 Differential patterns of functional connectivity changes following adaptive working memory updating training.

The present study investigated the pattern of task-based functional connectivity changes taking place following a WMU training protocol in healthy young adults. Both experimental and control groups practiced a visuospatial and a verbal WMU task over ten training sessions. Level of difficulty was dynamically adjusted for the experimental group whilst remained at a fixed level for the control group. fMRI data were collected at three time-points, i.e., pre-, early- and post-training, with participants' performance assessed on the trained criterion task and an untrained transfer task. A-priori we selected six subcortical seed regions of interest (ROIs) and performed functional connectivity analyses to investigate the training-related changes occurring for the criterion and transfer tasks. Our results showed differential patterns of functional connectivity changes for the criterion and transfer tasks, with decreases in connectivity associated with both tasks after the pre-training time point and increases evident only for the transfer task and only at the early–training time point. Connections from seed ROIs to frontal regions were found only for the transfer task throughout the training period whilst the criterion task exhibited connectivity re-organisation associated with the left putamen, involving early connections with the limbic system and subsequent connectivity with lateral occipital areas. No significant effects of group on task performance were identified for either of the scanned tasks. We interpret the lack of significant group effects together with the connectivity changes resulting from adaptive training as an indication of the neural system's flexibility, subsequently leading to neural changes but not successfully producing a plastic change in the system's pre-existing ability. Further neuroimaging research should focus on subcortical areas and employ training protocols which adequately isolate the cognitive process targeted for training.

Keywords: cognitive training; functional connectivity; task fcMRI; working memory training; plasticity

4.1 Introduction

In recent years cognitive neuroscientists have been particularly interested in assessing the experience-induced plastic neural changes following cognitive training. After earlier research demonstrating changes in behavioural performance induced by training strategies and cognitive processes, a plethora of studies have focused on various cognitive domains and employed a range of protocols (Karbach and Schubert, 2013; Melby-Lervåg and Hulme, 2013; Kelly et al., 2014; Hill et al., 2017; Nguyen, Murphy and Andrews, 2019; van Balkom et al., 2020). Neuroimaging methodologies have been frequently employed to investigate whether training-related changes are detectable (Dahlin et al., 2008; Bäckman et al., 2011; Kuhn et al., 2013; Buschkuehl et al., 2014; Lampit et al., 2015) with researchers successfully demonstrating that process-based cognitive training can induce neural changes in healthy populations (Klingberg, 2010; Hsu, Novick and Jaeggi, 2014; Pappa et al., 2021). These neural changes could manifest as alterations in: 1. brain structure, e.g., tissue volume, 2. molecular structure, e.g., receptor density and 3. brain function, e.g., functional activity and connectivity.

Training protocols targeting working memory (WM) processes have been particularly popular due to the WM system's involvement in goal-oriented behaviour, executive processes, and its links to general intelligence (Brehmer et al., 2014; Wiemers, Redick and Morrison, 2019). Functional MRI (fMRI) analyses on WM training-related changes in the brain's function have been most frequently conducted in healthy adult studies (Dahlin et al., 2008; Schneiders et al., 2012; Kuhn et al., 2013; Heinzel et al., 2016; Clark, Lawlor-Savage and Goghari, 2017; Miro-Padilla et al., 2018; Flegal, Ragland and Ranganath, 2019), with researchers reporting a mixture of activity decreases and increases in fronto-parietal and striatal areas following WM training. Drawing robust conclusions on the direction of the activity changes following WM training has been challenging due to the plethora of research protocols and task-specific features across studies (Baykara et al., 2020; Pergher et al., 2020; Pappa et al., 2021).

Regardless of the training protocol-specific features (e.g., process targeted, training task, modality, training duration etc.), however, most WM

researchers investigate the training-related effects as evidenced by outcomes on two tasks, 1. criterion and 2. transfer. The criterion task assesses performance change on the task participants trained on, whilst the transfer task assesses performance change on an untrained task, i.e., transfer of learning and generalisation. Transfer can be further subdivided to near transfer, i.e., transfer of learning to an untrained task of the same trained domain but still different to the criterion, and far transfer, i.e., transfer of learning to an untrained task of a different cognitive domain such as general intelligence. Some authors have presented findings supporting the idea of far transfer (Au et al., 2016) and others argue there is no compelling evidence for the existence of far transfer (Melby-Lervåg, Redick and Hulme, 2016; Soveri et al., 2017). Delving into the specifics of this debate, however, is beyond the scope of the present study but are discussed in chapters two and five.

In the fMRI literature researchers similarly assess training-related neural changes as evidenced by functional activity associated with the criterion and transfer tasks, although the focus has been almost exclusively directed towards training-related functional activity changes on the criterion task with little or no interest on the transfer task following WM training. Our recent meta-analysis focusing on WM updating as the trained process, however, concluded a relatively homogeneous pattern of post-training functional activity decreases in fronto-parietal regions whilst both increases and decreases were reported for striatal structures (Pappa et al., 2020). We further examined the pattern of functional activity changes for transfer tasks and found post-training activity increases were most consistently reported in the frontal and striatal regions.

Contrary to the plethora of fMRI studies investigating functional activity changes following WM training, functional connectivity analyses have been employed much less frequently. According to (Friston, 1994) *"Functional connectivity is defined as the temporal correlations between spatially remote neurophysiological events",* which in simpler terms means that when BOLD signal changes in two brain regions are statistically correlated with each other, it is presumed they belong to the same network. So, if reduced activity in one area is significantly correlated with reduced activity in another area, then these regions exhibit functional connectivity. It should be noted however that this does not

provide any information on the causal link nor on the direct connection between them; this connectivity could instead be mediated by other structures passing information from one area to the other. Therefore, performing functional connectivity analyses is a rather complex endeavor because the concept itself is very broad and can also be approached with various possible methodologies. With fMRI data, functional connectivity can be measured during a task-free resting state as well as in task-specific experimental paradigms and once again there are various connectivity measures to choose from: 1. seed-based measures which examine the connectivity patterns with an a-priori seed or region of interest (ROI), 2. ROI-to-ROI measures which examine the connectivity between all ROI pairs among a set of a-priori defined regions, 3. graph measures (ROI level) which are based on nondirectional graphs with nodes defined as ROIs, and edges defined as supra-threshold connections (Whitfield-Gabrieli and Nieto-Castanon, 2012). These are a just few examples of the existing connectivity measures.

In the field of WM training research, both resting-state and task-specific functional connectivity analyses have been conducted but thus far there are only a handful of published studies (Jolles et al., 2012; Takeuchi et al., 2013; Heinzel et al., 2014; Thompson, Waskom and Gabrieli, 2016; Finc et al., 2020). Researchers have mainly concentrated on fronto-parietal, default mode and attention networks and most frequently selected frontal seed ROIs such as dorsolateral prefrontal cortex (DLPFC) and medial PFC. This is not unexpected considering the very well-established WM fronto-parietal network involving the DLPFC, precentral gyrus, superior and inferior parietal lobules (Nee et al., 2013; Salmi et al., 2018). Due to the various study-specific approaches, drawing conclusions on the nature of the WM training-related functional connectivity changes has been challenging (Pappa et al., 2020; Pergher et al., 2020). Nevertheless, the connectivity studies focusing on frontal seeds reported post-training connectivity increases (Jolles et al., 2013; Takeuchi et al., 2013; Thompson, Waskom and Gabrieli, 2016) or null results (Heinzel et al., 2014).

Despite well-documented connections between frontal regions and the dorsal striatum (caudate nucleus and putamen) (Emch et al., 2019; Frank et al., 2001; Salmi et al., 2018; Wager & Smith, 2003), and reported training-related

functional activity changes in the striatum as well as its hypothesized role in mediating transfer of learning (Dahlin et al., 2008, 2009; Kühn et al., 2013; Salminen et al., 2016), no striatal seed ROIs have been selected in WM training studies investigating functional connectivity changes. A study by Finc et al., (2020) is unique in the WM training field as to our knowledge it is the only one investigating training-related network dynamics also including subcortical regions and performed more than two fMRI scan sessions. Participants completed eighteen 30-minute-long training sessions involving a dual n-back task paradigm and participated in four fMRI scanning sessions over a six-week study period. Analysis of the fMRI data followed a parcellation approach dividing the whole-brain into hundreds of ROIs comprising six large-scale systems, i.e., default-mode (DM), frontoparietal (FTP), salience (SA), dorsal attention (DA), cingulo-opercular (CO), and subcortical (SUB). This approach enabled delving into the pattern of integration between and within systems inclusive of subcortical ROIs. The authors observed decreases in integration between the default mode and subcortical systems early in the training followed by subsequent increases post-training, whilst the exact opposite pattern was true between subcortical regions and the dorsal/ventral attention, cingulo-opercular and auditory systems. A recent review on the broader field of cognitive training concluded there are consistent connectivity increases within relevant networks and decreases between networks due to training, leading to increased modularity and segregation (Baykara et al., 2020).

4.1.1 The present study

This study was exploratory in nature and aimed to investigate the pattern of task-based functional connectivity changes taking place following a WMU training protocol in healthy young adults. This is complementary to our voxel-based morphometry (VBM) analysis presented in chapter three and based on data from the original fMRI study conducted by Flegal, Ragland and Ranganath (2019). In the current study, both experimental and control groups practiced a visuospatial and a verbal WMU task over ten training sessions. In the experimental group, level of difficulty dynamically adjusted based on participants' performance while it remained at a fixed level across sessions for the control group. Adaptive difficulty has been identified as a common feature

of interventions that report significant training gains and is considered key for effective transfer (Anguera et al., 2013; Brehmer et al., 2012; Flegal, Ragland and Ranganath, 2019). This is made clearer if we consider Lövdén et al.'s (2010) theoretical framework describing plasticity and flexibility as two distinct yet interconnected concepts. Flexibility is viewed as the neural system's capacity to adapt to environmental demands utilising pre-existing resources. Plasticity on the other hand is viewed as the capacity for changes in flexibility, i.e., the capacity for changes in the pre-existing range of functional performance resulting from changes in the neural system. The authors further proposed a mismatch between functional "supply" (i.e., the individual's existing ability) and environmental "demands" (e.g., a continuously challenging training task) is a necessary condition for cognitive and neural plasticity to occur. Therefore, if a training task is not difficult enough to challenge the individual's existing neural resources, there is no mismatch between supply and demand and therefore no ground for plastic change to occur. However, if difficulty is dynamically adjusted, and continuously challenges the individual's proficiency levels, then further neural resources will become available in order to meet the demand— resulting in plastic change.

The changes in task performance and functional connectivity following adaptive WMU training were assessed with two scanned tasks (the trained criterion and a transfer task) at three time-points, i.e., pre-, early- and post-training. The study analysis focused on subcortical rather than frontoparietal ROI seed regions due to the striatum's involvement in WMU training functional activity studies, its hypothesised role in the transfer of learning as well as the established striatal links with frontal regions. More specifically we selected six subcortical seed ROIs based on the findings from the original fMRI study (Flegal, Ragland and Ranganath, 2019) indicating their sensitivity to adaptive training. These were the right and left putamen, right and left caudate and right and left hippocampus. This was an exploratory analysis, designed to address the following questions:

- Does adaptive WMU training promote task-based functional connectivity changes on the criterion task?

- Does adaptive WMU training promote task-based functional connectivity changes on the transfer task?
- Does the pattern of changes differ according to task type, i.e., criterion and transfer?

4.2 Methods

4.2.1 Participants

A total of N=38 healthy young adults (mean age = 20.55, SD = 2.37) were assigned to two groups: adaptive training (AT) group (N =19) and non-adaptive (NA) active control group (N=19). Participants were native English speakers with no history of neurological or psychiatric disorders and no known MRI contraindications. All participants gave informed consent and received compensation for their participation which was $10 for each training session, $20 for each MRI session and an additional $50 if all study visits were completed. This research was conducted at the University California at Davis (UCD) and was given UCD Institutional Review Board approval. The primary analysis of this dataset examined adaptivity-related fMRI activation changes (Flegal, Ragland and Ranganath, 2019); further study design and procedure details can be found in that report.

4.2.2 Training tasks

Both AT and NT groups completed 10 training sessions with two different tasks involving the process of WMU presented in different modalities: 1. visuospatial Matrix Updating (MU) and 2. verbal Keep Track (KT). Training stimulus delivery and response collection were performed using the Neurobehavioural Systems (NBS) Presentation software, (Version 20.1, www.neurobs.com) which is specifically designed for secure remote management of stimulus delivery in experimental research.

MU requires updating the location of four coloured dots presented on a 4 x 4 grid (Chen and Li, 2007). In each trial the four coloured dots first appear on the screen followed by coloured arrows (pointing up, down, left, or right). The participants had to mentally move the coloured dots as around the grid in the

direction indicated by the colour-corresponding arrows (Figure 4.2.1A). After a variable number of arrows, a coloured pointer would appear at the centre and participants were probed to respond by moving the pointer to the current location of the dot of that same colour. During training, participants performed the MU task for approximately 25-30min with five trials in each task block.

KT involves updating the identity of the most recently presented word from a series belonging to four semantic categories (Yntema, 1963). In each trial, the four categories were presented in boxes at the bottom of the screen and words from these categories appeared one at a time. Participants had to mentally assign each word to one of these categories, and after a variable number of words one of the category boxes was highlighted thus prompting the participant to respond by typing the last presented word belonging to that category box (Figure 4.2.1B). Four novel categories and related word lists were created for each of the training sessions and task duration was 20-25min.

For the AT group, the difficulty level of both training tasks dynamically adjusted based on the participant's performance while in the NA control group, difficulty was set at a fixed low level. The choice of tasks was specifically targeting the process of updating while ensuring WM load remained constant, i.e., always four dots and four categories. The difficulty level was dynamically adjusted to the AT participants' performance by varying the level of updates. For an extended training task description and presentation details please see Flegal, Ragland and Ranganath (2019).

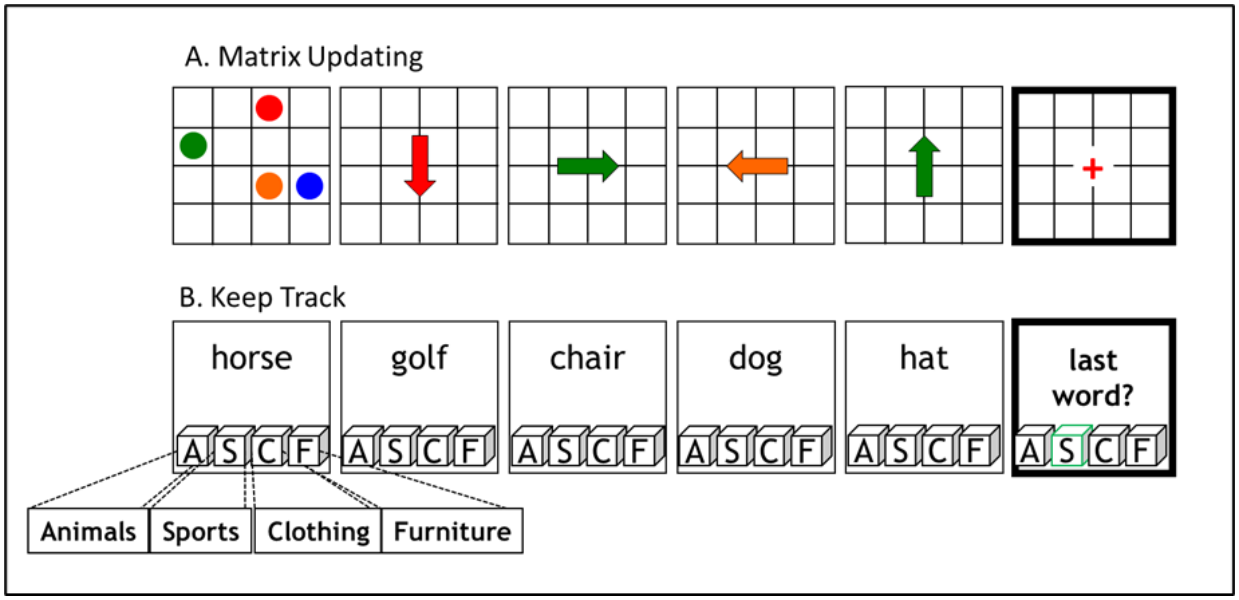

Figure 4.2.1: WMU training tasks, A. Matrix updating, B. Keep track. Images taken from Flegal, Ragland and Ranganath (2019).

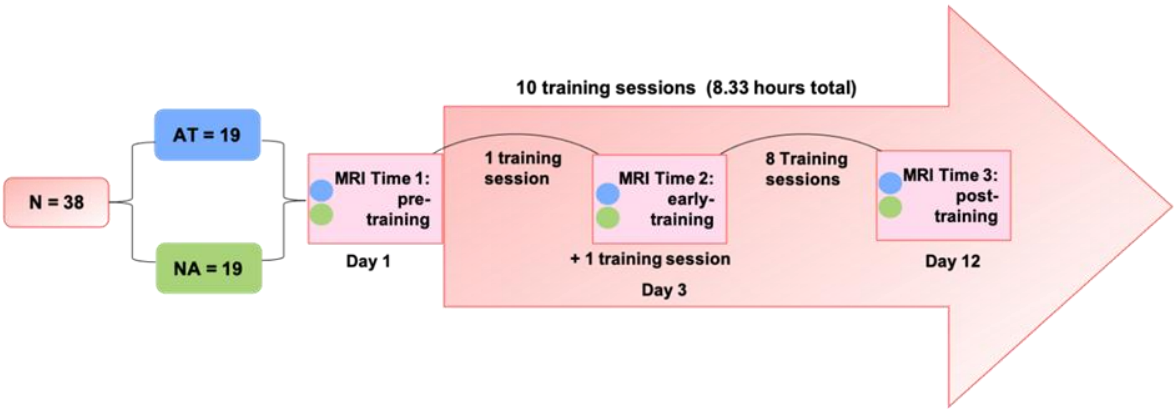

Figure 4.2.2: Twelve study days in total, including three fMRI sessions and ten training sessions spaced out over a three-week period. AT: adaptive training (experimental group), NA = non-adaptive (active control group).

4.2.3 Design, Procedure & fMRI acquisition

Participants completed twelve study visits in total over a three-week period (Figure 4.2.2). Functional images were acquired on a 3T Siemens Skyra at the UCD MRI Facility for Integrative Neurosciences, at three time points over the training period: pre-training (time 1; study visit 1), early training (time 2; study visit 3) and post-training (time 3; study visit 12), using a multi-band gradient-echo EPI sequence (multi-band factor = 2, TR = 1220 ms, TE = 24 ms, flip angle = 67°, FOV = 192 mm; 64 × 64 matrix; 38 slices; 3.0 mm isotropic voxels). High-resolution T1-weighted anatomical images were acquired using an MP-RAGE sequence (TR = 1800 ms; TE = 2.96 ms; flip angle = 7°; FOV = 256 mm; 256 x 256 matrix) at the end of each scanning session for all participants apart from N = 1 participant at time 2. Both AT and NA groups performed three scanned tasks: 1. Matrix Updating, 2. Spatial N-Back and 3. Object-Location Association. Behavioural data from the scanned tasks were collected using Presentation (www.neurobs.com) and E-Prime (Psychology Software Tools, Pittsburgh, PA). Detailed information on experimental procedures and task stimulus presentation can be found in Flegal, Ragland and Ranganath (2019).

In the present study, we only included data from the Matrix Updating criterion task and Spatial N-Back transfer task. The criterion MU task was modified from the training task version to an event-related fMRI design with

similar trial structure and timing but with a yes/no/don't know recognition probe type rather than freely indicating the updated dot location as in the training version (Figure 4.2.3). The MU task consisted of three trial types: 7 updates, 4 updates and a maintenance-only baseline where grey arrows were presented, and the recognition probe simply referred to the original location of the coloured dots on that trial. For each trial type, the dependent variable was the proportion of correct trials.

In the n-back task, blue squares appeared sequentially at one of eight locations on a 3x3 matrix with an unseen perimeter for 500ms each with a 2500ms interstimulus interval (ISI) (Figure 4.2.4). The participant had to respond by pressing one button when the current location matched the one presented n trials earlier and a different button when the location did not match. The task consisted of three trial types which were dependent upon the value of n: 3-back, 2-back, and 0-back, a baseline condition in which the target location was always the upper left corner of the screen. Overall accuracy served as the dependent variable for each block of trials.

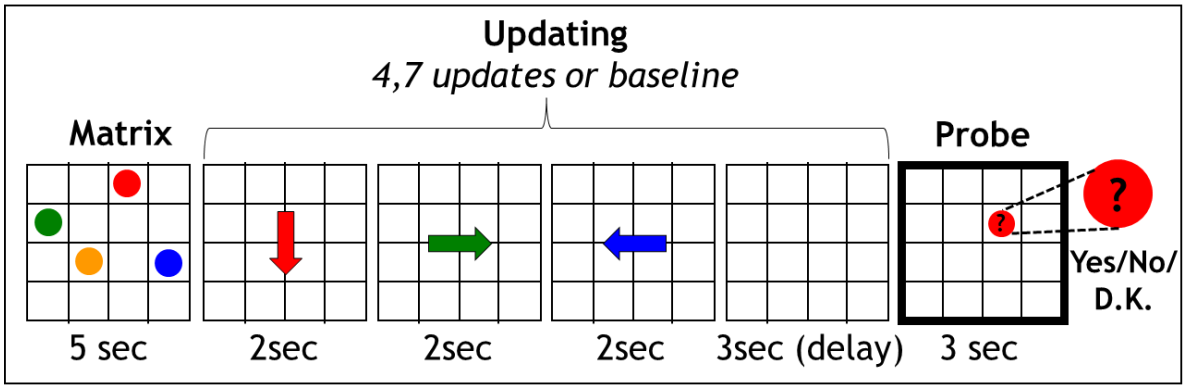

Figure 4.2.3: During each fMRI MU task trial, the matrix stimulus was presented for 5sec followed by either 4/7 coloured or grey arrows appearing for 2sec and a jittered intertrial interval varying between 2 and 10sec. The task was divided into four runs of eleven trials each (run duration = 5min approximately). The figure was adapted from (Flegal, Ragland and Ranganath, 2019).

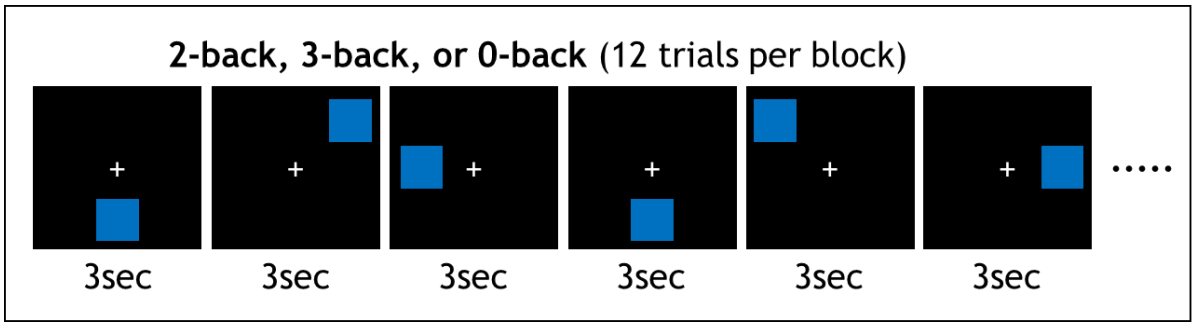

Figure 4.2.4: fMRI n-back trial duration was 3sec with a total of 12 trials per block. The task was divided into two runs of nine blocks each (run duration = 7min approximately). The figure was adapted from (Flegal, Ragland and Ranganath, 2019).

4.2.4 Pre-processing

Following a preregistered protocol published in open science framework (osf), (Pappa, 2020)[6]; a functional connectivity MRI (fcMRI) analysis was performed using CONN, an open source Matlab-based software (Whitfield-Gabrieli and Nieto-Castanon, 2012) (https://www.nitrc.org/projects/conn), in conjunction with SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) in the MatLab environment (www.mathworks.com). This toolbox was selected for its suitability in analysing task-related fcMRI data.

The fMRI dataset had been previously pre-processed and analysed in SPM, (for further details see Flegal, Ragland and Ranganath, 2019) and therefore most steps of the standard pre-processing CONN pipeline were omitted and instead the parameters of interest were extracted from the existing subject-specific SPM.mat file for each of the three time-points, i.e., three SPM.mat files per subject. Using the 'import' functionality in CONN, the functional and anatomical MRI data files, the number of conditions per subject and the onset for the conditions of interest, were extracted from the SPM.mat file. Motion parameters estimated at the realignment stage of SPM preprocessing and motion spikes identified using the ArtRepair toolbox[7] (Mazaika et al., 2009) were also included to setup as first level covariates.

[6] Pappa, K. (2021, June 28). Neural changes related to working memory updating training. https://doi.org/10.17605/OSF.IO/8RJ75

[7] cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html

From the CONN pre-processing pipeline we performed structural segmentation and normalisation, in addition to the outlier detection step to identify outliers from the global BOLD signal and subject-motion in the scanner. MRI acquisitions with framewise displacement above 0.9mm or global BOLD signal changes above 5 standard deviations were flagged as potential outliers. The output included a .txt file identifying potential outlier scans for each subject/session and a first-level covariate used in the denoising step described below.

For the MU task, CONN extracted twelve sessions per subject, i.e., four sessions/runs for each of the three time-points. Using the 'merge condition' (union) functionality, each set of four sessions/runs was merged and assigned into a pre, early, post condition specifying the events the condition was present within the corresponding four sessions/runs whilst at the same time indicated as not present for the remaining set of sessions/runs. The same procedure was followed for the n-back task, with CONN extracting two sessions/runs for each of the three time-points. Using the merge function, each set of two sessions/runs was merged and assigned into a pre-, early-, post condition. There was missing data for the early training time-point for one subject.

4.2.5 Denoising

A denoising pipeline within CONN was subsequently implemented to remove physiologic and motion artifact effects. Default band pass settings filtering out temporal frequencies below 0.008 and above 0.09 from the BOLD signal, normally fitting for resting-state analysis, were changed and instead data were denoised and filtered [0.008 infinity Hz], to reduce low frequency effects, settings suitable for task-based connectivity analyses as in (Nissim et al., 2019). To perform noise correction within CONN, the anatomical component-based noise correction procedure (aCompCor) was employed including noise components from cerebral white matter and cerebrospinal areas (Behzadi et al., 2007), estimated subject-motion parameters (Friston et al., 1996), identified outlier scans or scrubbing (Power et al., 2014), constant and first-order linear session effects, and constant task effects (Whitfield-Gabrieli and Nieto-Castanon, 2012).

After evaluating the denoising outputs, we took additional steps to improve data quality. Firstly, we applied the Friston24 method for the realignment parameters for both MU and n-back tasks (Friston et al. 1996). This included selecting polynomial expansion, i.e., quadratic effects, and second order derivatives for the MU task, in addition to quadratic effects and first order derivatives for the n-back task. Data from one subject were removed due to functional connectivity values for the MU task still exhibiting skewed distribution following denoising. Therefore, the final sample was N=37 for the MU and N=38 for the n-back task.

4.2.6 fcMRI Analysis

We performed correlational analyses of fMRI time-series data to investigate training related changes in task-based functional connectivity. For each scanned task, a first-level individual subject analysis was performed to compute weighted ROI-to-ROI connectivity (wRRC) and weighted seed-based connectivity (wSBC) matrices using a Weighted Least Squares (WLS) model with the following conditions of interest: high-difficulty, low-difficulty, and baseline trial types, defined as condition-specific boxcar timeseries convolved with a canonical hemodynamic response function (hrf) weighting, at each of the pre-training, early- training, and post-training time-points.

An event-related design modelling trial phases of matrix presentation, updating and probe presentation (see Figure 4.2.3), according to condition (7-, 4- and 0- updates) and response accuracy (correct/incorrect), was employed to analyse data from the MU criterion task. Conditions of interest included 7-, 4- and 0-updates correct trials. A block design modelling condition (3-,2- and 0-back) was employed to analyse data from the n-back transfer task. Conditions of interest included 3-,2- and 0-back blocks.

The wRRC matrices computed correlations between all ROI pairs of bilateral caudate, bilateral hippocampus and bilateral putamen sources (seeds) BOLD timeseries. The wSBC maps estimated the functional connectivity between these pre-selected ROIs and every voxel in the brain. First-level covariates included individual subjects' SPM covariates, realignment and scrubbing parameters. A second-level General Lineal Model (GLM) was estimated to

compute group results including AT and NA groups and age as the between-subjects regressors. F contrasts were defined to test for between-subjects and between-conditions effects. An FDR cluster corrected threshold of $p < 0.05$ was applied to control for false positives. Partial eta squared was used to calculate the effect size in group x condition interaction analysis. A two-sample t-test was performed to check for pre-training functional connectivity differences between groups at baseline.

4.2.7 Task performance analysis

Data analysis of behavioural performance on the scanned tasks was performed using a 2x3 mixed ANOVA with fixed factors: Group (AT/NA) and Time (Pre-/Early-/Post-) and accuracy levels for each measure serving as the dependent variable. Bonferroni adjustments were applied to correct for multiple comparisons. We further conducted two ANCOVAs with post-training performance as the dependent variable, group (AT/NA) as a fixed factor and pre-training (1) or early-training (2) performance as a covariate. These analyses were conducted using IBM SPSS Statistics for Windows, Version 27.0.

To investigate the relationship between functional connectivity changes and performance improvements over the course of training, we performed a set of partial correlation analyses. A training slope variable was computed to quantify the relative amount of improvement on the trained tasks for each AT participant. This was computed by averaging the linear slopes calculated from the maximum difficulty level achieved for each task at each training session. It was not possible to compute a training slope variable for the NA group since they trained at a fixed low level of task difficulty. This analysis focused on fcMRI data from the MU task condition with the high-difficulty updates load, i.e., 7-updates for consistency with the original fMRI analysis where the AT group exhibited larger performance improvements post-training compared to the control group for the highest difficulty MU task condition, i.e., 7-updates, (Flegal, Ragland and Ranganath, 2019). Two sets of partial correlations were performed between the AT group's training slope and functional connectivity values at: 1. post-training whilst controlling for functional connectivity pre-training and 2. early-training whilst controlling for functional connectivity pre-training, across all ROI pairs for the 7-updates MU task condition only.

We additionally examined the relationship between changes in functional connectivity and changes in task performance across ROI pairs for both scanned tasks. The ROI-to-ROI correlation matrix for each subject was extracted from the structure "Z" located in the CONN first level results mat file (conn_*/results/firstlevel/ANALYSIS_01/resultsROI_Subject##_Condition#.mat). The variable Z contains the Fisher transformed correlation coefficients between each pair of ROIs. Functional connectivity changes were then calculated by subtracting the connectivity values pre-training from post-training, i.e., dependent variable CONNChange, and similarly, performance change scores were calculated by subtracting pre-training scores from post-training scores, i.e., independent continuous variable TaskChange. Finally, we set up a separate regression model with a continuous-by-categorical interaction for each ROI pair, i.e., fifteen models in total. The regression model in detail:

```
CONNChange ~ TaskChange + Group + TaskChange:Group,
```

CONNChange = dependent variable, *TaskChange* = independent continuous variable, *Group* = independent categorical variable, *TaskChange:Group* = interaction term that means all possible main effects and interactions between the two independent variables. The categorical predictor *Group* was a dummy-coded variable taking on 0 for the NA group (baseline) and 1 for the AT group (alternative).

Partial correlation and regression analyses were conducted with the R studio application (Team R. RStudio, 2019) in R software (R Development Core Team, 2020) using the packages ppcor (Kim, 2015) and interaction (Long, 2020) respectively. The packages tidyverse (Wickham et al., 2019), dplyr (Wickham et al., 2021) and ggplot2 (Wickham, 2016) were additionally used for data manipulation and visualisation purposes.

4.3 Results

4.3.1 Task performance

Overall, participants in both training groups performed above chance and achieved high levels of accuracy across task conditions and time-points (table

4.3.1). We found a main effect of time for both MU criterion and n-back transfer tasks, with participants' performance improving over time irrespective of group. In more detail, we found a main effect of time for the 4-updates ($F=5.542$, $p=0.006$) and 7-updates ($F=8.969$, $p < 0.001$) MU task conditions. Pairwise comparisons revealed both AT and NA groups performed significantly better in the low-difficulty 4-updates condition post-training compared to early-training ($p=0.004$). For the high-difficulty 7-updates condition, AT and NA groups exhibited higher performance post-training when compared to early-training ($p=0.007$) and pre-training ($p<0.001$) time-points. A similar pattern emerged for the n-back transfer task, with a significant main effect of time for the 3-back ($F=4.379$, $p=0.016$) and 2-back ($F=6.457$, $p=0.003$) task conditions. Participants exhibited significantly higher accuracy in the 3-back and 2-back conditions early-training compared to pre-training ($p=0.05$ and $p=0.027$ respectively) as well as post-training compared to pre-training for the 2-back condition only ($p=0.004$). Our analysis did not reveal any significant group by time interaction effects nor a main effect of group for either of the MU or n-back tasks. Finally, our ANCOVA analysis focusing on post-training performance whilst controlling for pre-training/early-training performance did not reveal any significant group differences.

4.3.2 ROI to ROI connectivity (RRC)

We first conducted F tests to investigate any effects between groups and conditions for both the MU criterion task and the n-back transfer task. We found significant effects for both tasks and across all conditions of interest, i.e., 7, 4 and 0 (Baseline) update correct trials for the MU task, and 0 (Baseline), 2 and 3-back blocks for the n-back task (please see table 2.1 in Appendix 2), thus allowing us to proceed with further analysis.

Matrix Updating – criterion task

No significant main effect of group was found for any of the MU conditions of interest across any ROI pairs; we did however find a significant effect of time, mainly driven by post-training against early and pre-training comparisons, across all conditions. More specifically, we found increased post-training connectivity between left and right hippocampus as well as left and right caudate when

compared against pre- and early training for both 7 and 4 update conditions (please see table 4.3.2). Only one significant group by time interaction was found, for the 4 updates condition, revealing greater connectivity increases for the AT group than the NA group between left and right hippocampus post-training when compared to early in the training (Table 4.3.2, Figure 4.3.1). No significant group differences in functional connectivity between left and right hippocampus were present at pre-training.

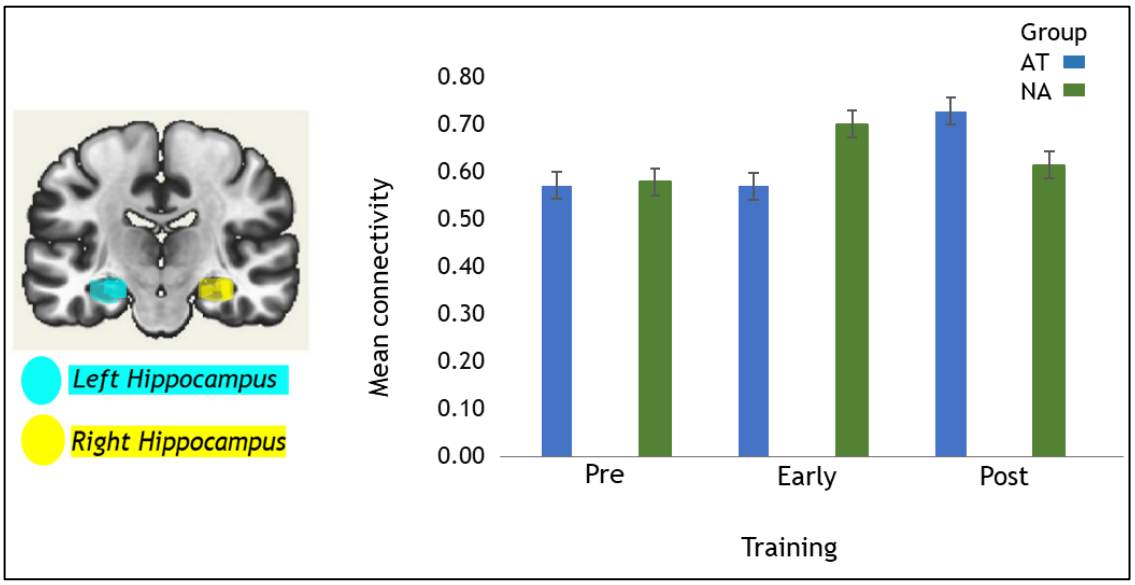

Figure 4.3.1: Significant interaction effect: greater functional connectivity increases between left and right hippocampus for the AT group than the NA group early-training to post-training on MU criterion task 4-update correct trials.

N-back - transfer task

Similar to the MU criterion task findings, we did not find a significant main effect of group for any of the n-back conditions of interest across any of the ROI pairs; we did however find a significant effect of time, for the 2- and 3-back conditions (table 4.3.3). In more detail, we found increased post-training connectivity between left and right hippocampus compared to early and pre training for the 2-back condition for both groups. Interestingly, we also found decreased connectivity between left and right hippocampus early in the training compared to pre-training for both groups. Our findings additionally showed decreased post-training connectivity between bilateral caudate and right hippocampus, as well as left caudate and left hippocampus, compared to pre-training for the 3-back condition. Finally, we did not find any significant interaction effects for any of the conditions of interest.

Table 4.3.1: fMRI task accuracy for the AT and NA training groups during pre-, early- and post- training time points.

	Adaptive Training Group (N=19)			*Non-Adaptive Training Group (N=19)*			*ANOVA*
	Pre	*Early*	*Post*	*Pre*	*Early*	*Post*	*Time by Group Interactions*
	M(SD)	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*	
Matrix Updating criterion task							
7-updates	0.80 (0.13)	0.84 (0.17)	0.93 (0.07)	0.81 (0.14)	0.83 (0.16)	0.87 (0.15)	*F=1.013, p=.368*
4-updates	0.91 (0.08)	0.90 (0.13)	0.95 (0.07)	0.89 (0.11)	0.86 (0.12)	0.92 (0.08)	*F=0.187, p=.830*
0-updates (Baseline)	0.93 (0.08)	0.95 (0.07)	0.97 (0.06)	0.93 (0.08)	0.93 (0.11)	0.92 (0.11)	*F=0.928, p=.340*
N-back transfer task							
3-back	0.68 (0.18)	0.81 (0.17)	0.81 (0.26)	0.75 (0.21)	0.80 (0.13)	0.84 (0.1)	*F=0.394, p=.676*
2-back	0.84 (0.15)	0.89 (0.11)	0.90 (0.16)	0.82 (0.13)	0.89 (0.1)	0.91 (0.07)	*F=0.175, p=.840*
0-back	0.94 (0.09)	0.96 (0.07)	0.95 (0.09)	0.95 (0.06)	0.92 (0.15)	0.96 (0.04)	*F=1.284, p=.283*

Table 4.3.2: Matrix Updating, significant RRC effects for all conditions of interest and ROI pairs.

Matrix Updating					
Connections	***Condition***	***Contrast***	***Statistic***	***p-unc***	***p- FDR***
Group by Time interaction					
L Hip - R Hip	4 updates	AT > NA & Post >Early	T(35) = 2.91	*.006*	*.031*
Main effect of Time					
R Hip - L Hip	7 updates	Post > Pre	T(35) = 4.42	*<.001*	*<.001*
L Cau - R Cau ***R Hip - L Hip***	7 updates	Post > Early	T(35) = 3.35 T(35) = 3.07	*.002* *.004*	*.010* *.021*
R Cau - L Cau ***L Hip - R Hip*** ***R Put - L Put***	4 updates	Post > Pre	T(35) = 3.28 T(35) = 2.66 T(35) = 2.44	*.002* *.012* *.020*	*.012* *.058* *.099*

R Cau – L Cau	4 updates	Post > Early	T(35) = 4.35	*<.001*	*.001*
R Cau - L Hip	0 updates (Baseline)	Post > Pre	T(35) = -3.57	*.001*	*.005*
L Cau – L Hip			T(35) = -3.37	*.002*	*.009*
R Cau – R Hip			T(35) = -2.97	*.005*	*.013*
L Cau – R Hip			T(35) = -2.85	*.007*	*.018*
R Hip – L Hip	0 updates (Baseline)	Post > Early	T(35) = 3.20	*.003*	*.015*
L Cau – R Cau			T(35) = 2.94	*.006*	*.015*
L Put – R Cau			T(35)= 2.89	*.007*	*.016*
L Put – L Cau			T(35)= 2.98	*.005*	*.016*
L Put – R Cau			T(35)= 2.64	*.012*	*.020*
R Put – L Cau			T(35)= 2.51	*.017*	*.043*
R Put – R Cau			T(35)= 2.10	*.043*	*.072*

R = Right, L = Left, Cau = Caudate, Put = Putamen, Hip = Hippocampus, unc = uncorrected, FDR = False Discovery Rate.

Table 4.3.3: N-back task, significant RRC effects for all conditions of interest and ROI pairs.

N-back					
Connections	***Condition***	***Contrast***	***Statistic***	***p-unc***	***p- FDR***
Main effect of Time					
R Cau – R Hip ***L Cau – R Hip*** ***L Cau – L Hip***	3-back	Post > Pre	T(35) = -3.75 T(35) = -3.65 T(35) = -2.33	*.001* *.001* *.026*	*.003* *.004* *.064*
L Hip – R Hip	2-back	Post > Pre	T(35) = 4.03	*<.001*	*.001*
L Hip – R Hip	2-back	Post > Early	T(35) = 3.25	*.003*	*.013*
L Hip - R Hip	2-back	Early > Pre	T(35) = -3.25	*.003*	*.013*

R = Right, L = Left, Cau = Caudate, Put = Putamen, Hip = Hippocampus, unc = uncorrected, FDR = False Discovery Rate.

4.3.3 Seed based connectivity (SBC)

F tests revealed significant effects for both tasks across all conditions of interest, i.e., 7, 4 and 0 (Baseline) correct updates for the MU task, and 0, 2 and 3-back for the n-back task, thus allowing us to proceed with further analysis (please see table 2.2, Appendix 2 for further details).

Matrix Updating - criterion task

Our findings did not reveal a main effect of group for any of the MU task conditions. We did however find a main effect of time for 0, 4- and 7-updates MU task conditions across seed ROIs (for more information please see table 2.3, Appendix 2).

7 updates: Findings exhibited greater reduction in functional connectivity between bilateral putamen seeds and bilateral lateral occipital cortex from early-training to late-training for the AT group than the NA control group (table 4.3.4, Figures 4.3.2, 4.3.3). Our results also showed greater decreases between left putamen seed and right cerebellum from pre-training to early-training for the AT group than the NA control group (Figure 4.3.4). No significant connectivity differences between groups at pre-training for the 7-update condition in any of these seed ROIs were reported.

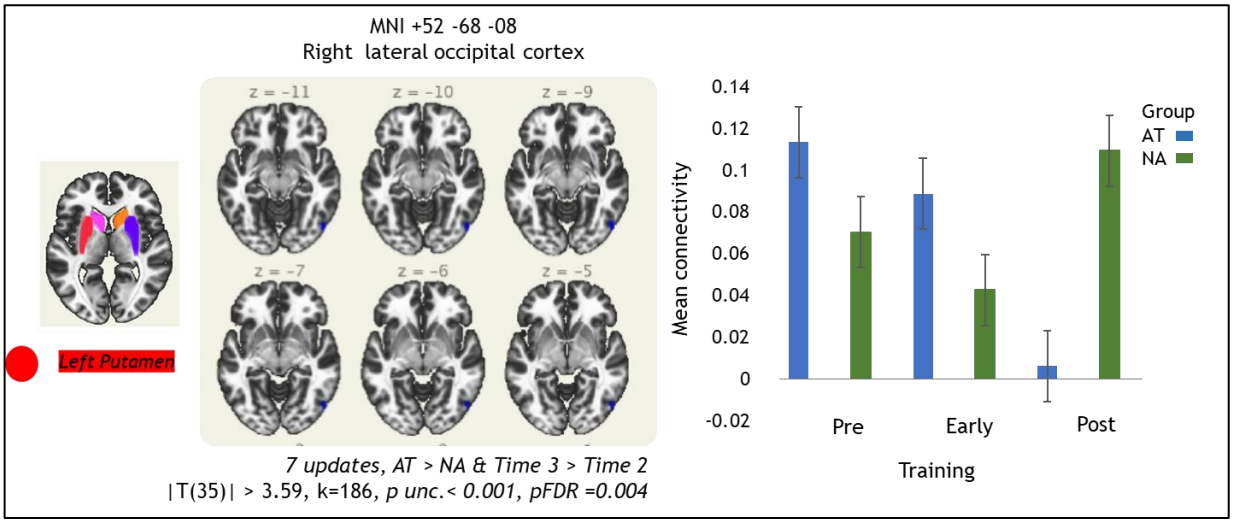

Figure 4.3.2: Greater connectivity decreases for the AT compared to the NA group early-training to post-training between the left putamen seed ROI and a cluster located in the right lateral occipital cortex.

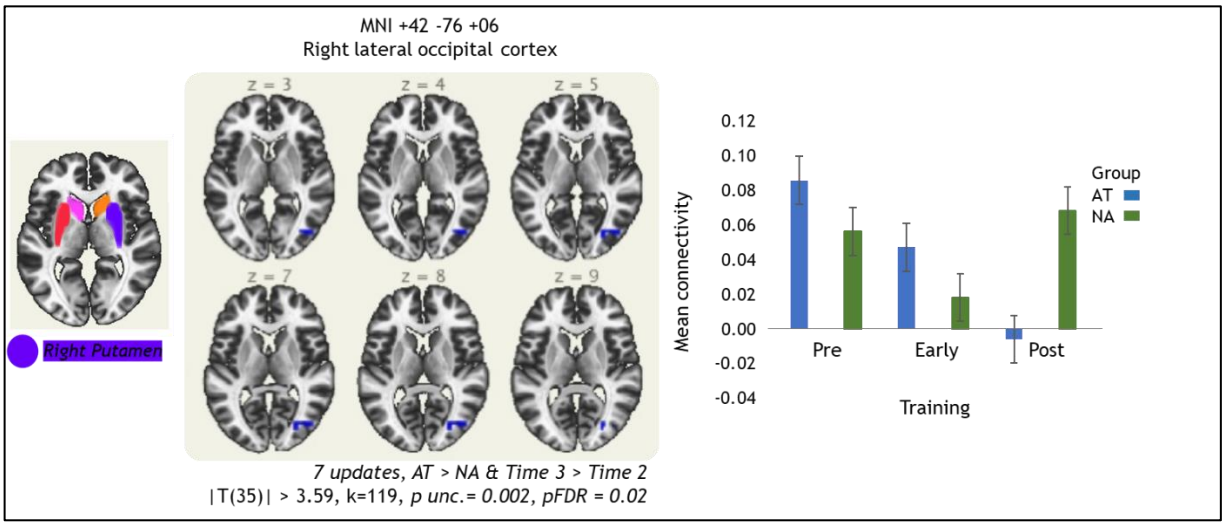

Figure 4.3.3: Greater connectivity decreases for the AT compared to the NA group early-training to post-training between the right putamen seed ROI and a cluster located in the right lateral occipital cortex.

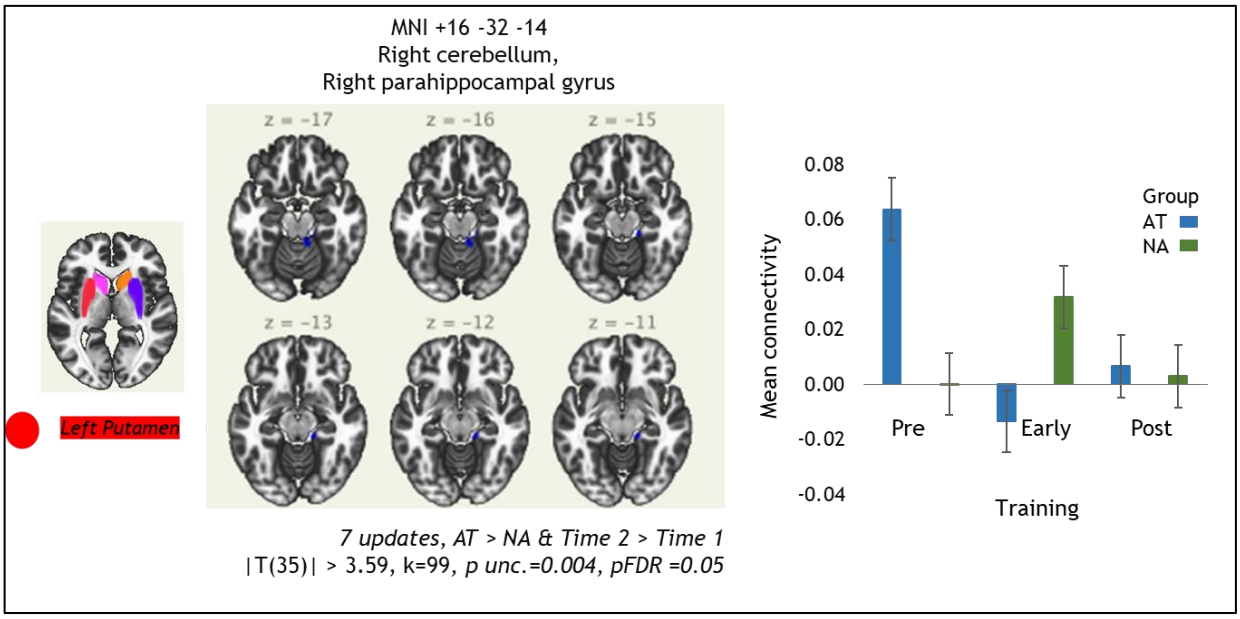

Figure 4.3.4: Greater connectivity decreases for the AT compared to the NA group pre-training to early-training between the left putamen seed ROI and a cluster located in the right cerebellum and right parahippocampal gyrus.

4 updates: We found greater functional connectivity decreases from early-training to late-training for the AT group than the NA control group between right hippocampus seed and right superior parietal lobule (Table 4.3.4, Figure 4.3.5). However, due to significantly higher pre-training connectivity between the right caudate seed and bilateral supramarginal gyrus, bilateral angular gyrus, superior parietal lobule, right occipital cortex, right post central gyrus (Figures 4.3.6A and 4.3.6B) and left middle frontal gyrus (Figure 4.3.6C) –

as well as between the left hippocampus seed and left precuneus, bilateral cuneal cortex, and left occipital pole (Figure 4.3.7) – for the AT group than the NA group, we cannot be certain that the significant interaction effects reported in Table 4.3.4 stem from our experimental manipulation or pre-existing differences at baseline.

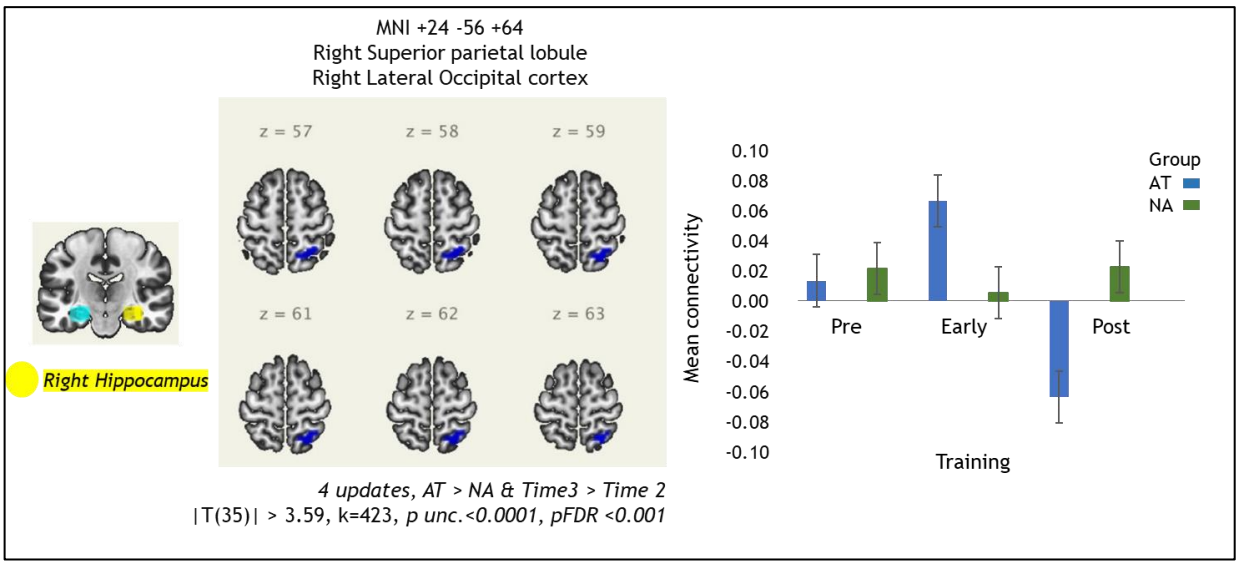

Figure 4.3.5: Greater connectivity decreases for the AT compared to the NA group early-training to post-training between the right hippocampus seed ROI and a cluster located in the right superior parietal lobule and right lateral occipital cortex.

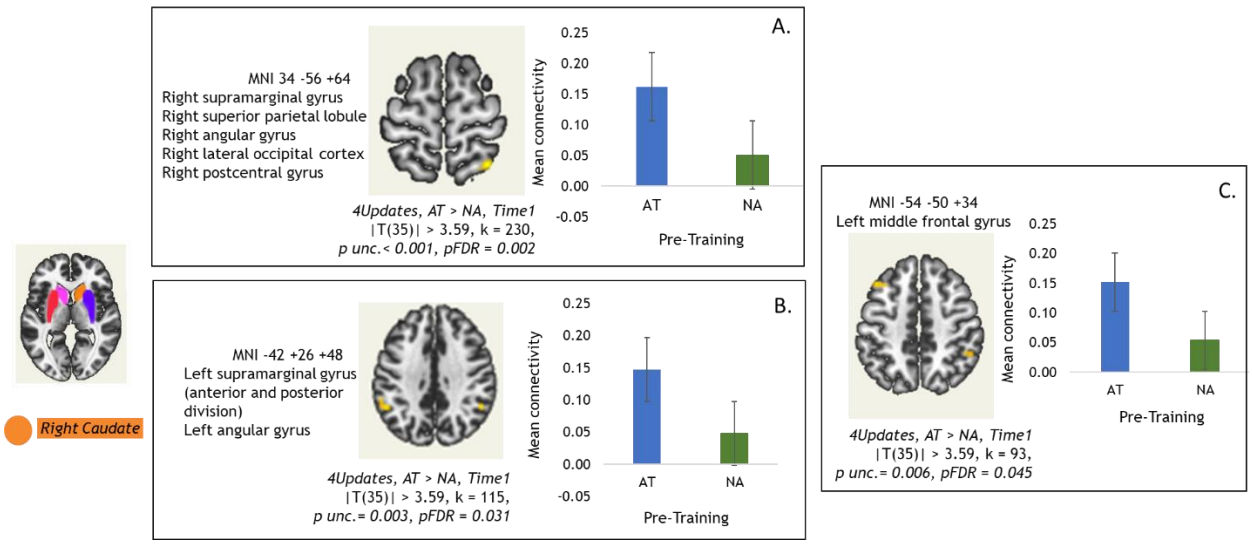

Figure 4.3.6: Significant baseline differences with the AT group exhibiting higher connectivity than the NA group pre-training, for the right caudate seed and clusters located in: (A) right occipito-parietal regions, (B) left supramarginal and left angular gyri and (C) left middle frontal gyrus.

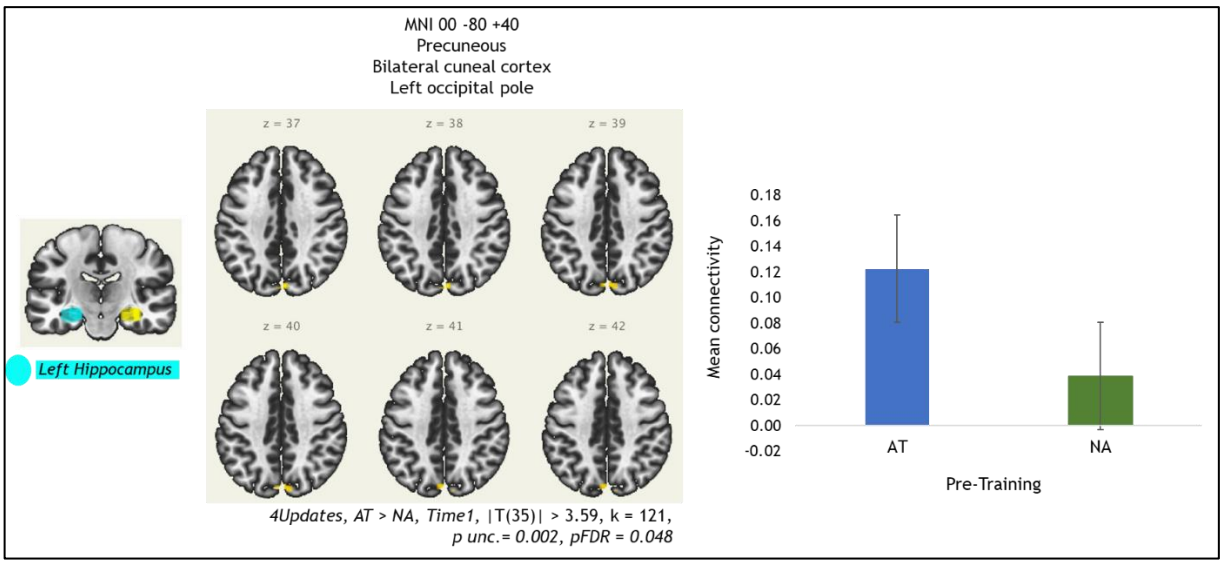

Figure 4.3.7: Significant baseline differences with the AT group exhibiting higher connectivity than the NA group pre-training, between the left hippocampus seed and clusters in the precuneus, bilateral cuneal cortex, and left occipital pole.

0 updates (Baseline): MU 0-updates trials required only WM maintenance, with no WMU demand. Findings showed greater functional connectivity decreases from pre-training to early-training for the AT group than the NA control group between right putamen seed and left lateral occipital cortex, occipital pole, temporal occipital fusiform gyrus as well as right angular gyrus. Similar decreases were revealed between the left putamen seed and bilateral lateral occipital cortex (Table 4.3.4). No group differences were found when examining functional connectivity differences at pre-training in any of these seed regions.

Table 4.3.4: Matrix updating task, significant SBC group by time interaction effects.

Matrix Updating						
Seed	***Condition***	***Contrast***	***Cluster size*** ***MNI coordinates*** ***Brain region***		***T Statistic***	***p-unc***	***p- FDR***
Right Putamen	7 updates	AT>NA & Post > Early	k = 119 +42 -76 +06 R Lateral Occipital cortex	↓	|T(35)| > 3.59	*.002*	*.022*
Left Putamen	7 updates	AT>NA & Early > Pre	k = 99 +16 -32 -14 R cerebellum R parahippocampal gyrus, posterior division R cerebellum	↓	|T(35)| > 3.59	*.004*	*.047*
		AT>NA & Post > Early	k = 186 +52 -68 -08 R Lateral Occipital cortex R Cerebellum R occipital fusiform gyrus	↓	|T(35)| > 3.59	*<.001*	*.004*
Right Caudate	4 updates	AT>NA & Post > Early	k =160 -02 -70 28 Precuneous R Cuneal cortex	↑	|T(35)| > 3.59	*<.001*	*.018*

			L Cuneal cortex			
			k = 132 -54 -14 -24 L Middle Temporal gyrus (posterior) L Middle Temporal gyrus (anterior)		*.001*	*.023*
Right Hippocampus	4 updates	AT>NA & Post > Early	k = 423 +24 -56 +64 R Superior parietal lobule R Lateral Occipital cortex	↓	|T(35)| > 3.59	*<.001*	*<.001*
Left Hippocampus	4 updates	AT>NA & Post > Early	k = 134 +22 +62 +18 R Frontal Pole	↑	|T(35)| > 3.59	*.001*	*.032*
Right Putamen	Baseline (0 Updates)	AT>NA & Early > Pre	k = 323 -36 -80 +24 L Lateral occipital cortex (superior) L Lateral occipital cortex (inferior)	↓	|T(35)| > 3.59	*<.001*	*<.001*
			k = 156 -18 -92 -08 L Occipital pole L Occipital fusiform gyrus	↓		*<.001*	*.008*
			k = 148 -42 -58 -14 L Temporal occipital fusiform cortex	↓		*<.001*	*.095*

			L Inferior temporal gyrus (temporoccipital part)			
			k = 97 +42 -56 +16		*<.001*	*<.001*
			R Angular gyrus R Middle temporal gyrus (temporoccipital part)			
			k = 328 -38 -68 +16		*<.001*	*<.001*
			L Lateral occipital cortex (superior, inferior) L angular gyrus L Middle temporal gyrus (temporoccipital part)			
Left Putamen	Baseline (0 Updates)	AT>NA& Early > Pre	k = 182 +54 -64 +12	|T(35)| > 3.59	*<.001*	*.003*
			R Lateral occipital cortex (superior, inferior) R Middle temporal gyrus (temporoccipital part) R Angular gyrus			

Red arrows indicate the direction of connectivity changes, i.e., increases / decreases. k = cluster size, unc. = uncorrected, FDR = False Discovery Rate.

N-back – transfer task

Our results revealed a main effect of group with AT participants exhibiting consistently lower connectivity between the left putamen and the posterior division of the cingulate gurus (|T(36)|>3.58, k≥129, *p unc.* = 0.002, *p FDR* = 0.037, cluster +00 -40 +30) for the 2-back task condition (Figure 4.3.8). We additionally found a main effect of time for the 0-,2- and 3-back conditions across seed ROIs (see table 2.3 Appendix 2 for detailed results).

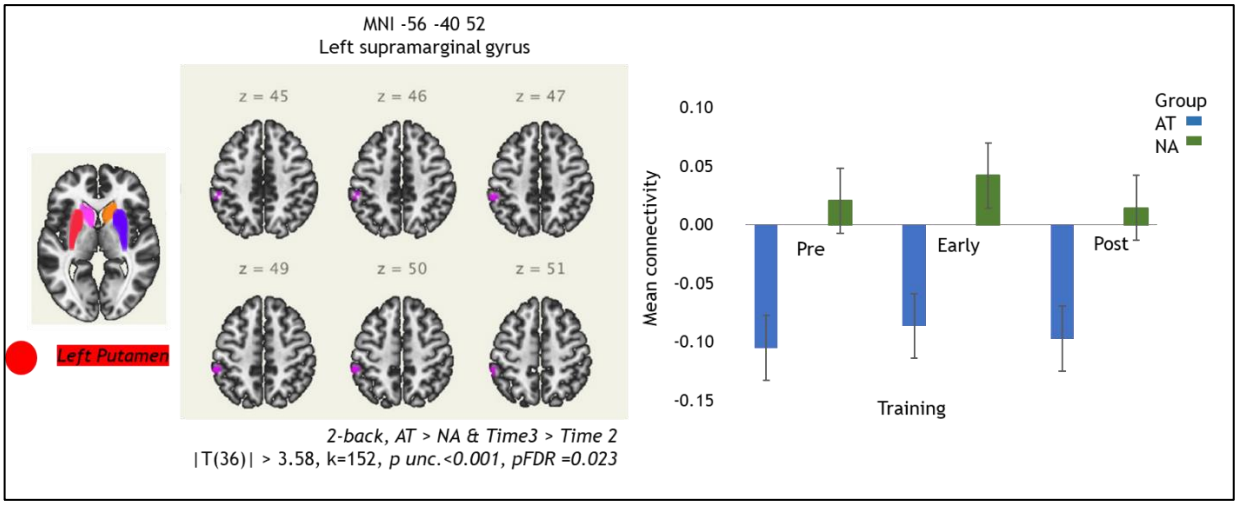

Figure 4.3.8: Lower connectivity between the left putamen seed ROI and a cluster located in the posterior cingulate gyrus exhibited by the AT group than the NA group across scanning sessions.

3-back: No significant group by time interaction effects were revealed for this condition in any of the seed ROIs.

2-back: We found greater connectivity decreases for the AT group compared to the NA group between the left-putamen and left supramarginal gyrus from early-training to post-training (Table 4.3.5, Figure 4.3.9), as well as the left pre-central gyrus from pre-training to post-training (Figure 4.3.10). We also found greater connectivity decreases between left putamen and the right postcentral and precentral gyrus for the AT than the NA group from pre-training to early-training (Table 4.3.5, Figure 4.3.11).

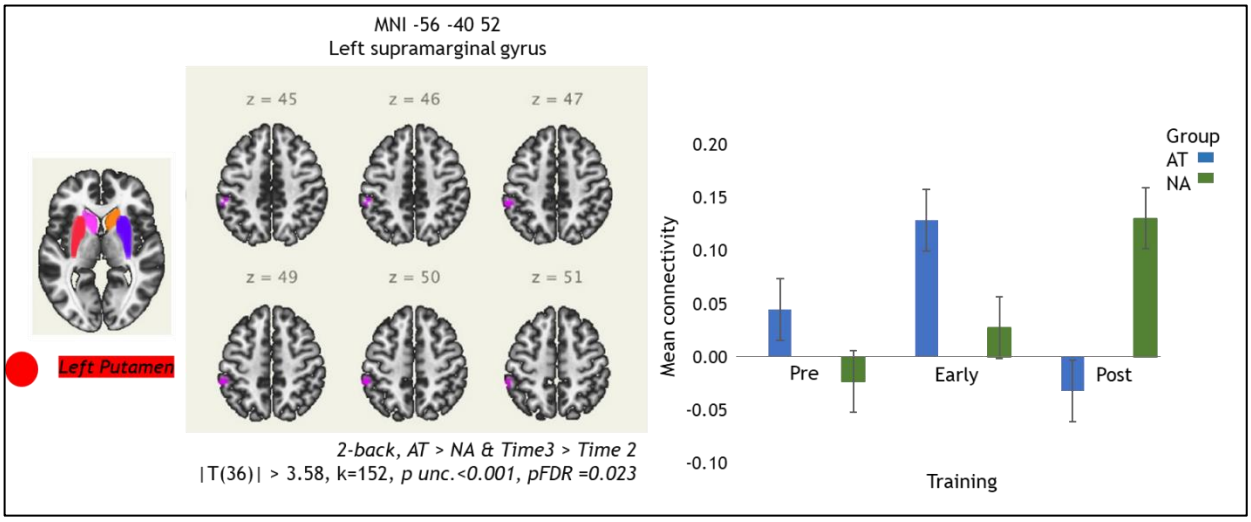

Figure 4.3.9: Greater connectivity decreases for the AT compared to the NA group early-training to post-training between the left putamen seed ROI and a cluster located in the left supramarginal gyrus.

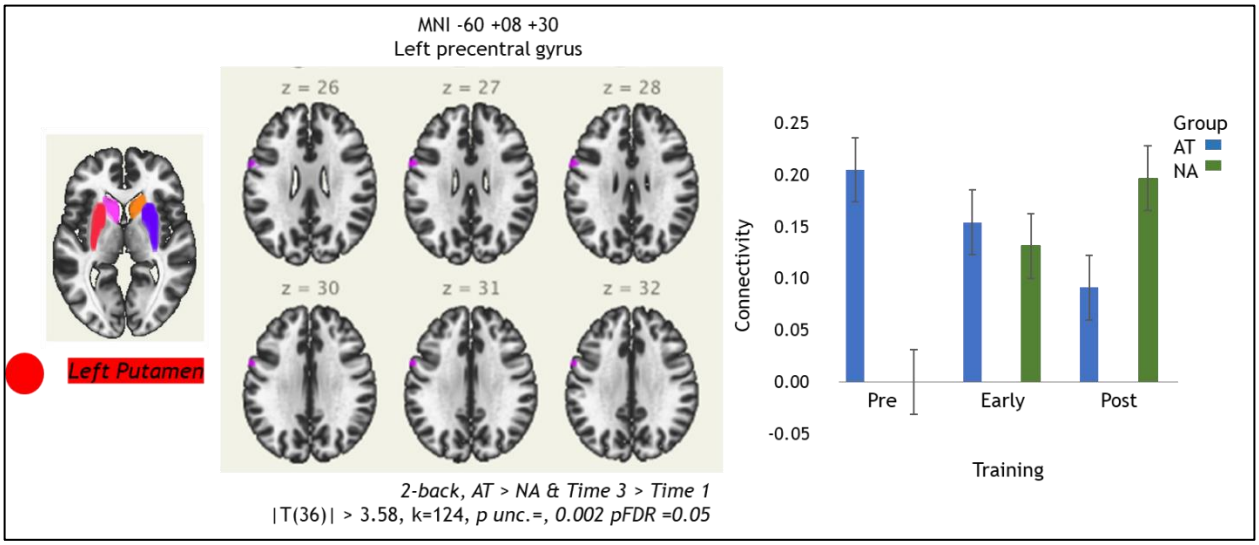

Figure 4.3.10: Greater connectivity decreases for the AT compared to the NA group pre-training to post-training between the left putamen seed ROI and a cluster located in the left precentral gyrus.

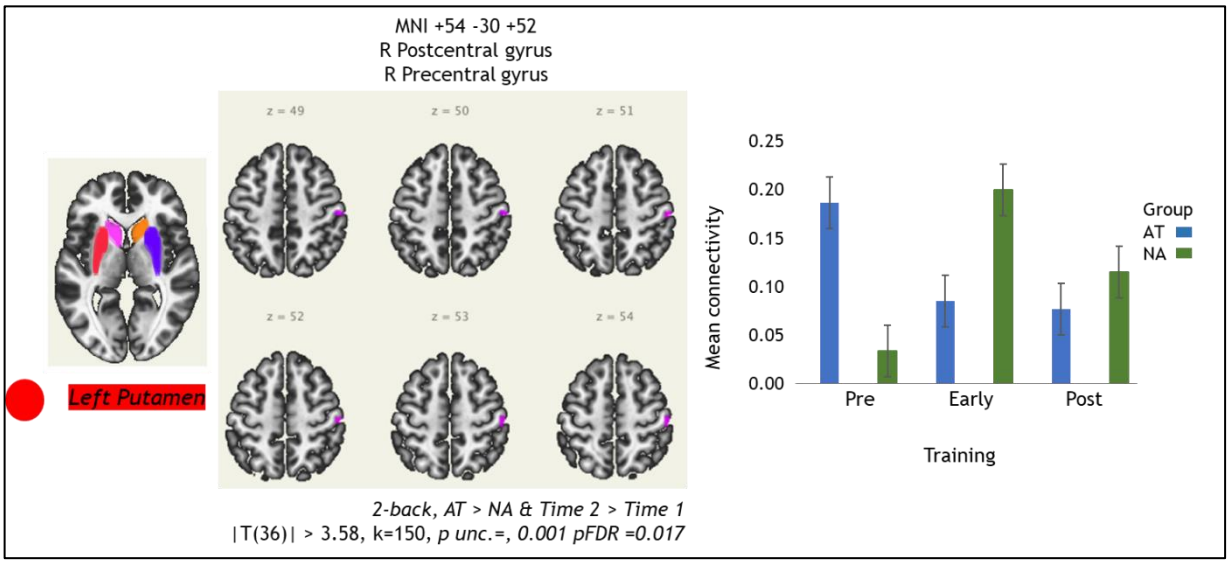

Figure 4.3.11: Greater connectivity decreases for the AT compared to the NA group pre-training to early-training between the left putamen seed ROI and a cluster located in the right postcentral and right precentral gyrus.

We additionally found greater increases in functional connectivity between bilateral caudate and left lateral occipital cortex (Table 4.3.5, Figure 4.3.12 & 4.3.13) as well as between left caudate and left precuneus (Table 4.3.5, Figure 4.3.14) for the AT group than the NA group from pre-training to early-training.

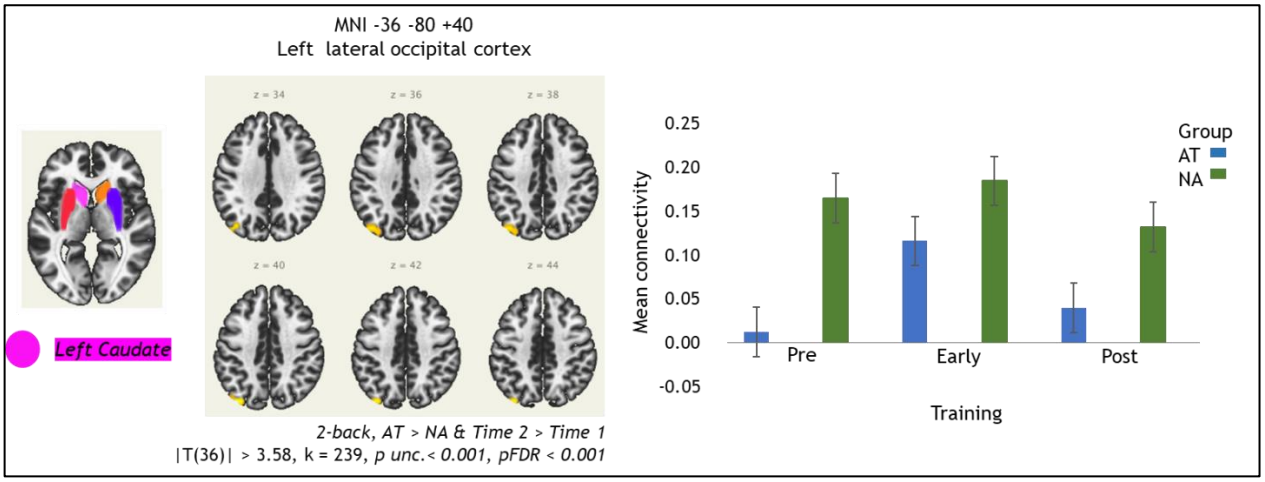

Figure 4.3.12: Greater connectivity increases for the AT compared to the NA group pre-training to early-training between the left caudate seed ROI and a cluster located in the left lateral occipital cortex.

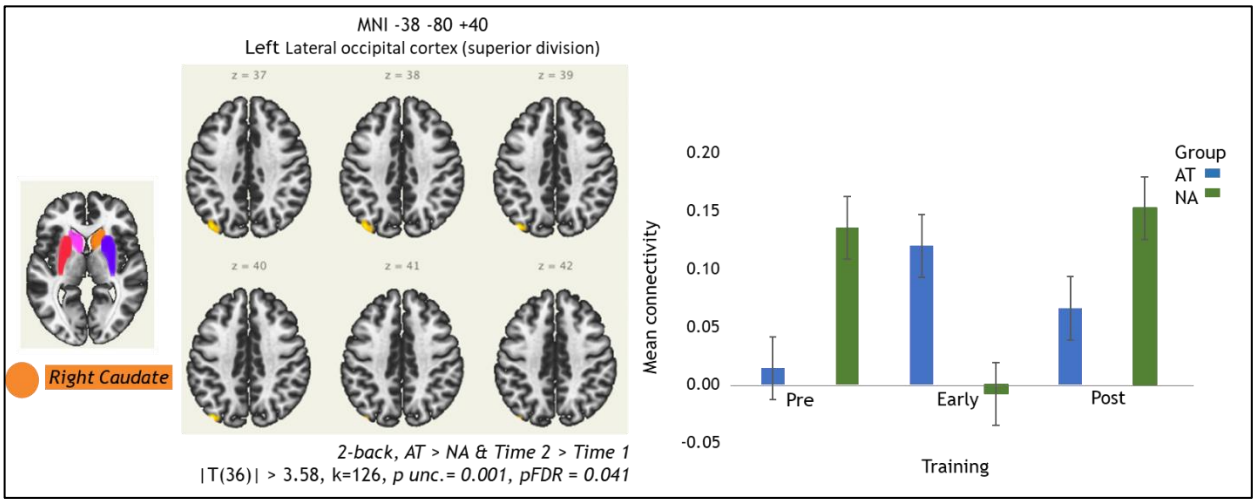

Figure 4.3.13: Greater connectivity increases for the AT compared to the NA group pre-training to early-training between the right caudate seed ROI and a cluster located in the left lateral occipital cortex.

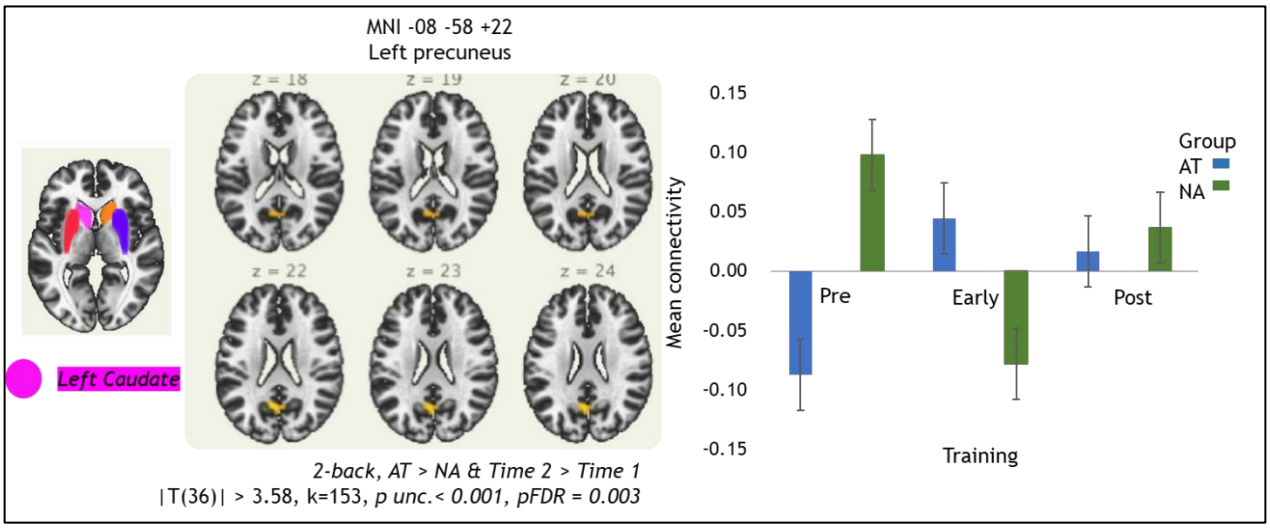

Figure 4.3.14: Greater connectivity increases for the AT compared to the NA group pre-training to early-training between the left caudate seed ROI and a cluster located in the left precuneus.

0-back: The 0-back condition required only memory for the target location, with no WMU demand. We found greater connectivity increases between bilateral caudate and left middle temporal gyrus for the AT group than the NA group from early-training to post-training (Table 4.3.5). Results further revealed greater connectivity increases for the AT group compared to the NA group between left putamen and bilateral paracingulate gyrus, right superior frontal gyrus, right paracingulate gyrus and right frontal pole from pre-training to post-training. However, we also found significantly lower connectivity between left putamen and bilateral paracingulate gyrus, anterior cingulate

gyrus, medial frontal cortex and right frontal pole for the AT group than the NA group pre-training (|T(36)|>3.58, k≥ 296). Greater connectivity increases for the AT than the NA group were also found between left hippocampus and right angular gyrus, right superior parietal lobule, right lateral occipital cortex, right supramarginal gyrus from pre-training to early-training, as well as decreases in connectivity with the left postcentral and gyrus and superior parietal lobule for the same comparison.

4.3.4 Functional Connectivity and Task Performance

To investigate individual differences in responsiveness to training and functional connectivity strength, partial correlation analyses were performed on the MU criterion task with a specific focus on the experimental condition with the highest WM updating load, i.e., 7-updates. A significant negative relationship was found between greater improvement on the trained tasks (i.e., higher training slope) and functional connectivity in the right and left hippocampi ROI pair post-training, controlling for functional connectivity pre-training (r = -0.491, *p* = 0.045,). We additionally found a negative relationship between higher training slope and functional connectivity in the left caudate and left hippocampus ROI pair early in the training, controlling for functional connectivity pre-training (p = 0.049, r =-0.483). After applying Bonferroni corrections for multiple comparisons, these results do not remain significant. Regression models did not reveal a significant relationship between changes in connectivity and changes in adaptive training task performance in any of the ROI pairs for either of the MU, NB scanned tasks.

Table 4.3.5: N-back task, significant SBC group by time interaction effects.

N-back						
Seed	***Condition***	***Contrast***	***Cluster size MNI coordinates Brain region***	***T Statistic***	***size p-unc***	***size p-FDR***
Right Caudate	2-back	AT>NA & Early > Pre	k = 126 -38 -80 +40 L Lateral occipital cortex Superior division ↑	|T(36)| > 3.58	*.001*	*.041*
Left Caudate	2-back	AT>NA & Early > Pre	k = 239 -36 -80 +40 L Lateral occipital cortex Superior division ↑	|T(36)| > 3.58	*<.001*	*.001*
			k = 153 -08 -58 +22 L precuneous ↑		*.001*	*.003*
Left Putamen	2-back	AT>NA & Early > Pre	k = 150 +54 -30 +52 R Postcentral gyrus R Precentral gyrus ↓	|T(36)| > 3.58	*.001*	*.017*
Left Putamen	2-back	AT>NA & Post > Early	k = 152 -56 -40 +52 L Supramarginal gyrus, anterior division ↓	|T(36)| > 3.58	*.001*	*.023*

			L Supramarginal gyrus, posterior division				
Left Putamen	2-back	AT>NA & Post > Pre	k = 124 -60 +08 +30 L Precentral gyrus	↓	|T(36)| > 3.58	*.002*	*.049*
Right Caudate	0-back	AT>NA & Post > Early	k = 135 -62 -04 -24 L Middle temporal gyrus (anterior division) L Temporal pole	↑	|T(36)| > 3.58	*.002*	*.021*
Left Caudate	0-back	AT>NA & Post > Early	k = 214 -62 -04 -24 L Middle temporal gyrus	↑	|T(36)| > 3.58	*<.001* *.005*	*.003* *.039*
Left Putamen	0-back	AT>NA & Post > Pre	k = 408 02 +44 +18 R, L Paracingulate gyrus	↑	|T(36)| > 3.58	*<.001*	*<.001*
			k = 130 +22 +38 +58	↑		*.002*	*.020*

			R Frontal pole R Superior frontal gyrus				
			k = 115 +22 +34 +40 R frontal pole R Paracingulate gyrus			*.003*	*.020*
			k = 113 +24 +46 +00 R Frontal pole			*.003*	*.020*
Left Hippocampus	0-back	AT>NA & Early > Pre	k = 321 +40 -52 +46 R angular gyrus R superior parietal lobule R Lateral occipital cortex, superior division R Supramarginal gyrus, posterior division		|T(36)| > 3.58	*<.001*	*<.001*
			k = 170 -54 -46 +52 L Supramarginal gyrus, posterior division			*.001*	*.006*
			k = 167 -30 -58 +36 L lateral occipital cortex, superior división			*.001*	*.006*

	L superior parietal lobule			
	k = 164 -12 -44 +60 L Postcentral gyrus L superior parietal lobule	↓	*.001*	*.006*

Red arrows indicate the direction of connectivity changes, i.e., increases / decreases, k = cluster size, unc. = uncorrected, FDR = False Discovery Rate.

4.4 Discussion

The present analysis focused on the task-based functional connectivity changes taking place over the course of a WMU training protocol, with a special focus on the differential connectivity patterns for the criterion and transfer tasks. Two groups of healthy young adults, i.e., an adaptive difficulty experimental group (AT) and non-adaptive fixed difficulty active control group (NA), practiced a visuospatial and a verbal WMU task for ten training sessions over the course of three weeks. fMRI and performance data were acquired at three time-points on MU criterion and n-back transfer tasks.

Our findings showed significant improvements in participants' performance on both criterion and transfer tasks over the training period regardless of the training group assignment. However, we did not find any significant effects of group, or group by time interactions, for performance on any of the criterion or transfer task conditions. Significant group differences reported in the original study by Flegal, Ragland and Ranganath (2019) were the results of analyses that focused solely on the pre- and post-training time points and included three participant groups: AT experimental group, NA active control group, and a no-contact control (NCC) group. The NCC group, included to assess any practice effects in the transfer task behavioural data, completed the same criterion and transfer tasks (without fMRI data acquisition) as the AT and NA groups but with no intervening WMU training. The present analysis, however, focuses on training related changes in functional connectivity and any differential patterns relating to the type of scanned task, i.e., criterion or transfer. We therefore included data solely from the AT and NA groups who took part in the fMRI sessions, and additionally considered all three time-points. The original study (Flegal, Ragland and Ranganath, 2019) reported a significant effect of group for post-training performance, controlling for pre-training performance, on 7-updates trials of the MU criterion task; the AT group was found to exhibit the highest performance increases. No significant effect of group was found for any of the n-back task conditions. Therefore, if we consider the original experimental design was chosen to isolate the effect of adaptive task difficulty which is similar for the present study analysis focus, then the lack of significant group differences when only examining AT and NA data is not unexpected.

This interpretation is more easily understood if we consider that both experimental and active control groups engaged in a challenging cognitive training protocol with the element of adaptivity being the sole difference. Level of training task difficulty adaptively changed according to participants' performance for the AT group while remained at a fixed level throughout the training for the NA control group. Consequently, when comparing the experimental group against an active control also engaging in a training protocol that taxes the process of WMU, any group effects are expected to be modest at best. For this reason, the choice of control group (CG) can substantially influence study findings, and naturally, it is a highly debated issue that has been extensively discussed in the cognitive training literature with some authors arguing a passive CG overestimates the training-related effects (Dougherty, Hamovitz and Tidwell, 2016; Melby-Lervåg, Redick and Hulme, 2016), and others suggesting that choosing between an active and passive CG does not influence the results (Au et al., 2016; Soveri et al., 2017). Recommendations include employing control tasks distinct enough from the training protocol to maximise the observable training effect (Green et al., 2014). One way to achieve this in the present study would be to have the active control group engage in an adaptive difficulty training protocol targeting a different cognitive process, e.g., processing speed, to the experimental group (Shipstead, Redick and Engle, 2012). Therefore, an adaptive non-WMU training control regime would shift the focus from the adaptivity element and concentrate on the plastic functional connectivity changes resulting from WMU training specifically.

4.4.1 Task-based functional connectivity changes on the criterion task following adaptive WMU training

The RRC findings on fMRI data from the MU criterion task revealed greater connectivity increases between the left and right hippocampus ROIs for the AT group than the NA group in the 4-updates condition, post-training compared to early-training; none of the other interaction effects examined were significant. Investigating changes in functional connectivity across the brain, our SBC findings showed consistent connectivity decreases over time between seed ROIs and parieto-occipital areas for the conditions of interest, i.e., 7- and 4- updates. More specifically, the AT group exhibited greater connectivity reductions than the NA control between bilateral putamen and right lateral occipital cortex,

post-training compared to early in the training for the 7-updates high difficulty condition. The same pattern of greater connectivity reduction for the AT than the NA group was revealed between the right hippocampus and the right superior parietal lobule and lateral occipital cortex for the low difficulty 4-update condition post-training compared to early-training. Changes in functional connectivity with parieto-occipital areas while performing the criterion task were consistent with training on a visuospatial WMU task, due to the regions' involvement in higher visual processing (lateral occipital cortex and fusiform gyrus), attention and visuospatial perception including manipulation and representation of objects (superior parietal lobule, SPL), as well as the close links between them (Johns, 2014). The SPL is also considered part of the dorsal attention (DA) network (Spreng, Shoemaker and Turner, 2017), with training-related connectivity decreases reported between subcortical and DA systems in a previous study (Finc et al., 2020) consistent with this finding.

Interestingly, we additionally found greater connectivity decreases for the AT group than the NA control group between left putamen and right posterior parahippocampal gyrus and right cerebellum for the AT group early-training compared to pre-training. Even though both cerebellum and parahippocampal gyrus would not traditionally be considered core WM regions, they are nevertheless known to be involved in various cognitive processes relevant to the tasks in this study. The parahippocampal gyrus has been associated with visuo-spatial processing (Aminoff, Kveraga and Bar, 2013) whilst previous research has reported cerebellar involvement in both verbal and spatial working memory tasks (Hautzel et al., 2009; Baier, Müller and Dieterich, 2014; Ashida et al., 2019) as well as cortico-cerebellar contributions in executive verbal working memory (Marvel and Desmond, 2010). Another study, investigating the respective roles of the basal ganglia and cerebellum in language processing, performed dynamic causal modelling (DCM) analysis on fMRI data collected on a rhyming judgment task presented in visual (word reading) and auditory modalities (Booth et al., 2007). The authors concluded the putamen and cerebellum have distinct roles in language processing with the putamen involved in cortical initiation of phonological representation and the cerebellum amplifying/refining these representations to facilitate decision making (Booth et al., 2007). It may therefore be that the connections between left putamen and

the right parahippocampal gyrus and cerebellum are directly associated with practicing and processing of visuo-spatial material and are very specific to the criterion's task features, i.e., the MU task involves making a decision on whether the updated location of the probe stimulus is correct. The observed pattern of changes revealed connectivity decreases with regions facilitating task-specific response features at first (pre-training to early-training) followed by connectivity decreases with right lateral occipital regions broadly involved in object perception (early-training to post-training). Thinking about this in reverse, the pattern of connectivity decreases between the left putamen and right posterior parahippocampal gyrus and right cerebellum early in the training could be indicative of neural processes relating to general task features at the early stages of training whilst connectivity decreases between the left putamen and right lateral occipital areas post-training might suggest neural processes focusing on more task-specific object processing.

Despite the location, direction and time of training, the AT group consistently exhibited greater connectivity decreases compared to the NA group in agreement with the adaptive task difficulty hypothesis. That is, dynamically adjusting task difficulty continuously challenges the individual's proficiency levels, thus creating a prolonged mismatch between pre-existing ability and environmental demands, evidenced by the greater changes in functional connectivity strength observed in the AT group compared to the NA.

Even though our findings also exhibited increases in connectivity, these were either associated with pre-existing group differences at pre-training, e.g., higher connectivity between the left hippocampus and the right frontal pole for the AT group than the NA group pre-training, or with the 0-updates baseline condition which is of no experimental interest.

4.4.2 Task-based functional connectivity changes on the transfer task following adaptive WMU training

The SBC findings exhibited a mixture of connectivity decreases between seed ROIs and fronto-parietal areas, and increases between seed ROIs and occipital areas, in the 2-back condition of the n-back transfer task. In more detail, the AT group exhibited greater connectivity reductions than the NA group

between the left putamen ROI and the left precentral gyrus post-training compared pre-training, as well as between the left putamen and right precentral and postcentral gyrus early in the training compared to pre-training. According to a coordinate-based meta-analysis that investigated the neural correlates of working memory, the precentral gyrus, otherwise known as the premotor cortex, may be divided into a dorsal and ventral part (Rottschy et al., 2012). In the context of working memory, the dorsal part is active during memorising object location and the ventral part is involved when object properties need to be remembered. Furthermore, the cluster location is adjacent to the frontal eye fields (FEF) region, an area known to be involved in visuospatial WM tasks (Curtis, 2006; Salmi, Nyberg and Laine, 2018). Reduced functional connectivity between the left putamen and precentral gyrus post-training could be suggestive of reduced task demands and overall task challenge and indicative of diminished need for task-specific process.

Greater connectivity increases in the AT group than the control were revealed between bilateral caudate seed ROIs and the superior division of the left lateral occipital cortex, as well as left caudate and left precuneus, early in the training compared to pre-training. We additionally found greater connectivity decreases in the AT group than the control between the left putamen and the left supramarginal gyrus (anterior and posterior division) post-training compared to early-training. As in the criterion task, functional connectivity changes with parieto-occipital areas were also expected on the transfer task. The precuneus is involved in various cognitive functions such as spatial function and navigation, integration of information, and cue reactivity; it has strong links with the parietal cortex and is part of the default mode (DM) network (Johns, 2014). Deactivations in the DM network are observed during task engagement. The left supramarginal gyrus is part of the inferior parietal lobule (IPL) involved in attention and sensory processing and is also thought to be part of the DM network (Spreng, Shoemaker and Turner, 2017). Consequently, there seems to be a re-organisation in functional connectivity between the striatal system and regions belonging to the DM network over the course of a WMU training protocol.

We further identified a main effect of group with connectivity between the left putamen and posterior cingulate gyrus being lower for the AT group than the NA group throughout the training. Since our analysis did not reveal a significant group by time interaction for that SBC cluster, we cannot draw conclusions on the nature of this finding.

4.4.3 Pattern of functional connectivity changes differ according to task type, i.e., criterion and transfer, following adaptive WMU training

We can conclude there is a qualitative distinction in the pattern of functional connectivity changes manifested in the criterion and transfer tasks following adaptive WMU training (see Figure 4.4.1 for a schematic representation).

Functional connectivity decreases were associated with the criterion task regardless of the brain regions involved and time of training. On the contrary, the connectivity changes on the transfer task involved a mixture of decreases and increases; reductions were observed between left putamen and fronto-parietal regions post-training compared to pre- and early-training as well as increases between bilateral caudate and occipital regions and left caudate with precuneus early in the training compared to pre-training. The literature on experience-induced plasticity posits that reduced functional activation following working memory training reflects increased neural efficiency or a more precise functional circuit (Kelly, Foxe and Garavan, 2006), and is suggestive of more automatised processing (Baykara et al., 2020). We could assume the connection strength decreases observed in the present study might also be indicative of a more precise functional circuit irrespective of task since the reported changes took place in both criterion and transfer tasks and irrespective of brain region involved, yet evidently related to adaptivity, i.e., dynamically adjusting task difficulty based on the individual's performance. Consequently, the pattern of greater connectivity decreases exhibited for the AT group compared to the NA control is directly related to the prolonged mismatch between existing functional supply, i.e., the AT groups' pre-existing ability, and environmental demands, i.e., a continuously challenging training task.

A striking difference in the pattern of functional connectivity changes between criterion and transfer tasks involved the nature of frontal connections with subcortical seed ROIs. They were absent for the criterion task altogether, whilst decreases in connectivity between left putamen and left precentral gyrus were observed throughout the training period for the transfer task. On the contrary, the left putamen seed exhibited decreased connectivity with clusters located in the right cerebellum and right parahippocampal gyrus at the beginning of training followed by decreased connections with right lateral occipital areas at the late training stage for the criterion task.

The training-related patterns of connectivity in the left putamen differ for the criterion and transfer tasks suggesting a distinct role for that seed ROI. The fact that connections between the left putamen and precentral gyrus persist post-training for the transfer task, even though reduced, could be indicative of task demands still in place. On the other hand, reduced connections between the left putamen and right parahippocampal gyrus and right cerebellum followed by connectivity decreases with right lateral occipital regions for the training task might suggest changes in neural processes relating to general task features in place at the early training stage followed by changes associated with task-specific object processing as training progresses.

Another difference between criterion and transfer tasks involved connectivity increases for the transfer task only between bilateral caudate and the superior division of the left lateral occipital cortex as well as left caudate and left precuneus. This differential pattern in functional connectivity changes could be considered congruent with models of neural plasticity dynamics relating to functional activity changes (fast-early and slow-late stage changes occurring at different motor learning stages (Doyon and Benali, 2005) and structural volumetric changes (the expansion reorganisation model of initial grey-matter volume increases followed by a partial or even complete return to baseline volume levels (Wenger et al., 2017).

Taking these models into account we could hypothesise any training-related functional connectivity changes to occur between early- and post-training time points with the direction of those changes reflecting initial increases and subsequent decreases. As illustrated in Figure 4.4.1, there are

differential patterns of change for the criterion and transfer tasks. In the criterion task, we indeed found connectivity changes to occur mostly between early- and post- training times. Rather than initial connection strength increases and subsequent decreases, though, our findings exhibited a re-organisation of connectivity decreases between the left putamen with the limbic system's right parahippocampal gyrus and the right cerebellum taking place initially (pre-training to early-training) and subsequently followed by decreases between bilateral putamen and right lateral occipital areas (early-training to post-training). On the contrary, the pattern of connectivity changes for the transfer task revealed connectivity strength decreases between the left putamen and precentral gyrus extending throughout the training period whilst decreases with the left supramarginal gyrus took place early in the training period only. We additionally found increases between the left caudate and the left lateral occipital cortex and precuneus early in the training. At the same time, the strength of the connection changes was greater for the AT than the control group irrespective of direction, i.e., increases/decreases, thus indicating the key role of adaptivity. Therefore, it can be concluded that dynamically adjusting task difficulty based on individual performance facilitates training related connectivity changes post-training.

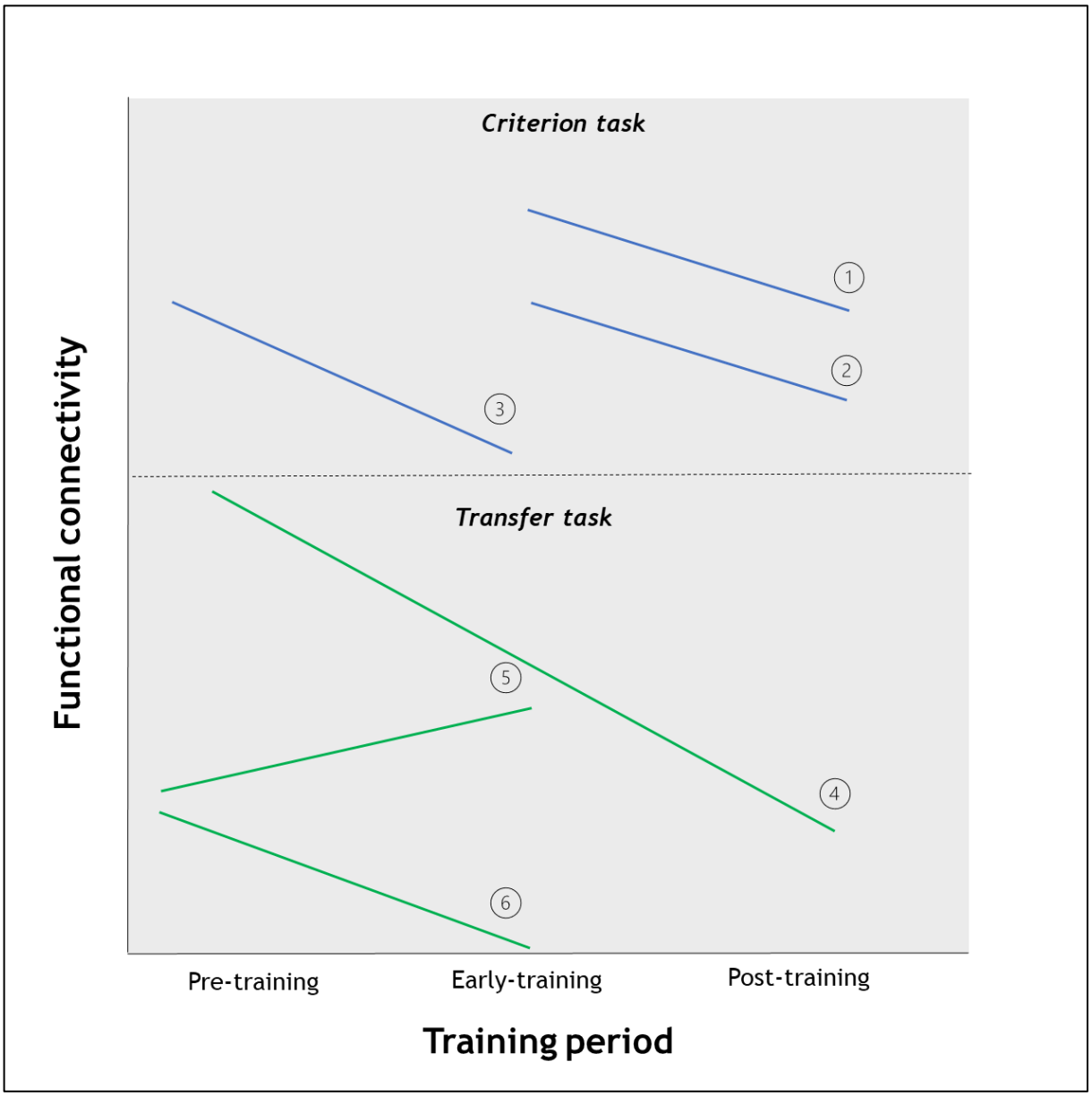

Figure 4.4.1: Changes in functional connectivity patterns between subcortical ROIs and frontal, parietal and occipital regions over time for the criterion and transfer tasks. 1. Right Hippocampus - Right lateral Occipital cortex & right Superior Parietal lobule, 2. Bilateral Putamen - Right lateral Occipital cortex & right Occipital fusiform gyrus, 3. Left Putamen - Right cerebellum & right parahippocampal gyrus, 4. Left Putamen - Left Precentral gyrus, 5. Left Caudate – Left lateral Occipital cortex & left precuneus, 6. Left Putamen - Left supramarginal gyrus.

4.4.4 Task-based functional connectivity changes in absence of group effects

Functional (activity/connectivity) brain changes can indeed occur in the absence of behavioural effects (Baykara et al., 2020; Beauchamp, Kahn and

Berkman, 2016) as is the case in the present study comparing two groups of healthy young adults who both completed a WMU training protocol. Even though our neural findings exhibited interesting differential patterns of connectivity changes for the adaptive group across the criterion and transfer tasks, task performance on the contrary did not show any significant group or interaction effects. Performance increased over time with both AT and NA groups improving with training, so changes in functional connectivity appear to be associated with improved performance. Our partial correlation analyses further corroborated this although our results did not remain significant after applying corrections for multiple comparisons. A few points of discussion emerge which we will address by considering the theoretical framework of adult plasticity by Lövdén et al. (2010).

The first point to consider is whether we can interpret the neural changes evidenced by functional connectivity metrics as plastic in the absence of cognitive plasticity. The theoretical framework by Lövdén and colleagues makes a distinction between the concepts of plasticity and flexibility and their relationship to the neural system. Flexibility is the neural system's ability to adapt to environmental demands and use the neural processes necessary to perform a given task. Plasticity is considered the neural system's response to meeting those demands through learning, training, and changes in the neural system, which produces changes in the system's pre-existing ability. The study training protocol employed adaptive difficulty to trigger and achieve the necessary mismatch between the AT participants' existing resources and environmental demands, and subsequently lead to changes in the neural system and pre-existing ability. Our findings suggest the adaptive WMU training protocol was indeed successful in promoting the neural system's flexibility, i.e., improved performance overall, as well as the initial stages of plasticity, i.e., training related changes in functional connectivity. The adaptive element though was ultimately unsuccessful in producing significant changes in the neural system's pre-existing ability, i.e., absence of significant group differences. This brings us to the second point of discussion, i.e., the relationship between flexibility/plasticity and the timeline of learning.

The theoretical framework developed by Lövdén et al. (2010) further proposes plasticity to be a sluggish capacity where a prolonged mismatch between existing functional supply and environmental demand is necessary to overcome the sluggishness of the neural system and eventually push it away from its balanced state. Consistent with this, it could be further argued that 1. flexibility and plasticity take place at distinct time-points during the learning period and 2. flexibility precedes plasticity. We could then draw a parallel between a fast-early learning stage and flexibility and a subsequent slow-late learning stage and plasticity. The distinct phases at which flexibility and plasticity are hypothesised to occur also produce differential changes in the neural system evidenced by the present study's training-related changes in functional connectivity evident at different stages of training. This is consistent with previous fMRI training studies employing multiple scanning sessions focusing on the temporal dynamics of WM training reporting initial activity increases followed by decreases (Kuhn et al., 2013; Hempel 2004). In more detail, Kuhn et al. (2013) reported an inverted u-shape pattern of the functional activity changes taking place over the training period where striatal regions and primarily bilateral putamen exhibited activity increases followed by subsequent decreases. We additionally support the notion that the relationship between flexibility and plasticity is not linear, we rather think of it as a circuit and/or feedback loop where the system could revert to the flexibility stage as many times as necessary or even situations where the state of flexibility and plasticity co-occur, i.e., the time just before the neural system's response stabilises to produce a change in the pre-existing ability.

4.4.5 Limitations

Even though the present study has several strengths, i.e., three fMRI time-points, a very well controlled experimental design and appropriate sample sizes, we do need to consider its limitations. First, due to the original study's focus on the element of adaptivity as a factor influencing transfer of training, the present findings represent the patterns of functional connectivity changes following adaptive training rather than specific to the trained process, i.e., WM updating. As described at the beginning of the discussion section, the latter could be achieved by comparing an adaptive WMU experimental group to an adaptive control group training on a different cognitive process. Therefore, the

element of adaptivity would be cancelled out and the training-related changes would instead reflect the specific trained process. Another limitation is the relatively brief training duration or training frequency; a total of ten hours of training may not be enough to produce changes to the neural system's pre-existing ability, or the frequency of training may not have been sufficiently intense.

4.4.6 Conclusions

The present study investigated the task-based functional connectivity changes associated with a WM updating training protocol in healthy adults. Participants were assigned to adaptive and non-adaptive groups, trained for a total of ten hours and fMRI and performance data were acquired at pre- early- and post-training sessions. Our connectivity analysis focused on connections between, and across all voxels in the brain from, subcortical ROIs and further investigated the differential patterns of change over time between the criterion and transfer tasks. From our findings, we can conclude that the training element of adaptivity successfully promoted neural changes as evidenced by the changes in functional connectivity strength for both criterion and transfer tasks. Adaptive training task difficulty additionally exhibited a distinct pattern of subcortical connectivity changes for the training and transfer tasks. We observed a training-related re-organisation in functional connectivity within the left putamen for the criterion task, where reduced connectivity with the limbic system occurred at first and was subsequently followed by reduced connections with occipital regions. Furthermore, there was a training-related functional connectivity re-organisation between the left caudate and left putamen and regions belonging to the DM network, where connectivity increases were revealed between left caudate with the left precuneus and left lateral occipital regions early in the training followed by decreases between the left putamen and the left supramarginal gyrus post-training compared to early-training. Another difference between the two scanned tasks was the observation of reduced fronto-striatal connectivity strengths throughout the training period in the transfer task and their absence in the criterion task. Despite the observed changes in functional connectivity, there were no associated group differences in task performance. The adaptivity feature was found to successfully trigger the neural system's flexibility, as manifested with the functional connectivity changes taking place

and overall improved performance, but ultimately unable to produce changes in the neural system's pre-existing ability, i.e., absence of significant group x time interactions. Finally, we propose a non-linear relationship between flexibility and plasticity and additionally link these two concepts with the fast-early and slow-late stages of learning, respectively. Future studies should further focus on the functional connectivity changes following WM training with emphasis on subcortical ROIs.

5 Working memory training: Taking a step back to retool and create a bridge between clinical and neuroimaging methods

This chapter is a modified version of the article published in the journal of Applied Neuropsychology: Adult (Pappa et al. 2021).

Improvements in patient outcomes and mortality after brain injury alongside increasing ageing population have resulted in an increasing need to develop cognitive interventions for individuals experiencing changes in their cognitive function. One topic of increasing research interest is whether cognitive functions such as attention, memory and executive functioning can be improved through the use of working memory training interventions. Both clinical and neuroimaging researchers are working to evidence this, but their efforts rarely come together. We discuss here several issues that may be hindering progress in this area, including the tools researchers utilise to measure cognition, the choice between employing active or passive control groups, the focus on transfer effects at the expense of well-characterised training effects, and the overall lack of neuroimaging studies in individuals with neurological disorders. We argue that the only way to advance the field is to build bridges between the disciplines of clinical neuropsychology and cognitive neuroscience. We suggest a multi-level framework to validate the efficacy of working memory interventions and other forms of cognitive training that combine both clinical and neuroimaging approaches. We conclude that in order to move forward we need to form multidisciplinary teams, employ interdisciplinary methods, brain imaging quality rating tools and build national and international collaborations based on open science principles.

Keywords: brain injury, neuropsychological rehabilitation, cognitive training, working memory, neuroimaging

5.1 Introduction

In recent decades life expectancy has increased across the globe (Oliver et al., 2014). At the same time, patient outcomes and mortality rates from acquired brain injuries (ABI) such as stroke and traumatic brain injury (TBI) have improved (Feigin et al., 2014; Lawrence et al., 2016). As a result, there is a growing proportion of the population experiencing long-term changes in their cognitive function from ABI or experiencing cognitive decline due to ageing even in the absence of disease (Andrews-Hanna et al., 2007; Bishop et al., 2010). Neurodegenerative disorders can also be a cause of cognitive decline and there has been a plethora of research on developing pharmaceutical (Heiss et al., 1994; Loewenstein et al., 2004) and behavioural (Marshall et al., 2011; Tárraga et al.,2006; Hill et al., 2017) interventions in that context. However, this review will concentrate on research addressing the cognitive impairments resulting from ABI. Cognitive impairments impact upon everyday functioning and can turn previously simple activities of daily living (ADL), such as cooking, shopping and using public transport, into hazardous tasks (Chung et al., 2013; Galetto and Sacco, 2017; Krasny-Pacini, Chevignard and Evans, 2014). There is therefore a need for effective rehabilitation interventions that address the cognitive deficits arising from ABI or ageing to enable people to lead independent, fulfilled lives.

In neuropsychological rehabilitation there is a strong emphasis on supporting people to become independent in ADL. One domain of cognition that is critical for effective independent living is executive functioning – which refers to the ability to problem-solve, to plan, and manage tasks effectively. Clinical guidelines in relation to the rehabilitation of executive functioning following ABI recommend the use of 'meta-cognitive strategy training' (Ponsford et al., 2014; Tate et al., 2014; Velikonja et al., 2014). Meta-cognitive strategy instructions focus on encouraging the individual to 1. set goals, 2. break the task/goal down to smaller sub-tasks/goals, 3. regularly bring their attention back to the task/goal at hand and 4. actively monitor their performance. This has informed the development of a standardised and validated tool called Goal Management Training (GMT) (Levine et al., 2000; 2011). The overall efficacy of meta-cognitive strategy instructions has been investigated in several randomised controlled trials (RCTs) including adults suffering from executive dysfunction (Levine et al., 2000; McPherson et al., 2009; Rath et al., 2003; Spikman et al.,

2010; Stamenova and Levine, 2018) as well as problems with memory (Kaschel et al., 2002; Ryan and Ruff, 1988; Shum et al., 2011) and attention (Fasotti et al., 2000). The use of environmental supports such as external memory aids and reminders, e.g., mobiles/smartphones, notebooks, virtual digital assistants, have also been evaluated in RCTs (Fish et al., 2011; Wilson et al., 2001) and is clinically recommended for use with adults who have memory difficulties (Velikonja et al., 2014). These types of strategy-based interventions, familiar to many clinical neuropsychologists, are classified as 'compensatory' (compensating for impairments of cognitive functioning through the use of external aids or instructed strategies).

Researchers in the field of cognitive neuroscience, however, have been interested in process-based interventions that are often characterised as 'restorative' (aiming to restore to normal, or near-normal, underlying core cognitive processes including executive functions) (Brehmer et al., 2014). Consequently, there has been increasing research interest among cognitive neuroscientists in the development and evaluation of computerised cognitive training process-based paradigms. These have been utilised in two different contexts: 1. for "boosting" healthy young and older adults' cognitive function (Au et al., 2015; Brehmer et al., 2014; Brehmer et al., 2011; Jaeggi et al., 2008; Lampit et al., 2014) and 2. for cognitive rehabilitation in individuals with neurological damage such as ABI (Bogdanova et al., 2016; Galetto and Sacco, 2017; Hallock et al., 2016), dementia and mild cognitive impairment (MCI) (Gates et al., 2011; Hill et al., 2017; Sherman et al., 2017). The availability of non-invasive human neuroimaging methods (such as Magnetic Resonance Imaging, MRI) has contributed to the popularity of cognitive training research in cognitive neuroscience, enabling the measurement of experience-dependent changes in brain structure and function from experimentally controlled interventions.

A large number of cognitive training paradigms have been employed in both clinical and neuroimaging research studies, with working memory (WM) training regimes being the most popular and extensively examined to date (Backman et al., 2017; Buschkuehl et al., 2014; Clark, Lawlor-Savage and Goghari, 2017; Dahlin et al., 2008; Finc et al., 2020; Flegal, Ragland and

Ranganath, 2019; Heinzel et al., 2016; Kühn et al., 2013; Miro-Padilla et al., 2018; Salminen et al., 2016; Thompson, et al., 2016). According to the influential three-part WM model (Baddeley and Hitch, 1974), the phonological loop and the visuospatial sketchpad are two slave systems responsible for the storage of verbal and visuospatial information, respectively; whilst the central executive component is considered to be a cognitive control system that allocates attentional resources and is necessary to support executive processes such as planning, inhibition, problem-solving, organisation, shifting, maintenance and updating. Given the WM system's involvement in complex cognitive tasks, goal-oriented behaviour and regulation of executive processes, as well as its relationship with cognitive constructs such as fluid intelligence and language comprehension (Wiemers, Redick and Morrison, 2019), researchers have hypothesized that training WM processes can result in cognitive improvements extending beyond the specific task participants trained on, and thus represents an important target for intervention.

In the WM training literature, emphasis is placed on measuring the size of training and transfer effects in order to draw conclusions about the success of a training protocol. The training effect refers to performance on the task participants train on, also known as the criterion task; while the transfer effect refers to performance on an untrained task following training, i.e., transfer of learning. Transfer effects can be further subdivided into near transfer of learning (i.e., performance improving on an untrained task that is superficially different to the criterion task but shares the same trained WM process) and far transfer of learning (i.e., performance improving and/or generalising to an untrained task in a different cognitive domain such as general intelligence). This leads to one of the most controversial and debated topics in this field. Some researchers support the idea that far transfer to general intelligence tasks is possible following WM training (Au et al., 2015), and cite improvements on measures of cognitive function as showing the potential of WM training for clinical application (Weicker et al., 2016). Others argue there is no convincing evidence for the generalisability of any training effects beyond the specific tasks on which participants train and are sceptical as to whether far transfer could occur (Melby-Lervåg, Redick and Hulme, 2016; Soveri et al., 2017), therefore questioning the value of cognitive training for improving performance on

activities of everyday living (Melby-Lervåg et al., 2019). One issue behind this fundamental disagreement is that there are inconsistencies in the way researchers categorise near and far transfer effects across studies, and therefore the existence of transfer ultimately depends upon researchers' subjective classification of what constitutes near and far (Barnett and Ceci, 2002; Pappa et al., 2020). Secondly, cognitive neuroscientists rarely -if ever- include outcome measures to assess improvement in ADL following WM training (Pappa et al., 2020), whereas in a clinical setting, the ultimate goal is for individuals to improve in ADL after completing cognitive rehabilitation. Consequently, even if we accept that transfer of learning is possible, what would this mean for cognitive rehabilitation? Would we expect significant improvements in ADL following WM training; and if so, would we categorise this as near or far transfer of learning? Naturally, that would depend on the specific ADL. For example, it could be argued that improvements in shopping and cooking activities following WM training would provide evidence for near transfer, based on the demand those tasks place upon WM processes, while improvements in managing one's own finances would likely be categorised as far transfer. One reason for the spotlight on transfer of training is that if it is possible and we find a way to understand its mechanisms, the circumstances under which it occurs, as well as for whom, then we should be able to facilitate this transfer. This has potential to be a game changer in clinical neuropsychology, and to revolutionise the way we think about cognition and cognitive rehabilitation. Alas we are not there yet.

To date, WM training research has included paediatric and adult populations, both healthy and those with clinical conditions, and employed a wide variety of training paradigms. Although most neuroimaging studies are conducted with healthy adults, vast differences between studies relating to important training task features such as stimulus modality, training adaptivity (i.e., difficulty of the trained tasks adapting to the individual's changing performance), and protocol length, together with the use of various measurements of training efficacy, have made between study comparisons extremely challenging (Pergher et al., 2020). Therefore, drawing clear conclusions on the efficacy of WM training in healthy adults has been difficult so far. The translation of cognitive neuroscience research to clinical applications is further impeded because training studies using neuroimaging outcome measures

rarely include adults with neurological disorders, assess ADL outcome measures nor follow gold standard RCT methodologies (Galetto and Sacco, 2017; Pappa et al., 2020). In addition, currently there are no tools to specifically assess the methodological quality of neuroimaging training studies (Pappa et al., 2020) comparable to the many tools for evaluating randomised controlled study designs (e.g., the PEDro-P scale – Maher et al., 2003; Sherrington et al., 2000). We can only presume the reason for the lack of neuroimaging-related quality assessment tools is directly related to two main points: 1. the overall lack of training-related neuroimaging studies with neurological samples; and 2. the small number of clinical rehabilitation studies including neuroimaging methods. To put it simply, the need for having such tool has not emerged yet.

This short introduction has focused on the complexities behind the controversial and intriguing field of cognitive training research with a specific focus on WM training. We argue that one of the most important causes for the inconsistencies in training efficacy results is the lack of convergence between studies utilising neuroimaging outcomes and studies that focus on clinical methodologies. There are significant practical challenges in conducting both neuroimaging-focused studies (e.g., scanning costs, access to qualified radiographers) and clinically focused research (e.g., access to clients with neurological damage, the heterogeneity related to neurological damage and its functional impairment, the involvement of clinical staff). However, we believe there is a deeper issue that is rooted in a historical chasm between clinical and neuroimaging research. We believe that each field could benefit from the other through collaborative, rather than siloed, working. Different research fields are working towards tackling the same problem utilising methods and scientific approaches specific to their field, but we consider the only way forward is intersection, interaction and interdisciplinarity to investigate this scientific question of mutual interest; to put it simply, we need to look together at the same problem from different angles and perspectives. This review places emphasis on studies targeting WM processes due to their popularity in the field of cognitive training research. We will discuss some key issues that need to be taken into consideration in order to advance the field. In addition, we will focus in particular on the tools utilised by researchers to evaluate the efficacy of training and the use of complementary neuroimaging methods and analyses.

Even though the present review focuses on WM, we consider these issues common across the research area of cognitive training more broadly.

5.2 Measuring cognitive performance: What are we measuring?

The need to effectively measure cognition is at the heart of psychological research whether in the field of clinical neuropsychology or cognitive neuroscience. In summarising the types of validated psychometric tools used in clinical rehabilitation settings to assess cognitive abilities, we would say there are three broad categories: 1. construct-driven, 2. ecologically focussed and 3. functional ability in ADL. The first approach refers to tests that were designed to measure specific cognitive constructs; for example, the construct of inhibition is measured by the Stroop test (Stroop, 1935); cognitive flexibility and processing speed can be assessed with the trail making test (TMT) (Reitan, 1958); planning and problem solving is measured by the Tower of London (Culbertson and Zillmer, 1998). Many such tests were devised by early cognitive neuropsychologists to examine dissociations in cognitive functions between patients with brain damage and were later adapted into clinical psychometric tools, with normative samples against which individual patients may be compared (Parsons, 2016). Recently, there have been efforts to utilise modern technology and adapt existing construct-driven tests into computerised assessments such as CANTAB (CANTAB®, 2019) and Cambridge Brain Sciences (Owen et al., 2010) software, although use of these tools in clinical settings remains limited for a variety of reasons, including their cost.

The construct-driven test approach has been criticised, however, due to the inability to effectively relate performance with everyday functioning. Consequently, many researchers argued for an approach that emphasises ecological validity and developed tools designed to be more closely related to everyday function, e.g., the Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson, 1996) and the Rivermead Behavioural Memory Test (RBMT) (Wilson et al., 1989). This shift from a construct-driven approach to a more ecologically focussed approach, as well as the need to conclude whether cognitive rehabilitation outcomes are meaningful in a real life context, also led to the use of validated scales assessing functional ability in ADL, e.g., the

Rivermead ADL Scale (Lincoln and Edmans, 1990) and the Functional Independence Measure (FIM) (Keith et al.,1987). A systematic review on the efficacy of computerised cognitive training in ABI concluded that very few RCTs report outcomes on ADL and further emphasised the potential for employing neuroimaging methodology to better understand the mechanism behind such interventions (Sigmundsdottir, et al., 2016).

In the field of cognitive neuroscience, on the other hand, researchers mainly rely on lab-based experimental tasks to measure cognitive performance changes at a group level following training. In the WM training literature, for example, the most frequently used experimental paradigm involves the n-back task. It taxes various WM processes simultaneously such as updating, encoding, monitoring and maintenance (Jaeggi et al., 2010). The n-back task is popular for a variety of reasons: it provides a straightforward way to manipulate WM load (cognitive performance effectively worsens as load increases), it induces consistent activation in WM related brain regions (i.e., bilateral frontal and parietal areas), and performance on n-back high load levels is predictive of individual differences in measures of general intelligence and other cognitive functions (Jaeggi et al., 2010). Across studies using the n-back task there have been multiple variations of key task features such as the task modality (i.e., visuo-spatial, verbal, auditory), the number of load levels, and whether the task is presented in a single or dual modality. A major issue is that this variability in important task features, as well as other differences in the various WM training protocols, makes it very difficult to compare findings across training studies (Pergher et al., 2020).

Due to the various difficulty levels and task conditions in WM paradigms, observed enhancements in post-training performance might originate from improvement in just one level or condition of the experimental task rather than across all levels and conditions. Consequently, researchers draw conclusions based upon performance changes where participants have improved the most rather than on the average across levels or conditions. When meta-analytic studies average across levels and conditions to present unbiased results and test for publication bias and heterogeneity across studies, the training related effects overall turn out to be smaller (Pappa et al., 2020). Furthermore,

neuroimaging researchers seldom use clinically validated psychometric tools to measure training efficacy and when they do, performance on these tasks typically does not improve significantly (Backman et al., 2017; Biel et al., 2020; Colom et al., 2013; Thompson et al., 2013). Additionally, tests that are considered more ecologically valid or scales assessing functional ability in ADL are very rarely used in the WM training field (Pappa et al., 2020); and cognitive training field in general (Sigmundsdottir, Longley and Tate, 2016). As a result, these issues pose a major drawback for implementing such training regimes in a clinical setting because of difficulty ascertaining that the size of the cognitive improvement following training is accurate, clinically meaningful and/or relevant for better managing the challenges of everyday living.

5.3 Active Vs Passive Control Groups: Does it make a difference?

Central to good science in relation to the evaluation of intervention efficacy is the use of control groups (CGs) to control for effects not specific to the intervention. The two types of CGs are: 1. active CG, i.e., participants receive an alternate intervention, which controls for non-specific aspects of the experimental intervention, and 2. passive CG, also known as no contact CG, i.e., participants do not engage in any intervention. The findings across various WM training studies and meta-analyses have not been conclusive on which is the most appropriate type of CG or how this choice affects the size of the training and transfer effects. Some authors suggest the type of CG does not influence the transfer effect size (Au et al., 2020; Soveri et al., 2017) whilst others conclude that the employment of a passive CG overestimates the transfer effect (Dougherty, Hamovitz and Tidwell, 2016; Melby-Lervåg, Redick and Hulme, 2016). A recent meta-analysis on the effects of WM updating training found that when comparing the training group (TG) against an active CG the training effect is mild to moderate. By contrast, comparing against a passive CG resulted in very large effect sizes, indicating the training effect is overestimated (Pappa et al., 2020). This inconsistency has given rise to concerns regarding training efficacy. Active CGs are methodologically stronger for determining the specific effects of an intervention but are likely to result in smaller effect sizes (as they control for non-specific effects on outcomes) and thus require substantially larger sample sizes. This has implications for clinical studies in particular since larger sample

sizes can be quite challenging without substantial funding and multiple recruitment sites and teams collaborating together.

Passive CGs provide an evaluation of an intervention against no-intervention but do not control for non-specific effects (Green et al., 2014), of which there are a number. For example, outcomes from WM training could be influenced by the expectancy of improvement (i.e., due to the TG and CG being treated differently, then a larger training improvement favouring the TG might stem from the participants' expectation) and greater social contact with the experimenters (Boot et al., 2013; Shipstead et al., 2012). Therefore, researchers should work towards matching expectations of improvement in both TG and CGs (Shipstead et al., 2012). A recommendation for active CGs is creating a control task distinct enough from the training task to maximise the observable training effect (Green et al., 2014). To achieve this, some researchers have proposed the use of an adaptive difficulty training protocol for the active CG but on a different cognitive domain (Shipstead et al., 2012), e.g., adaptive WM protocol for the TG versus an adaptive processing speed protocol for the active CG. Alternatively, others have emphasised achieving a balance between a passive CG and an overly challenging active CG by employing a lower-level task paradigm (von Bastian and Oberauer, 2014), e.g., adaptive WM protocol for the TG and a fixed low level difficulty WM protocol for the active CG. However, as Green et al. (2014) correctly pointed out, while devising a "standard" CG protocol across studies would be useful but probably unachievable, the optimal CG ultimately depends upon the specific research questions and study aims. For example, in a clinical rehabilitation setting, the group receiving a cognitive intervention may be compared against a "treatment as usual" CG, which may be no intervention at all. Even though theoretically this CG is not controlling for expectancy effects or other confounding variables, it can still prove useful in assessing overall effectiveness in the early stages of a trial, or once efficacy has been demonstrated against an active CG, comparison with 'treatment as usual' provides evidence of the added benefit of the intervention in clinical practice.

5.4 Shifting the focus back on to the training effect: What steps are needed?

WM training researchers from either a clinical or neuroscience background measure participants' performance at (at least) two time points, i.e., before and after the training interval. In addition to performance changes on the training task, a number of transfer tasks are usually included to assess near and/or far transfer of learning following WM training. As introduced above, near transfer of learning refers to improved performance on an untrained task of the same domain, while far transfer refers to improved performance on an untrained task of a different cognitive domain. For this reason, research studies very frequently measure the success of a training paradigm based on whether transfer occurred and therefore, researchers are particularly interested in the existence, nature and size of the transfer effect. However, studies focusing on developing and validating any cognitive interventions rarely find large effect sizes, especially on measures of everyday functioning. This finding is consistent with clinical trials of medications where improvements in cognitive function and ADL tend to be small when compared against a placebo (Birks et al., 2015). Therefore, if the training effect itself is likely to be moderate, especially when comparing the TG against an active CG (Pappa et al., 2020), this raises questions regarding whether transfer of training effects can be anything other than small, and therefore only detectable in adequately powered studies with very large sample sizes. One way to address this is to break-down the experimental process into smaller steps, or phases, an approach that is consistent with the MRC Guidelines on developing and evaluating complex interventions to improve health (Craig et al., 2008). To adapt this approach to streamline the evaluation of cognitive training studies, we suggest the following three stages:

Stage 1: Small-scale feasibility studies to assess delivery of the intervention, bring together data on drop-out rates, sample size, recruitment, outcome measures etc. Both active and passive CGs would be informative at this stage. RCT methods are not essential when investigating all aspects of feasibility, but pilot studies that look at feasibility of running an RCT are important options. Statistically significant training effects are not expected due to small sample sizes while neuroimaging methods are not essential at this stage. It could be that a number of small-scale feasibility studies may be

required to refine the study design before progressing onto Stage 2. In cases of multiple refinements, the later ones should be as close to a larger trial in design as possible.

Stage 2: A well-controlled and sufficiently powered study with an emphasis on assessing training efficacy. Comparing the TG against an active CG in a well-controlled experimental setting is recommended. This stage is ideal for examining core training features before proceeding to the next stage. The outcome measures focus on training and transfer tasks, and follow a construct-driven approach. Neuroimaging methods are essential at this stage to explore the training related neural changes and facilitate understanding of the learning mechanism.

Stage 2 could be further subdivided if the estimated sample sizes for sufficient power to detect training related effects differ for the behavioural and neuroimaging components:

Stage 2a Behavioural component: a well-controlled and sufficiently powered study emphasising the efficacy of training with a specific focus on measuring the training and transfer effects following a construct-driven approach. Adding a qualitative evaluation component relating to the intervention and ADL would provide valuable information especially for studies with clinical groups, although it is not essential at this stage.

Stage 2b Neuroimaging component: a well-controlled and sufficiently powered study employing pre-test and post-test scanning sessions to explore the training related neural changes. A combination of functional and structural neuroimaging analyses could be employed.

Stage 3: Large-scale trials for evaluating the training effectiveness with an emphasis on real world conditions rather than a well-controlled experimental setting. Comparing the TG against a passive CG or “treatment as usual” might be preferrable at this stage to reflect real life settings. Researchers should select a few outcome measures with particular focus on ecological tasks, ADL alongside a key outcome used in the previous stage and may consider assessing maintenance

of intervention gains and evaluating long-term cost-effectiveness. Neuroimaging methods are not essential at this stage.

5.5 Other training related factors: What else to consider?

Another issue to consider is whether training gains are influenced by individual differences, including pre-training baseline performance. Two opposing approaches to understanding this issue have been prominent so far: compensation and magnification. In the first case, compensation hypothesizes that individuals starting from low baseline level exhibit larger training gains because they have more room for improvement, through compensating for inefficient pre-training performance, whilst those with higher performance at baseline, i.e., at or close to ceiling, will benefit less because there is less room for improvement. On the other hand, magnification suggests that any pre-training differences between individuals are magnified due to training. Larger gains are predicted for those with higher cognitive performance at baseline, through employing more pre-training resources, while those performing poorer at baseline are expected to improve less due to limited pre-training resources constraining their potential to adopt and implement the trained skills and/or strategies (Lövdén et al., 2012). In fact, there is evidence in favour of compensation (Jaeggi et al., 2011) as well as magnification (Foster et al., 2017; Wiemers, Redick and Morrison, 2019) in the cognitive training literature.

An interesting study by Lövdén et al. (2012) employed an episodic memory training protocol with individualised mnemonic strategy instructions for the first two training sessions followed by an assessment session and then individualised adaptive difficulty training for the remaining five training sessions. The authors computed a score for instruction training gains and practice training gains and suggested that among three age groups (children, young adults, and older adults), those starting at a lower baseline level compensate after instruction training and between-individual differences reduce, while continued practice exposes evidence of magnified between-individual differences with those starting at a higher baseline level benefiting more following training. Hence, the relationship between baseline performance and training gains might not be explained by a straightforward compensation or magnification approach; rather it might additionally depend upon other factors such as training type (strategy-

or process-based) and difficulty level (fixed or adaptive). Examining hypotheses for a time-dependent account, i.e., during the early training period those starting off at a lower level compensate and performance differences between individuals reduce; while following training completion those with higher baseline performance benefit more and individual differences become evident; requires both early training and post-training assessment sessions.

As a further consideration regarding the temporal dynamics at play, using a combination of neuroimaging and behavioural methods to investigate the timeline in which performance gains occur throughout the training period and also shortly thereafter could further delineate the learning mechanism. A longitudinal study design with only two time-points, i.e., pre and post, might only provide a small snapshot of the training related changes in performance and neural function whereas additional assessment points allow us to construct, piece by piece, the timing in which those changes occur. For example, do individuals exhibit rapid changes early on in the training period or is there a slow and steady growth curve? Do these training-related changes plateau after a while and thus render lengthy training periods unnecessary? Additionally, does the timing of changes depend upon individual differences such as age or baseline performance? These are all important questions that could be answered by adding more assessment points during the training period. The next question one might wish to answer is, are training-induced changes maintained over time? Once again, the nature of the research question determines the exact time-point when the additional post-training assessment session(s) should be conducted. One final question that is of particular mechanistic interest to us, is whether individuals with neurological disorders exhibit a learning curve similar to a control sample with the training-related changes following a similar timeline.

Since most WM training studies have been conducted in healthy adults and findings on who will likely benefit more are still inconclusive, making predictions in relation to clinical samples' response to training is challenging. Sala and Gobet (2019) raised the question of whether the training benefit might be greater for populations starting from a baseline of cognitive impairment, consistent with a compensation approach. Indeed, cognitive training studies on participants with a diagnosis of schizophrenia suggest that those starting off the

intervention with the greatest impairment are more likely to benefit from it (DeTore et al., 2019; Harvey et al., 2020). On the other hand, those with milder cognitive deficits could also be predicted to benefit from a cognitive intervention by maintaining their cognitive functioning at a stable level and preventing it from worsening. This could be particularly relevant for older adults without a neurodegenerative condition who experience cognitive deterioration due to natural ageing process (Lustig et al., 2009). This intriguing issue clearly needs to be further addressed in the clinical populations of interest. Thus, once again, it is fair to conclude the field needs more training studies involving individuals with neurological disorders and participants exhibiting various levels of baseline cognitive function.

Another under-studied factor of particular interest in the training literature is motivation. It has been suggested that if a participant holds the belief that cognitive training can improve outcomes such as intelligence, then that in itself is a motivating factor that can influence the training outcome (Katz et al., 2016). Therefore, it could be argued that an individual with a brain injury has an even stronger motivation to complete the intervention and put in extra effort to improve their performance and cognitive abilities compared to healthy controls. Then again, those with neurological injury are often unaware of their own impairment, i.e., suffer from anosognosia (Arnould et al., 2016). This can substantially hinder their motivation and willingness to engage in cognitive training and it is a factor that should be accounted for in studies including adults with neurological impairments. Therefore, motivation is of particular importance in clinical samples and should be further investigated and taken into consideration when interpreting training effects. Further to this, participants' motivation is more likely to be enhanced by knowing they will be involved in some kind of training activity as opposed to nothing and will be an important point to consider when deciding how active and passive CGs are framed.

Furthermore, the concept of cognitive reserve (CR), i.e., the hypothesis that certain individuals are more resilient to brain damage (Stern, 2002), is also relevant. The factors associated with CR could relate to the individual's level of education, occupational attainment, amount of physical exercise as well as social stimulation; and thus, information related to these should ideally be

collected (Stern, 2012). Baseline cognitive performance, motivation, presence of anosognosia, severity of cognitive deficit and CR are key factors that could be influencing the individual's response to training and should be considered in studies with neurological samples.

5.6 Combining neuroimaging analyses

Most cognitive neuroscientists employ functional MRI (fMRI) to examine changes in patterns of brain activity induced by WM training and therefore research studies presenting findings from other neuroimaging modalities, such as training-related alterations in brain structure and functional connectivity, are disproportionately fewer. Even though there is inconsistency across studies in the direction of functional activity changes following training, a recent meta-analysis identified a more homogeneous training-related pattern of activity reductions and attributed this to focusing on studies that trained the specific process of WM updating (Pappa et al., 2020). Unfortunately, as yet there are too few studies exploring other brain MRI modalities (e.g., volumetric or surface-based morphometry and network measures of connectivity within and between brain regions involved in the learning process) to draw any conclusions on training-induced changes, as noted in the meta-analysis by Pappa et al. (2020) and another review focusing on executive function training in older adults (Nguyen et al., 2019) where only four of the twenty studies employed structural imaging analyses.

Examining the functional activity response following training undoubtedly gives an important insight into the neural workings of learning but fMRI analysis alone is not sufficient to understand the underlying mechanisms. It could be that the subtle changes following training, as exhibited by moderate behavioural training and transfer effect sizes, are more reliably captured by analyses of functional connectivity which would instead give an indication of the neural changes at the network level rather than within separate brain regions. Along the same lines, positron emission tomography (PET) is an alternative neuroimaging methodology that enables researchers to investigate the function of neurotransmitter systems. This can provide invaluable converging data on the mechanism of learning due to the link between dopaminergic neurotransmission,

for example, and functional activity in the WM related striato-frontal brain areas understood to be involved in the mechanism of learning (Bäckman et al., 2011).

That is not to deny the suitability of fMRI analysis for exploring neural changes following training; it is just to highlight that valuable information is missing if additional complementary analyses are not used. Similarly, if we hypothesize that a short WM training regime is not sufficient to produce significant volumetric brain changes in conventional structural MRI analysis, as exhibited when acquiring new visuo-motor skills (Draganski et al., 2004; Taubert et al., 2010) or following a longer learning period (Draganski et al., 2006), then employing diffusion tensor imaging (DTI) to examine training-related changes in the microstructural integrity of white matter tracts might be a more effective method to delineate the learning mechanism. The point here is that employing more than one neuroimaging analysis for the same dataset can give a more complete picture of the neural process of learning and thus enable researchers to draw more consistent conclusions. The combination of different neuroimaging analyses to fully investigate the neural mechanisms involved in WM training could be equated to evaluating the effectiveness of a training intervention using different types of quantitative measures (i.e., construct-driven, ecologically focussed or functional ability in ADL) in quantitative behavioural studies or likened to mixed methods evaluations utilising both quantitative and qualitative measures (e.g., qualitative interviews of participant's perceptions or experiences in addition to quantitative measures).

Finally, even though there are disproportionately more studies investigating the pattern of training-related changes in fMRI activity than employing functional connectivity and structural imaging analyses, still the most considerable oversight in the field is the lack of neuroimaging studies on neurological samples overall. In their systematic review, Galetto and Sacco (2017) identified only eleven published studies that employed neuroimaging and neurophysiological methods in individuals with TBI. The authors were unable to draw meaningful and consistent conclusions due to the very small number of included studies, the heterogeneity amongst the training protocols in terms of the trained cognitive function, the absence of CGs in many cases, as well as the small sample sizes. Despite these limitations, however, the authors suggested

that cognitive training can successfully promote neural modifications in individuals with brain injury. Another systematic review with a specific focus on WM updating identified only four published studies employing neuroimaging methods in people with neurological damage. Once again, these either had small sample sizes, did not include CGs or were case studies, and therefore reaching meaningful conclusions was not possible (Pappa et al., 2020). These reviews highlight that the need for neuroimaging studies in clinical samples is apparent. Their inclusion is absolutely necessary if we want to move the field forward.

5.7 How do we move forward?

5.7.1 Cognitive Neuroscientists and Clinical Researchers

Even though this review focused on studies employing WM training protocols, the proposed suggestions could prove useful for a variety of cognitive processes and training protocols. Therefore, we suggest that researchers interested in conducting cognitive training studies overall -and not limited to WM- should consider some key issues before starting data collection. To begin with, there is a move towards open science and research practices, so scientists are encouraged to pre-register their studies, including the proposed research questions, hypotheses, and intended data analysis before commencing data collection via published pre-registered reports, trial protocols and registrations or via open-science platforms such as the Open Science Framework (OSF) and PROSPERO the International prospective register of systematic reviews. We believe peer reviewing research at the very early stages is the optimal way to minimise publication bias, improve experimental design and promote high quality research as well as national and international collaborations. At the same time, employing systematic reviews and/or meta-analyses of previous research is a useful first step to gaining a deeper understanding and knowledge of the field, its limitations, and omissions.

In terms of experimental design, aiming towards including more adults with neurological disorders in neuroimaging studies would be a major contribution in this field and a step closer to increasing the translation of research into clinical practice. With the exception of very early feasibility development, randomised controlled trial methods should be used with an active

CG to control for expectancy effects, selecting CG task features fitting the specific research question and exploring motivating factors for completing the training. In terms of outcome measures, reporting averaged scores if there are multiple experimental conditions or multiple tasks assessing the same cognitive function, similar to meta-analyses methods, enables more accurate and unbiased training and transfer effect sizes to be obtained. Further to this, including additional assessments throughout the training interval enables us to examine how training-related changes develop over time. Naturally the next step would be to investigate whether those training gains extend beyond the end of the intervention and for this a follow-up assessment post-training is necessary. A closer look into how individual differences impact training gains, how the timeline of those changes emerges and whether these are preserved beyond the end of the intervention will be important for informing clinical guidelines. Finally, devising tools to assess the quality of neuroimaging training studies would be very useful for bringing standard practices closer together for cognitive neuroscientists and clinical researchers.

Understandably, a combination of psychometric tools, lab-based experimental tasks, scales measuring ADL and neuroimaging methods is not often feasible within a single study. Alternatively, we suggest following a three-stage programmatic approach to evaluate different aspects of the training protocol and focus on one component at a time. Adapting the MRC guidelines on developing complex interventions (Craig et al., 2008) to cognitive training research, the first stage could involve a small-scale feasibility study aiming to integrate valuable information on recruitment, drop-out rates, sample size and outcome measures. Multiple small-scale studies may be needed to further refine the study methods. The second stage would involve a sufficiently powered study measuring the training efficacy in a well-controlled experimental design and setting together with, or followed by, the employment of neuroimaging methods to investigate the neural learning mechanism. The final development stage focuses on measuring the effectiveness of the training intervention in real world conditions and involves a combination of ecologically valid tasks and ADL measures. Employing these steps on a linear trajectory is not a necessity; and each step has a role to play in informing and modifying the others. The ability to adapt the training protocol throughout the various stages while keeping in line

with external factors such as funding resources, timelines, stakeholders etc. is an equally important aspect of the process and should not be neglected.

Research design practices aside, there are other issues to consider that could improve the way we conduct cognitive training research. Greater use of functional neuroimaging methods and analyses in neuropsychological rehabilitation settings could reveal clinically valuable information that would otherwise be missed, e.g., neural patterns of activity and connectivity post-injury. The combination of multiple methodologies both within and across the disciplines of cognitive neuroscience and clinical neuropsychology presents a unique opportunity to develop rich datasets with information on individuals' cognitive abilities, relationship between brain structure and function, response to cognitive training and/or rehabilitation, mental health history, demographics, and clinical diagnosis. Further to this, making use of open science platforms and pooling data from multiple organisations will accelerate research progress. We can then integrate these data to build models to predict an individual's response to therapy and identify which factors have the biggest role to play. These models can potentially account for individual differences and assist clinicians in devising individualised and optimal rehabilitation regimes. We acknowledge that such an endeavour would be very expensive and in need of neuroimaging expert members of staff within health service organisations, though this does not mean we should not be actively working towards this as our end goal.

5.7.2 Health Organisations, Regulatory and Funding Bodies

Naturally, researchers themselves cannot progress unless they are supported by the associated health organisations and funding bodies. One of the reasons for the lack of neuroimaging studies including people with neurological disorders is perhaps because the data governance and ethical review processes are often stricter and lengthier than for healthy populations. However, we think researchers should be actively encouraged to conduct cognitive training studies with a translational aspect, and this should be reflected in the relevant regulations and policies. Partnerships between health organisations and academic institutions could help to support the intersection of clinical neuropsychology and cognitive neuroscience research, with a particular focus on federated data systems that strictly protect patient identifiable information. At

the same time, funding bodies should urge award recipients to conduct multidisciplinary work, employ interdisciplinary methods and collaborate with other research groups, both nationally and internationally. A similar approach should be followed by academic institutions themselves by promoting and assisting early-stage researchers to visit and work in other research settings. Even if physical presence is not possible due to mobility problems, limited project finances, personal caring responsibilities or any other reason, recent circumstances have demonstrated that this is not an obstacle that cannot be overcome (Holmes et al., 2020; Spagnolo et al., 2020). Connecting with other researchers by sharing datasets and discussing analyses can be achieved remotely and facilitated with the use of decision-making flowcharts. Nowadays, we can access data any time, from anywhere in the world and it would be a shame not to take advantage of this extraordinary opportunity. A few examples of exciting initiatives promoting collaboration and multidisciplinary approaches relevant for cognitive training and cognitive rehabilitation studies are 1. the International initiative for TBI Research (InTBIR) (Tosetti et al., 2013) with a focus on collecting, standardizing, and sharing clinical data for comparative effectiveness research, 2. the Medical Informatics Platform with an aim to create a bridge between brain-science and clinical research and patient care, as part of the EU-cofounded Human Brain Project[8] and 3. the International Neuroinformatics Coordinating Facility (INCF) with a mission to develop, evaluate and promote best research practices, open science and reproducibility[9].

To conclude, we recognize these recommendations cannot be employed by everyone and/or all at once. However, we want to place emphasis on the unique opportunity to capitalise the knowledge, information, and technology we already have by promoting the formation of multidisciplinary teams and employment of interdisciplinary translational research projects and analyses. There is a need for bridging clinical and neuroimaging research methods in order to develop effective rehabilitation interventions for cognitive impairment – while also expanding knowledge about functional organisation of the human brain and its capacity for experience-dependent reorganisation. Through intersection,

[8] https://www.humanbrainproject.eu/en/medicine/medical-informatics-platform/

[9] https://www.incf.org/about-incf

interaction and interdisciplinarity, the field of cognitive training research can be substantially and more rapidly advanced with more researchers working together towards tackling the same problem.

6 Integrated PRocess and StrategieS training: I-PRESS Training

Date:	**6th January 2021**
Sponsor's Protocol Number:	**RandD reference number: GN19NE479**
Sponsor:	**NHS Greater Glasgow and Clyde**
Protocol version:	**Version 1.2 (January 2021)**

6.1 Summary

There is a pressing need to develop more effective interventions to remediate cognitive deficits in highly prevalent disabling conditions such as stroke, head injury and other forms of acquired brain injury (ABI). Neuropsychological rehabilitation interventions developed in a clinical setting have shown some beneficial effects, but the effectiveness of clinical interventions have potential to be enhanced if informed by findings from cognitive neuroscience. Research into cognitive training using methods such as functional magnetic resonance imaging (fMRI) has contributed to an understanding of factors that promote changes in brain function, but this approach seldom includes individuals with brain damage or cognitive deficits. Its potential for application with clinical populations is therefore uncertain, meaning that people who may benefit do not have access to interventions that may improve their health and wellbeing.

The proposed research brings together methods from neuropsychological rehabilitation and cognitive neuroscience to investigate 1) the feasibility of, and effect sizes arising from, combining an existing clinical intervention targeting mental strategies with an adaptive training programme targeting core cognitive processes, and 2) whether the novel treatment combination promotes changes in brain function that are detectable using fMRI.

This project will develop and evaluate a training intervention that aims to improve outcomes from a strategy-based rehabilitation intervention, Goal Management Training (GMT), by adding process-based cognitive training with adaptive difficulty to enhance the executive function of working memory updating (WMU). People with ABI (n=32) will complete 9 sessions of GMT, a recommended treatment for deficits in frontal-lobe executive functions, with

the addition of 8 WMU training sessions with or without adaptive training. Measures of feasibility, acceptability, and fidelity will be taken, and effect sizes of differences in pre- to post-training changes on neural, cognitive, and functional measurements will be determined by comparing two experimental groups in which difficulty of the WMU training tasks either adaptively increases in response to performance or is fixed.

6.2 Introduction

Globally, stroke and head injury are leading causes of disability. Deficits in cognitive functions are common in these conditions, including impairment in frontal-lobe 'executive' functions such as working memory and the ability to solve problems, plan, and regulate actions in order to achieve intended goals. These deficits affect individuals' ability to live independently, work, and maintain social relationships. We propose that improving outcomes for people with acquired brain injury (ABI) requires an interdisciplinary approach in which neuropsychological rehabilitation and cognitive neuroscience complement one another.

In neuropsychological rehabilitation, interventions are classified as 'restorative' (restoration of underlying core cognitive processes including executive functions) or 'compensatory' (compensation of function through the use of external aids or learned strategies). Clinical guidelines recommend the use of 'meta-cognitive strategy training' for the treatment of deficits in frontal-lobe executive functions (Cicerone et al. 2011). Goal Management Training (GMT) is one such validated meta-cognitive strategy. GMT trains compensatory mental strategies to manage attention during multi-step tasks. GMT has been evaluated behaviourally in randomised controlled trials with positive, albeit modest, outcomes in individuals with ABI (Tornås et al., 2016).

In cognitive neuroscience, an emerging research area concerns experience-induced neural changes referred to as neural plasticity. These may involve neural changes in: 1) task-based functional activation patterns, i.e., activity increases, decreases, or reorganisation, 2) brain structure, i.e., grey matter and white matter volume changes (Brehmer et al., 2014) and 3) functional connectivity, i.e., changes in connectivity between brain regions that

are recruited for a mental procedure as well as changes in the strength and magnitude (Constantinidis and Klingberg, 2016).

Neuroimaging studies have demonstrated that programmes to train core cognitive processes including working memory (WM) executive functions can drive changes both in behavioural and neural measures (Klingberg, 2010; Hsu, Novick and Jaeggi, 2014). Performance gains after process-based training have been observed by several authors employing different training tasks and including both younger and older populations (Westerberg and Klingberg 2007; Dahlin et al., 2008; Jaeggi et al., 2008; Jolles et al., 2010; Buschkuel et al., 2014). In addition, generalisation to broad cognitive abilities such as reasoning, episodic memory, after process-based training, has been observed in both young and older adults (Dahlin et al., 2008;2009; Brehmer et al., 2014) although this area is under debate (Melby-Lervag and Hulme 2013; Brehmer et al., 2014). This work has primarily involved healthy adults and whether the same findings apply to those with ABI needs to be investigated.

This research study aims to develop and evaluate a novel treatment intervention for people with ABI that combines a process-based cognitive training with a strategy-based GMT rehabilitation intervention, and to acquire functional magnetic resonance imaging (fMRI) data before and after the intervention to measure patterns of brain activity associated with a task requiring executive functions.

We propose that outcomes from GMT might be improved by an adaptive, process-based intervention aimed at enhancing working memory processes. Adaptive task difficulty involves dynamic adjustment of training task demands so that the individual remains within an optimal range of performance. In a cognitive training literature review, Dahlin et al. (2009) identified adaptive difficulty as a common feature of interventions that reported significant training gains. Lövdén et al. (2010) explained this by theorising that a mismatch between functional "supply" (i.e., neural resources) and environmental "demands" (e.g., a continuously challenging training task) is a necessary condition for cognitive and neural plasticity to occur. If training task difficulty does not tax the upper limits of available resources, there is no mismatch between supply and demand, thus no impetus for plastic change. However, if difficulty is progressively increased,

and continues to tax increasing levels of proficiency, then more neural resources will become available through plastic change.

There is some promising evidence that cognitive deficits in clinical populations can be remediated through behavioural interventions (Bahar-Fuchs et al., 2013; Hallock et al., 2016; van de Ven et al., 2016), and clinical research is starting to use fMRI to investigate normalisation of brain activation patterns after cognitive training (Nordvik et al., 2014). Yet, the results of these studies will be more interpretable, and the design of future intervention studies will be better informed, if theoretically driven research is carried out to identify the factors that promote training gains. Adaptive difficulty may be one such factor. A recent study conducted by Flegal, Ragland and Ranganath (2019), in which healthy adults completed a process-based intervention aimed at enhancing the executive function of working memory updating (WMU), found that adaptive training task difficulty influences neural plasticity, consistent with the Lövdén et al. (2010) theoretical framework. This is an important hypothesis to test further in the context of neurological conditions, where there is a reduction in neural resources from premorbid levels.

6.3 Aims

The primary aim of the study is to investigate whether it is feasible and acceptable to deliver a novel intervention combining GMT with WMU training, within a randomised controlled trial (RCT) context in a sample of ABI individuals. A further aim is to examine the behavioural and neural changes related to the novel intervention as well as the effect sizes.

6.4 Research Question

This project will combine methods from neuropsychological rehabilitation and cognitive neuroscience to answer the following: 1) Is it feasible to combine an existing treatment for executive dysfunction, GMT, with an adaptive WMU training and how much benefit is gained? 2) Does the novel treatment combination promote neural plasticity that is detectable using fMRI?

Primary: Primary outcomes will be measures of feasibility, acceptability, and fidelity.

Secondary: Secondary outcomes will be pre- to post-training change in behavioural data (i.e., neuro-psychological assessment battery, measures of cognitive task performance and everyday functioning) and fMRI data (i.e., task-related brain activity), analysed by training condition. In addition, exploratory analyses of individual differences in responsiveness to WMU training will be performed, by calculating correlations between amount of adaptive training task improvement and pre- to post-training change on neural, cognitive, and functional measurements.

6.5 Design and Methodology

6.5.1 Design

Randomised controlled trial methodology; specifically stratified randomisation in conjunction with permuted block random allocation, using an active control group will compare two conditions: (1) GMT combined with adaptive training [AT]; (2) GMT combined with non-adaptive [NA] training. Thirty-two adults with non-progressive ABI sustained in adulthood will be recruited from the NHS. Participants will complete a combination of standard GMT (9 sessions) and 8 WMU (AT or NA) training sessions, delivered in small groups. Neuropsychological and functional assessments will be performed before and after the intervention. In addition, fMRI scanning sessions will be conducted pre- and post-training at the Clinical Research Imaging Facility (CRIF), Queen Elizabeth University Hospital (QEUH) in a 3T Prisma Siemens scanner.

6.5.2 Participants

Adults with non-progressive ABI sustained in adulthood will be recruited primarily from the Community Treatment Centre for Brain Injury (CTCBI), the main service for community based cognitive rehabilitation in Glasgow. Participants will also be recruited from other NHS services within Scotland.

Inclusion Criteria

- Only those able to give informed consent and able to comply with the training protocol will be included.

- ≥ 6 months post-ABI at time of recruitment (expression of interest to participate either verbally or in writing)

- Adults over the age of 18.

- English language fluency (speaking)

- a combination of self/relative/friend/carer reports of everyday organisation/memory problems

Exclusion Criteria

- Individuals with contra-indications to MRI (e.g., heart pacemaker)

- Comorbid progressive neurological disorder or neurodegenerative condition (e.g., dementia)

- Major psychiatric disorder considered likely to prevent engagement in the intervention programme (pre-ABI history of mood disorder or stable antidepressant medication will not lead to exclusion)

- History of major substance abuse problems if the clinical and research team think it is likely to prevent engagement in and/or interfere with the intervention programme. There will be a degree of flexibility on this, and the clinical team will be consulted on an individual basis when deemed necessary.

- Unable to give informed consent

- Unable to cooperate with the study protocol (e.g., severe impairment of hearing, vision, or language)

These criteria are necessary in order that the outcome measures can be administered validly, and to increase the likelihood that any neuropsychological impairment present is due to ABI rather than any other pre-existing disorder.

COVID-19 mitigating circumstances regarding inclusion/exclusion criteria

Even though collecting neuroimaging data remains one of the main components of this research project, we understand there may be some participants who feel uncomfortable with travelling and/or coming in contact with others during the COVID-19 crisis. Therefore, individuals with MRI contraindications can still be included to take part in the behavioural intervention sessions without completing the fMRI sessions as an exception; nevertheless, the focus still remains on recruiting participants suitable for brain imaging.

6.5.3 Procedure

The study will entail twelve visits overall. Details regarding the components and content of each visit are described in the following subsections of the protocol (please refer to Table 6.5.1 below for a brief summary). No changes in routine care will take place while participating in the study.

Table 6.5.1**:** Research procedure

Visit Number	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Type of Visit	*Screening*	*Baseline T0*	*fMRI Time 1 (T1)*	*Treat Wk 1*	*Treat Wk 2*	*Treat Wk 3*	*Treat Wk 4*	*Treat Wk 5*	*Treat Wk 6*	*Treat Wk 7*	*Treat Wk 8*	*fMRI Time 2 (T2)*	*Immediate Follow-up T3*
Time since last visit			≤ 1 wk from Visit 1	≤ 1 wk from visit 2	1 wk from visit 3	1 wk from visit 4	1 wk from visit 5	1 wk from visit 6	1 wk from visit 7	1 wk from visit 8	1 wk from visit 9	≤1 wk from visit 10	≤1 wk from visit 10
fMRI session			x									x	
GMT Introductory session		x											
GMT session				x	x	x	x	x	x	x	x		
WMU AT session				x	x	x	x	x	x	x	x		
WMU NA session				x	x	x	x	x	x	x	x		

Neuropsychology Assessment	x		x
Functional Assessment	x		x
Post-Intervention Participant Feedback			x

6.5.4 Recruitment

The sample will be recruited, screened, and enrolled into the study from the CTCBI, NHS Greater Glasgow and Clyde (NHS GGC) and other NHS sites. The estimated recruitment period will be twelve months. Potential participants will be initially identified by the direct team working in CTCBI. These will then be approached by Dr Nicola Goudie, the clinical psychologist at the CTCBI. Dr Goudie will provide the study information sheet, discuss the study, and ascertain interest. If the client expresses definite interest to participate at this point, they will undergo screening by Dr Goudie to determine eligibility according to the above criteria. If the patients have given permission, then Dr Goudie will pass their details to the PhD researcher (Katerina Pappa) undertaking the study who will then contact the participant to schedule a time to further discuss the study and obtain consent (Please see relevant consent form document, Appendix 3.1). The PhD researcher will only obtain consent if certain the client has had sufficient time to study the participant information leaflet (Appendix 3.2) and is making an informed decision. Baseline neuropsychological and functional assessments will take place either the same day as taking consent or at a separate session, according to the participants' preferences and availability.

If the client has been discharged from CTCBI before being consented into the study, Dr Goudie will contact them to obtain verbal permission for the PhD researcher to make contact with them. The PhD researcher will then ascertain interest, screen the participant, and obtain written informed consent. With the participant's permission, relevant medical information about their medical history will be obtained from their medical notes. The PhD researcher will not be able access this information before written informed consent has been obtained. The recruitment procedure will be adapted for other NHS sites with a member of the immediate care team performing the initial identification and then passing on the details to the PhD researcher to proceed with taking consent.

Recruitment Sites: NHS GGC, NHS Lanarkshire

The same recruitment procedure will be followed across the different sites. More specifically the lead contact for each study site is:

- Dr Nicola Goudie, CTCBI, NHS GGC
- Dr Jane Moir, Community Brain Injury Team, NHS Lanarkshire
- Dr Louise Roach, Stroke team, NHS Lanarkshire

6.5.5 MRI Safety Assessment

One of the radiographers at the CRIF at QEUH, will go over the MRI Screening form to ensure the participants are safe to undergo an MRI scan (please see the MRI screening form for further details). This procedure will take place on two occasions: On each fMRI session prior to entering the MRI scanning room, i.e., study visits 2 and 11. The radiographers on site are: Rosie Woodward, Evonne McLennan, Laura Dymock, Nicola Tynan, and Fiona Savage. The lead research radiographer on site is Tracey Hopkins.

6.5.6 Letter to General Practitioner (GP)

The PhD researcher will inform the participants' GP of their participation in the study. The PhD researcher will send a letter addressed to the GP practice enclosing the study information sheet (Please see GP letter for further details, Appendix 3.3)

6.5.7 Baseline neuropsychological and functional assessments

Participants who meet all eligibility criteria following screening will undergo baseline neuropsychological and functional assessment using standardised measures prior to the study training interval. The assessments will be administered by the PhD researcher at the CTCBI or at the University of Glasgow. The assessment measures selected are those which would be most relevant for a future full-scale trial to determine treatment efficacy and mechanism of effect. Specific tests have been chosen to be relevant to current clinical practice and sensitive to key neuropsychological constructs while keeping administration time at a minimum. Equivalent parallel versions of cognitive test materials will be used during subsequent assessment sessions where available, to minimise practice effects. In recognition that some participants may experience difficulties in remembering appointments following

ABI, participants will be offered a reminder phone call or text message of their appointment 1-2 days prior to neuropsychological assessment sessions.

Baseline neuropsychological and functional assessment will last between one and one and a half hours taking into consideration extra time for providing instructions, task practice and individual differences regarding speed.

The following neuropsychological tests will be used:

- Trail Making Test (TMT) A and B (Reitan, and Wolfson, 1985) to get an estimate of attention, speed and mental flexibility (~5min).

- Hotel task (Manly et. al., 2002) to measure executive function in daily life activities (~20min).

- Digit Span taken from the Wechsler Adult Intelligence Scale (4th edition), (Wechsler, 2008), to assess verbal memory (~7-10min).

- Tower test, taken from the Delis Kaplan Executive Function System battery (D-KEFS) (Delis et al., 2001) to obtain scores in a task requiring planning, rule learning and inhibition (~20min).

- Colour Word Interference (CWI) test from the D-KEFS battery (Delis et al., 2001), assessing inhibition of an overlearned response and flexibility (~10min).

- Functional measurements will be obtained using the Dysexecutive Questionnaire (DEX) (Wilson et al., 1996) (~5min).

These neuropsychological tests have been carefully reviewed and selected as they have been previously used for assessing individuals with ABI in the following studies examining changes after a cognitive intervention: 1. TMT (Sohlberg et al., 2000; Novakovic Agopian et al., 2011;), 2. Hotel task (Manly et al., 2002; Levine et al., 2011; Tornas et al., 2016), 3. Digit Span (Westerberg et al., 2007; Miotto et al., 2009; Vogt et al., 2009), 4.Tower test (Levine et al.,

2001; Tornas et al., 2016), 5. CWI test (Lundqvist et al., 2010; Novakovic Agopian et al., 2011;) and 6. DEX (Miotto et al., 2009; Spikman et al., 2010).

These assessments are essential in characterising the participant sample in terms of cognitive function and capturing changes resulting from the cognitive intervention. Information about participant's current medications and ABI rehabilitation will also be collected. The PhD researcher will also write to the participants' GP to let them know that they are taking part in the study.

Following all baseline neuropsychological assessments, participants will be randomly allocated to either: (1) GMT combined with adaptive WMU training [AT]; (2) GMT combined with non-adaptive [NA] WMU training. The two groups will be stratified by the following factor: aetiology of brain injury (two strata, i.e., traumatic brain injury (TBI) or stroke).

Please note that these neuropsychological tests are copyrighted, and the relevant references are listed below. The test forms will be uploaded but they will have no version numbers as in this case it is not applicable. The authors of these tests are referenced in text above and in the end. Finally, in cases where the forms mention "Subject's Name", the participant ID will be used instead.

6.5.8 Intervention

Goal Management Training (Levine, Manly and Robertson, 2012)

GMT teaches the use of mental strategies to support sustained attention during complex (multi-step) task performance following an interactive programme. GMT is structured into nine modules, with interactive discussions designed to raise awareness of various aspects of goal management, tasks that illustrate goal management concepts in action, and homework assignments designed to facilitate the transfer of concepts to real life. GMT comes as a complete kit, with slides, a trainer's manual, participant workbooks, and all the necessary components to run GMT sessions in a group setting. Except for the first introductory session, all GMT interventions will be delivered by the PhD researcher on a group basis (group size N = 2 - 6) taking place either at the CTCBI or Psychology department, University of Glasgow. Additional groups may

also be run at other recruiting services, providing that premises, numbers and space requirements allow it. The GMT group sessions will last two hours.

The first GMT module will be conducted on an individual basis for each participant separately prior to starting the combined GMT-WMU intervention. It will last about one hour and will take place on the same day as the baseline neuropsychology assessment (please see Table 6.5.1). The reason for administering Module 1 individually is to introduce the idea of the intervention, explain some key concepts, give the participant the opportunity to familiarise themselves with the general notion of the GMT as well as to discuss questions and concerns they might have. Thus, the PhD researcher will ensure each individual participant has understood and familiarised themselves with the GMT concepts before entering the fully combined GMT-WMU group-based intervention. The GMT sessions will be run by the PhD researcher plus another member either from the supervisory research team or the clinical team from the respective research site.

Brief overview of the GMT modules (Levine, Manly and Roberton, 2012)

In the first module the intervention begins by defining the concepts of absent mindedness, and present mindedness and by providing patients with illustrative examples. Absentminded slip-ups (e.g., forgetting to pick up the dry-cleaning on the way home) are introduced during module two. The “automatic pilot,” a metaphor for habitual or stimulus-bound task execution, is introduced in module three. Module four teaches patients how to stop the automatic pilot. The “mental blackboard,” a metaphor for working memory (i.e., where goals are kept in mind), is introduced in module five. Modules six to nine are devoted to teaching patients how to stop, state their goal, and make decisions in the context of competing tasks. Patients are also taught to create to-do lists and to split more complex tasks into sub-tasks. Module nine is devoted to checking ongoing behaviour to ensure that the patient is still staying on task. Please see Table 6.5.2 below for further details. At the end of each training module patients are given homework assignments to practice the concepts they learn during each session. These will be reviewed and discussed during the following session. In addition, patients will perform mindfulness and breathing exercises both at home and during the training sessions.

Table 6.5.2: GMT modules and concepts covered

Module	Concepts covered
Module 1	Introduction of goal hierarchies, mental laboratory, absentmindedness and present-mindedness by providing patients with illustrative examples.
Module 2	Relation of absentmindedness to other abilities, consequences of slips, conditions for slips and how the GMT will reduce slips.
Module 3	The automatic pilot and how it leads to errors.
Module 4	Training to stop the automatic pilot.
Module 5	Mental blackboard.
Module 6	Goal loss and reinstatement.
Module 7	Goal conflict and decision-making.
Module 8	Dealing with overwhelming tasks by splitting them into smaller tasks.
Module 9	Checking (reducing slip-ups).

Working Memory Updating Training

The training consists of computerised working memory updating tasks in which trial accuracy and response time are recorded. All 8 WMU interventions will be delivered by the PhD researcher on a group basis (group size N = 2 – 6). Two computerised WMU tasks will be trained based on the study conducted by Dr Flegal on healthy adults (Flegal, Ragland and Ranganath, 2019). These tasks will be delivered via two modalities: (1) a visuospatial WMU task, i.e., Matrix Updating (MU) and (2) a verbal WMU task, i.e., Keep Track (KT). MU requires updating the location of multiple dots within a 4 x 4 matrix (Chen and Li, 2007) while KT requires updating the identity of the most recently studied words in multiple semantic categories (Yntema, 1963). For both training tasks, level of difficulty can be modulated by increasing or decreasing the update level, i.e., the number of updates on each trial. For AT participants, difficulty of the training tasks is progressively increased in response to task performance, in order to adaptively increase environmental demands. For NA participants,

however, task difficulty is fixed at a relatively low level across all sessions. Training of the MU task lasts between 25-30 minutes while the KT training lasts between 20-25 minutes. The WMU training sessions will last between one hour to one hour and fifteen minutes taking into consideration time to provide instructions and practice.

6.5.9 Post-intervention Feedback

After the end of the intervention all participants will have the opportunity to rate the perceived usefulness and experience of the interventions including any adverse effects using Likert scales (for further details please see the feedback form Appendix 4.2). This information will be used to guide the possible development of a future full-scale trial. This will be carried together with the immediate follow-up session after the end of the intervention (i.e., visit 12) by the PhD researcher.

6.5.10 Outline of Study Visits

Visit 1: Baseline Neuropsychological and Functional Assessment and Introductory GMT session

Full details of baseline assessment is given in section V: Baseline neuropsychological and functional assessments. Following completion of the assessments, the PhD researcher will then proceed with the introductory GMT session where the idea behind the intervention as well as its usefulness in people with ABI will be presented. Emphasis will be given on the importance of having goals in everyday life and a few key concepts central to GMT will be mentioned. In addition, the PhD researcher will discuss the expectations clients should have from this intervention, i.e., learn strategies, practice relaxation techniques, take control by stopping and thinking about their goals when performing a task. The overall duration of Visit 1 will be around three hours (approximately one to one and half hours for the neuropsychology assessment, half an hour for a break and one hour for the first introductory GMT session).

There is a very small possibility the PhD student might be required to make a few home visits as an exception (assuming the participant has a great

difficulty travelling themselves on a day) in order to complete neuropsychological assessments, which carry a potential personal safety risk. To minimise these risks, all home visits will be carried out during office hours and the PhD student will be required to carry mobile phones and to let a member of the research team (or if not possible, a member of staff at their usual place of work) know when and where their appointments are and when they have finished. Hence, the University of Glasgow lone study policy will be followed.[10]

Visits 2 and 11: Time 1 and Time 2 fMRI sessions

There will be two fMRI sessions, Time 1 (T1) and Time 2 (T2), to measure functional brain activity pre- and post- intervention, respectively. These sessions will last approximately two hours in total. The PhD researcher together with one of the qualified radiographers at the CRIF will first perform the MRI screening form. Then the PhD researcher will give a detailed description of the scanning procedure and answer any potential questions; this step will last approximately half hour. The PhD researcher together with the radiographer will then move the participant to the scanner area. At both T1 and T2, participants will perform three tasks inside the scanner: (1) Matrix Updating serving as the criterion task, i.e., scanner version of visuospatial WMU training task, (2) Spatial N-Back task assessing transfer of learning to a closely related untrained task, i.e., near transfer, and (3) Object-Location Association, a visual episodic memory task assessing transfer of learning to an unrelated untrained task, i.e., far transfer. In each task run, a gradient-echo EPI sequence will be used to obtain functional images sensitive to BOLD contrast. One of the radiographers at the CRIF will conduct the scanning sessions together with the PhD researcher at all times.

Spatial N-Back is selected as a scanned task representing near transfer, based on the prediction that it and the WMU training tasks engage overlapping processing components and brain areas. Based on the scanned N-Back paradigm used by Flegal and colleagues (2019), stimuli will appear in one of eight locations and the task is to respond by pressing one button when the current

[10] https://www.gla.ac.uk/media/Media_500540_smxx.pdf

location matches the location presented n trials earlier and pressing a second button when there is not a match.

Object-Location association is a measure of visual episodic memory, selected as a scanned task representing far transfer. Based on a paired associate learning paradigm adapted for fMRI testing as in Flegal, Ragland and Ranganath (2019), the task consists of blocks of trials arranged into an encoding phase followed by a retrieval phase. During encoding, a sequence of stimuli will appear in different locations, then during retrieval, each one of the locations will be cued and the task is to respond by pressing a button corresponding to one of three stimuli choices which had appeared in that location.

At both T1 and T2 the task runs will be followed by a T1-weighted sequence to obtain high-resolution anatomical images. In conducting fMRI data analysis, the functional images will be spatially realigned using a six-parameter rigid body transformation and coregistered to their T1-weighted anatomical image. In total, visits 2 and 11 will take around two hours to complete, i.e., thirty minutes for the safety procedure prior to the scan and another one hour and a half for the scanning procedure itself. Comparisons in scanned task performance between T1 and T2 will allow us to examine how much benefit is gained due to the training intervention and if there is evidence of generalisation to other untrained tasks. In addition, we will examine neural changes in terms of task-related brain activity.

The procedure and tasks will be identical at T1 and T2, with the exception of three structural imaging sequences acquired only at T1, in addition to the T1-weighted anatomical image, for the purposes of a comprehensive, accurate and detailed neuroradiologist report (please see sections 6 and 7 below). These additional sequences are: 1. Axial T2-weighted, 2. Axial T2-weighted fluid attenuation recovery (FLAIR), and 3. A haemosiderin sensitive sequence. For both fMRI sessions, the participants will spend no more than one hour inside the scanner.

Visits 3- 10: GMT+WMU Intervention sessions

There will be 8 weeks of a combined GMT and WMU intervention. Each GMT session will be two hours long while the WMU session will last between one hour and one hour and fifteen minutes. There will be a break between the training sessions allowing participants to have a rest and relax lasting between thirty minutes to an hour. The intervention visits will be conducted either at the Psychology department, University of Glasgow or at the CTCBI. Both GMT and WMU sessions will be administered by the PhD researcher undertaking the project. These will be conducted weekly on a group level at the same day; that means each intervention visit will last approximately three hours and forty-five minutes to four hours including the break in between. If attending both intervention sessions at the same day is not feasible for some participants, due to reasons such as getting easily fatigued or not being able to commit this long on the same day, the following guidelines will be implemented:

The option of coming for the two interventions separately within the same week will be offered, i.e., arranging the GMT and WMU interventions at two different times.

The option of conducting the WMU intervention in one's own time at home will be offered after the PhD researcher makes sure the necessary requirements are in place, i.e., the participant has a laptop at home to perform the training tasks, they have fully understood the tasks and are practicing according to the guidelines. Under these conditions, task performance will be monitored from encrypted anonymised data files (logging trial accuracy and response time) transmitted to the PhD researcher via e-mail at the end of each at-home training session.

Visit 12: T3, Immediate follow-up: neuropsychological and functional assessments

All standardised measures that were administered at baseline (Visit 1) will be re-administered after the end of the intervention (please see Table 6.5.1) by the PhD researcher. An acceptable period between the end of the intervention and neuropsychology assessment will be within three weeks. In addition, a feedback form will be given to the participants to rate the perceived usefulness

and experience of the interventions. This final visit will last around one and a half hours.

The PhD researcher will have access to supervision and will be given advice regarding what steps to take, including sharing relevant information, if they become concerned about the welfare of the participant at any stage during the study.

6.5.11 COVID-19 mitigation plan- Online option for study visits 1, 3-10 and 12.

An online alternative will be offered to run the study visits remotely in order to minimise the risk of infection due to COVID-19. As a result, no unnecessary travelling nor physical group sessions will be taking place. In more detail:

Neuropsychology assessment - Visits 1 and 12

The assessments listed in section 4vii will be adapted to be conducted remotely through an NHS approved software. Those tests that cannot be adapted for online use will be discarded and no further assessments will be used in their place, or, where feasible, these assessments may be adapted for delivery with social distancing when people come to CRIF for the scanning sessions, i.e., visits 2 and 11. After each participant, the test materials will be disinfected for use with the next individual. Another alternative is the use of a validated software via a secure web-based, GDPR compliant platform such as CANTAB, which is designed and validated by Cambridge Cognition: https://www.cambridgecognition.com/cantab.

GMT- Visits 3-10

The GMT sessions will be conducted remotely via NHS IT systems to ensure security and data protection and the PhD researcher will use an NHS approved software (please see further information below). The session duration will remain the same while more regular breaks will be introduced. The PhD researcher will provide practice sessions, so participants familiarise themselves

and feel comfortable using the software prior to starting the intervention. These will be part of visit 1 or any other time that is suitable for participants. The material, content and duration of the GMT will remain unchanged as described earlier. The PhD researcher will additionally record a brief five-minute video providing: 1. a recap for each session, 2. a brief summary of the key concepts explored and 3. a reminder of the homework for the next session. The video recording will be provided at the end of each GMT session only to those participants that were in attendance.

WMU Training - Visits 3-10

The WMU training sessions will take place remotely. A computer with Windows Vista/7/8/10 is required to run the WMU training tasks using the Presentation software by Neurobehavioural Systems specifically designed for secure remote management of stimulus delivery in experimental research[11]. If participants have no personal computer access, then the research team is able to provide the necessary equipment for the duration of the intervention depending on numbers and availability. The PhD researcher will be offering individual practice sessions and detailed step-by-step guidance for using the presentation software prior to starting the training sessions. The training tasks, session duration and content will remain unchanged as originally planned. All devices will be disinfected before given to a new participant using alcohol based sanitising products, i.e., 60-80% alcohol, as recommended per NHS guidelines[12].

Scanning sessions – Visits 2 and 11

The scanning sessions at CRIF will adhere to COVID-19 related NHS regulations and guidelines. Consequently, the sessions will be conducted as originally planned while ensuring the necessary precautions are taken to protect participant's health and safety. If participants feel uncomfortable taking part in the scanning sessions for reasons relating to COVID-19, then those people will only participate in the intervention component of the study.

[11] https://www.neurobs.com/

[12] https://coronavirusexplained.ukri.org/en/article/pub0006/

NHS-approved software

The online version of the intervention will be conducted using NHS approved software, such as Attend anywhere, Microsoft Teams and National Video Conferencing Service (NVCS) Cisco Meeting Server (CMS) which have already been adopted by the NHS to run their service remotely, i.e., one to one sessions and group meetings. These are ideal for sharing content, e.g., GMT module slides, for taking part in a group chat as well as support larger size group meetings effectively. The softwares will be accessed remotely through NHS networks to ensure data security and protection.

6.6 Randomisation and Bias prevention

Stratified randomisation in conjunction with permuted block random allocation will be used to allocate participants to one of two study groups of equal size. The sample will be stratified by the following factor: aetiology of brain injury (two strata, i.e., TBI or stroke). Participants will be blinded to study allocation. The sample will be randomised by Dr Kristin Flegal, a member of the PhD researcher's supervisory team. Dr Flegal is a neuroscience researcher with an expertise in fMRI methodology and thus she is less likely to come in direct contact with the participants through the clinical domain. The randomisation procedure will be conducted in a computerised manner. A code for randomisation will be created using Matlab programming software. Two databases will be created: 1. a patient's database that lists basic information such as participant ID, recruitment site, age, aetiology of brain injury and 2. a "randomisation" database that holds data on which participants have been registered and their treatment allocation. The participants' database will be password protected and accessed only by Dr Flegal. The PhD researcher will have no way of knowing which participant is allocated into which intervention arm prior to the individual starting the trial or change it afterwards. For the purposes of the present project stratified randomisation with blocking will be used and thus several participants will be randomised at once. Alternatively, if Dr Flegal is unable to perform the randomisation for any reason Dr Viveka Biswas will conduct the procedure instead.

6.7 Sample size

Thirty-two participants will be randomised (16 per group) to estimate recruitment, adherence and retention rates, and the variance of outcome measures. The sample size was based upon what could be feasibly expected to be recruited as part of a small-scale PhD feasibility research study whilst accounting for eligibility restrictions especially in regard to MRI contra-indications as well as the duration of the study. i.e., committing to the study for 12 weeks. Given that one of the primary aims is examining feasibility and acceptability of the novel intervention, the study is not designed to be powered to detect differences in outcomes between the two groups.

6.8 Neuroradiologist Report of Structural Scans

Dr Natasha Fullerton is the collaborator Neuro-radiologist in this study. She will review structural brain images acquired with the following sequences: 1. T1-weighted, 2. Axial T2-weighted, 3. Axial T2-weighted FLAIR, and 4. a haemosiderin sensitive sequence (e.g., gradient-echo or susceptibility-weighted). These scans will be transferred to NHS PACS in order to be linked to each participant's medical record. This way Dr Fullerton will be able to produce a comprehensive report in CRIS for each participant to:

1. Discern between the pre-existing brain injury and any new potential incidental finding, as per protocol (please see section 6 below).

2. Comment on the location and size of lesion as well as nature of injury, presence of atrophy or diffuse axonal injury.

3. Compare the current anatomical images with earlier ones if available and comment on the differences.

4. In addition to being recorded in PACS, the neuroradiologist's report containing information on exact anatomical location, size, and number of lesions will facilitate accurate and high quality fMRI data analysis, i.e., coregistration and spatial normalisation steps, accounting for

abnormalities in the participants' T1-weighted anatomical images resulting from their brain injury.

5. The participants' anatomical scans will be automatically transferred to NHS PACS through the direct link between the CRIF and NHS PACS.

6.9 Incidental Findings Report

Incidental finding refers to the unlikely event where an abnormality is detected, by chance, in the scan of a volunteer by the radiographer or one of the investigators. Because participants in this study all will have an existing brain injury, a modified approach will be taken to allow for the expectation of some abnormality. In this study, Dr Natasha Fullerton will examine the anatomical brain scan for each participant and provide a report (please see section 6 above). In cases of an incidental finding extending beyond the existing brain injury the following procedure will be implemented:

1. The participant's GP will be informed

2. The participant will be referred to an appropriate clinician for further investigation

The procedure will be outlined in the study information sheet (Appendix 3.2).

6.10 Statistical methods

Quantitative behavioural data will be analysed using SPSS 21 software or equivalent. Data on recruitment, adherence and retention rates will be summarised as percentages with 95% confidence interval (CI). Baseline characteristics of the sample will be presented using descriptive statistics. Measures of cognition (overall and domain specific composite scores) and psychological and functional constructs will be summarised by group and overall with 95% CI, and analysed using correlational analyses and t-tests or their non-parametric equivalents to estimate effect sizes (ES). The estimated ES, Cohen's d (Sullivan and Feinn, 2012), will be calculated using linear regressing adjusted for baseline and factors. The sample means, SD and change scores on these

outcome measures will form the basis of sample size calculations for a further full-scale study, if indicated.

fMRI BOLD responses will be analysed using the general linear model implemented in SPM12 developed at the Wellcome Center for Human Neuroimaging, UCL (www.fil.ion.ucl.ac.uk/spm). Data preprocessing will include each participant's functional images being realigned using a six-parameter rigid body transformation and coregistered to their anatomical image. Covariates of interest will be constructed by convolving vectors of predicted neural activity with a canonical hemodynamic response function. To account for residual variance because of head movement, motion parameters will be estimated at the realignment stage of pre-processing and motion spikes will be identified using the ArtRepair toolbox (cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) and included in each model as covariates of no interest. For group analysis, functional images will be normalised to MNI (Montreal Neurological Institute) space using affine and nonlinear transformations, and spatially smoothed.

6.11 Data Storage and Sharing

All sensitive information such as participants' names, addresses, phone numbers etc will remain on NHS systems. All electronic anonymised data will be stored on secure University of Glasgow networked drives accessed via password-protected university (laptop) computers to ensure that the data is automatically backed-up. All participants will be assigned a study ID and all electronic data will be anonymised using this unique identification number. Physical data will be stored in locked filing cabinets in locked offices on University of Glasgow premises. The index of ID codes and identities will be stored separately from the study data. A secure University network drive will be used for the purpose of sharing raw data between the PhD researcher and investigators. If the data were to be shared, it would be completely anonymous (i.e., the link between participant name and study ID would be broken and a random ID number would be given instead).

6.12 Dissemination plan

The study participants will not be debriefed of the randomisation they underwent. However, they will be notified when the study results are published, and the journal article will be shared with them. Findings from this study will be further disseminated to the funder and the wider research community via presentation at conferences and publication in peer reviewed journal(s) in line with the Neurosciences Foundation (NSF) open-access policy (or in line with the University of Glasgow policy in the absence of NSF policy). The findings will also be shared with individuals with ABI and their families via local networks. No personally identifiable information about participants will be included in these reports and presentations. If the novel intervention is shown to be feasible and acceptable, we plan to arrange workshops for healthcare professionals in conjunction with patient, care, and public involvement (PCPI) with a view to apply for postdoctoral funding after completion of the PhD research project.

6.13 Timeline

The duration of the study is 18 months, and it is anticipated that recruitment will commence on Autumn 2019. A summary of the study timetable is given in Figure 6.13.1.

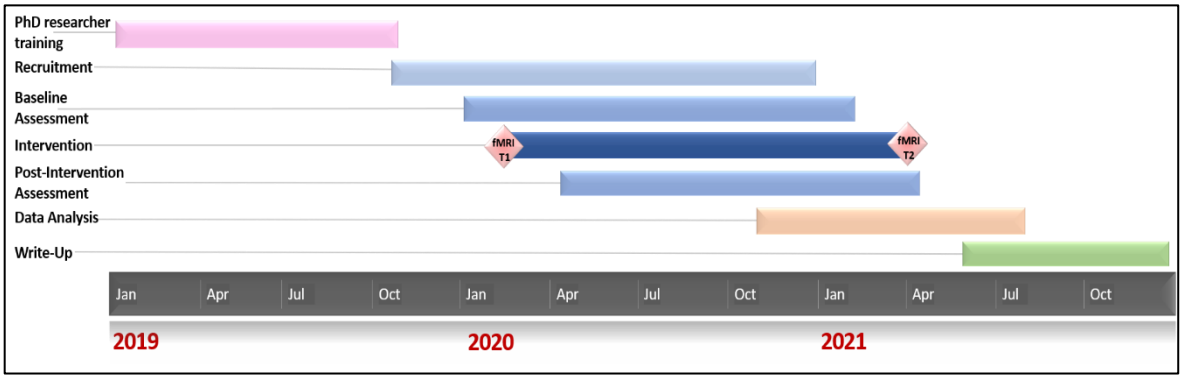

Figure 6.13.1: Study Timeline

COVID-19 mitigating circumstances – delay in study timeline

Due to the significant delay in starting data collection for this research project, the study timeline has been amended as depicted in Figure 6.13.2 below. The study comprising Katerina Pappa's PhD research project will reach its

end around late 2021. However, data collection for the overall project will continue for another year to allow study completion.

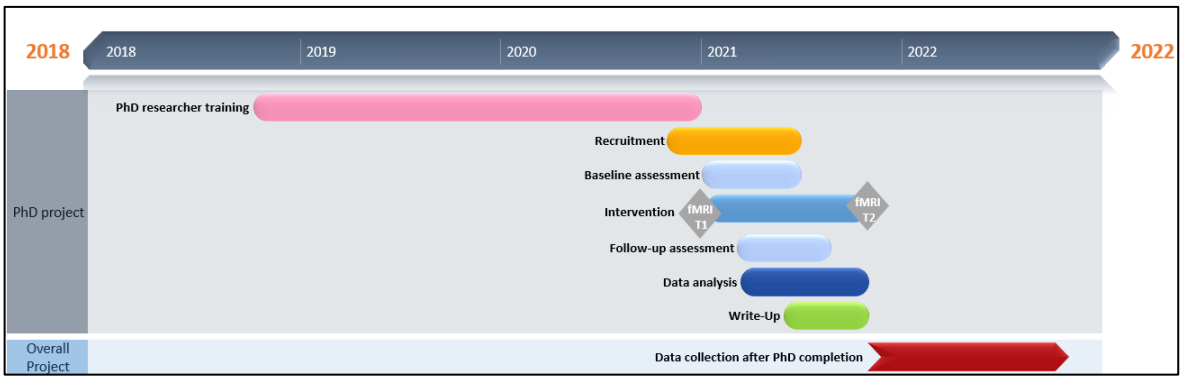

Figure 6.13.2: Updated study timeline

6.14 Outcomes and Outputs

Results from this work will contribute new knowledge that may improve outcomes for patients with ABI long term and will lay the groundwork for further research extending the adjunctive cognitive training approach to other clinical populations with cognitive deficits. Additionally, by establishing a new interdisciplinary research collaboration and strengthening the links between cognitive neuroscientists and clinical psychologists in the west of Scotland, this study will facilitate further development of the pipeline for translation of basic cognitive neuroscience research into clinical applications. Potential funding sources for subsequent grant applications include Brain Research UK, the Medical Research Council and the Wellcome Trust.

6.15 Funding Arrangements

This study is supported by a Neurosciences Foundation/ Sackler Foundation PhD studentship (2018-2021, £75,000) awarded to Professor Jonathan Evans and Drs Kristin Flegal and Satu Baylan. In addition, an NHS GG&C Endowment Research Funding (£14,960) has been awarded to further support with MRI scanning costs.

7 i-PRESS online pilot

The present study focuses on a small pilot of the amended remote iPRESS protocol described in chapter six. This is an interdisciplinary intervention combining goal management strategy and computerised working memory updating (WMU) process training targeting adults with acquired brain injury (ABI). The aim was to examine the feasibility of delivering the iPRESS intervention remotely and collect data on recruitment rate, adherence, and drop-out rate, as well as test the fMRI protocol on an individual with ABI. Five participants with ABI were included in this pilot and attended eight sessions of the goal management training (GMT) which took place remotely on Microsoft teams and completed eight training sessions of the WMU program on their laptop/mobile. Before and after the intervention, neuropsychology assessments were conducted remotely using the CANTAB web-testing functionality to assess performance pre- and post- training. Participants engaged with the GMT despite its remote delivery and most of them were able to complete the WMU training. The fMRI protocol included three tasks: a visuospatial matrix updating task, an n-back visuospatial task, and an object location association episodic memory task. The protocol was tested on one participant who was able to complete all tasks and remained in the scanner for the total session duration. Overall, the small pilot exhibited positive results evidenced by the low drop-out rate, group attendance as well as participants' positive feedback together with the tolerability of the fMRI protocol.

Keywords: acquired brain injury; cognitive rehabilitation; goal management training; working memory training; fMRI

7.1 Introduction

Following the step-wise approach described in Chapter five (section 5.4), this chapter presents stage one of three in developing the iPRESS intervention. The sections below focus on the feasibility of the novel intervention integrating goal management strategy and working memory updating process training for individuals with acquired brain injury (ABI). The purpose of this research pilot was two-fold. Firstly, to investigate the feasibility of running a remotely delivered version of the iPRESS intervention to ensure participant safety in accordance with COVID-19 ongoing restrictions and regulations (please see chapter six, section 6.5.11) and secondly to assess the fMRI task protocol on an individual with ABI. The small samples in both the behavioural and imaging components did not allow for statistical analysis; we obtained, however, valuable information on the overall feasibility of the iPRESS remote intervention, recruitment numbers and rate, participant feedback, technical specifications, as well as the suitability and tolerability of the fMRI protocol.

7.2 Methods

7.2.1 Participants

Participants were identified and screened by the stroke and brain injury teams at NHS Lanarkshire to ensure they were over the age of eighteen, at least six months post-injury, able to give informed consent, fluent in the English language and reported everyday organisation/memory problems (combination of self/relative/carer reports). Participants were excluded if they suffered from any comorbid progressive neurological disorder, had a history of major psychiatric disorder or major substance abuse problems, or exhibited any other severe cognitive impairment likely to prevent engagement with the study protocol. Participants were additionally screened to ensure they had access to a computer device and/or mobile tablet with internet connection. Six participants were enrolled in the study (3 males, 3 females) with a mean age of 56 years (SD = 8.22). All participants had suffered an ABI, including three cases of stroke, two cases of traumatic brain injury (TBI) and a case of ruptured aneurysm (Table 7.2.1). Lesion location was variable and most frequently in temporo-parieto-occipital areas. One participant withdrew following the first appointment and

therefore, five participants were included in the iPRESS online pilot. Everyone was assigned to the Adaptive Training (AT) WMU training condition due to the study being a small-scale feasibility pilot. The study was approved by the South East Scotland Research Ethics Committee 01, Lothian NHS board (REC reference: 19/SS/0112).

Table 7.2.1: Participant characteristics

Participant ID	**Age** (years)	**Education level**	**Injury**	**Lesion**
PT001	62	Undergraduate degree	Stroke	right frontal
PT002	52	Left formal education age 16	Stroke	bilateral parietal and occipital
PT003	59	Left formal education age 16	Aneurysm	
PT004	42	Left formal education age 16	TBI	left temporal and occipital
PT005	65	Left formal education age 17-18	TBI	left parieto-temporal, right occipital
PT006	56	PhD or equivalent	Stroke	bilateral superior cerebellar, left inferior cerebellar

7.2.2 Cognitive Assessment

Cognitive assessments were conducted remotely with the web-based testing functionality available within CANTAB software (CANTAB®, 2019). CANTAB web-testing was accessible on any Windows 7, 8, 10 desktop/PC or Mac OS or iPad. CANTAB tests concentrated on executive function and working memory functions focusing on planning, problem-solving, shifting, maintenance, flexibility, visuospatial working memory capacity, working memory and strategy. We selected tests that were validated for web-testing as well as test variants which provided normative data (Backx et al., 2020), and were recommended for longitudinal studies (Table 7.2.2). The participants performed the same test

variants at two time-points, before and after the intervention. We also administered the Dysexecutive Questionnaire (DEX) (Wilson, 1996) asking participants, to provide a rating of their experience, i.e., self-rating, and forwarding to a friend/partner/family member to complete their rating, i.e., independent rating.

The experimenter created a study-specific assessment battery with the CANTAB software which listed the specific test variants, number of sessions, subject demographic information and enabled the web-based functionality. Each new participant was set up with a study ID code to ensure anonymisation and was assigned a unique subject link to open the CANTAB assessment webpage. Each participant was sent their unique link just before their scheduled appointment. Test responses were automatically recorded and stored in the CANTAB software and were subsequently available for download by the experimenter. The CANTAB web-testing platform provided secure HTTPS data encryption in accordance with General Data Protection Regulation in addition to SOC-II certified data storage.

Table 7.2.2: CANTAB tests selected for cognitive assessments.

Test *(Cognitive function)*	**Test Variant (duration)** *Outcome measures* *(CANTAB recommendation)*	**Normative Data**
Stockings of Cambridge (SOC) *(Planning, problem-solving)*	**Recommended Standard Repeated (10min)** 1. *SOC mean moves:* The mean number of moves that the subject required to complete problems. This measure is calculated over 5 moves assessed problems only. 2. *SOC minimum moves:* The number of assessed problems that the subject successfully completed in the minimum possible number of moves. Calculated over all assessed trials. *(This variant is recommended for use in longitudinal studies testing at multiple time points.)*	18 – 85+years

Intra-Extra dimensional shift (IED) *(Attention set shifting, maintenance, flexibility)*	**Recommended Standard Lines First Repeated (7min)** 1. *IED total errors:* number of times the subject failed to select the stimulus compatible with the current rule on the stage where the extra-dimensional shift occurs. This is a measure of the subject's ability to shift attentional set. 2. *IED total errors adjusted:* Total Errors (problems reached) + [(number of unreached problems) * (25)]. This is a measure of the subject's efficiency in attempting the test. *(IED is not recommended for repeated testing, as subjects tend to exhibit significant learning effects. Historically, however, IED has been used for repeat testing in some studies and therefore this variant is recommended for use in longitudinal studies testing at multiple time points.)*	18 – 85+years
Spatial Span (SSP) Forwards *(Visuospatial working memory capacity)*	**Standard Forward 2.0 (5min)** *SSP forward span length:* the longest sequence of boxes successfully recalled by the subject. *(Subjects are required to recall the order that some boxes change colour. This variant can be used in combination with Standard Reverse 2.0, or on its own.)*	18 – 85+years

Spatial Span (SSP) Reverse *(Visuospatial working memory* capacity)	**Standard Reverse 2.0 (5min)** *SSP reverse span length*: The longest sequence of boxes successfully recalled by the subject. *(Subjects are required to recall in reverse (last box first) the order that some boxes change colour. This variant can be used in combination with Standard Forward 2.0, or on its own.)*	18 – 85+years
Spatial working memory (SWM) *(Working memory & strategy)*	**SWM Recommended Standard 2.0 Extended (6min)** 1. *SWM between errors:* The number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials. 2. *SWM Strategy:* The number of times a subject begins a new search pattern from the same box they started with previously. If they always begin a search from the same starting point it is inferred the subject is employing a planned strategy for finding the tokens. Calculated across assessed trials with 6 tokens or 8 tokens. *(This variant can be used in populations with a wide variance in ability. This variant can be used in impaired populations, but also healthy controls, due to the more difficult stages mitigating ceiling effects.)*	18 – 85+years

7.2.3 Training Material

Goal Management Training (GMT; Levine et al., 2012)

Even though the GMT modules were not delivered in person, as originally intended by the GMT authors, we used the material, content, and structure as per manual guidelines. GMT is structured into nine modules (Table 7.2.3), with interactive discussions on various aspects of goal management, tasks that illustrate goal management concepts in action, and homework assignments designed to facilitate the transfer of concepts to real life. Participants additionally performed mindfulness and breathing exercises both at home and during the training sessions. After each group session, the experimenter sent a summary of the between-session assignments to complete and additionally sent a reminder prompt before the next group session. The homework assignments were reviewed and discussed during the following group sessions. The first session, i.e. module 1, was delivered remotely in a one-to-one fashion as an introduction to goal management, thus giving the opportunity to familiarise with the concept, aims and target of GMT before commencing with the online group intervention. The remaining online appointments were conducted in small groups of two to four participants and were arranged over eight weekly sessions.

Table 7.2.3 Overview of GMT modules as described in Levine, Manly and Robertson (2012).

Module ***(Visit, Mode)***	**Concepts covered**
Module 1 *(Visit 1, One-to-one)*	Introduction of goal hierarchies, mental laboratory, absentmindedness and present-mindedness by providing patients with illustrative examples.
Module 2 *(Visit 2, Group)*	Relation of absentmindedness to other abilities, consequences of slips, conditions for slips and how the GMT will reduce slips.
Module 3 *(Visit 3, Group)*	The automatic pilot and how it leads to errors.

Module 4 *(Visit 4, Group)*	Training to stop the automatic pilot.
Module 5 *(Visit 5, Group)*	Mental blackboard.
Module 6 *(Visit 6, Group)*	Goal loss and reinstatement.
Module 7 *(Visit 7, Group)*	Goal conflict and decision-making.
Module 8 *(Visit 8, Group)*	Dealing with overwhelming tasks by splitting them into smaller tasks.
Module 9 *(Visit 9, Group)*	Checking (reducing-slip-ups).

WMU Training (Flegal, Ragland and Ranganath, 2019)

The training paradigm was based on the study conducted by Flegal et al. (2019) on healthy adults and involved practicing two Working Memory Updating tasks in different modalities: (1) a visuospatial WMU task, i.e., Matrix Updating (MU) and (2) a verbal WMU task, i.e., Keep Track (KT), for a total of eight training sessions. Training task stimulus delivery and response collection were performed using the mobile experiment feature of Neurobehavioural Systems (NBS) Presentation software, (Version 20.1, www.neurobs.com) which is specifically designed for secure remote management of stimulus delivery in experimental research. After each training session, the participants' anonymised and encrypted data were automatically uploaded on the NBS servers using the "data upload" functionality provided when assigning "hosted experiments" through NBS.

MU requires updating the location of three dots within a 4 x 4 matrix (Chen & Li, 2007) (Figure 7.2.1A). At first, the matrix with the coloured dots, i.e., red, green, and blue, would be presented for 5000ms. Following that, coloured arrows were sequentially presented for 2000ms each with a 500ms inter-stimulus interval and they would point up, down, left, or right to indicate the updated location for the dot of the same colour. After a varying number of arrows, a coloured pointer would appear in the center of the empty matrix as a prompt for the participant

to respond by clicking with the mouse or tapping with a finger on the updated location for the dot of the same colour as the pointer.

KT requires updating the identity of the most recently studied words in three semantic categories (Yntema, 1963) (Figure 7.2.1B). At first, the category names would be presented in boxes at the bottom of the screen whilst exemplar words belonging in these categories would appear one after the other for 2500ms each with a 1000ms inter-stimulus interval. After a variable number of words, one of the boxes for the category names would be highlighted prompting the participant to make their response by typing the last word presented in that category.

For both training tasks, level of difficulty was modulated by increasing or decreasing the update level, i.e., the number of updates on each trial. Update level corresponded to the number of arrows shown before a response was prompted for MU, and to the number of words shown before a response was prompted for KT. If participants answered at least four trials in a block correctly, i.e., 80% accuracy criterion after every five trials; then the update level would increase by one in the next block, alternatively the update level would decrease by one. For all pilot participants, difficulty of the training tasks was progressively increased in response to task performance to adaptively increase environmental demands. Training duration for the MU task was between 25-30 minutes whilst the KT training lasted between 20-25 minutes.

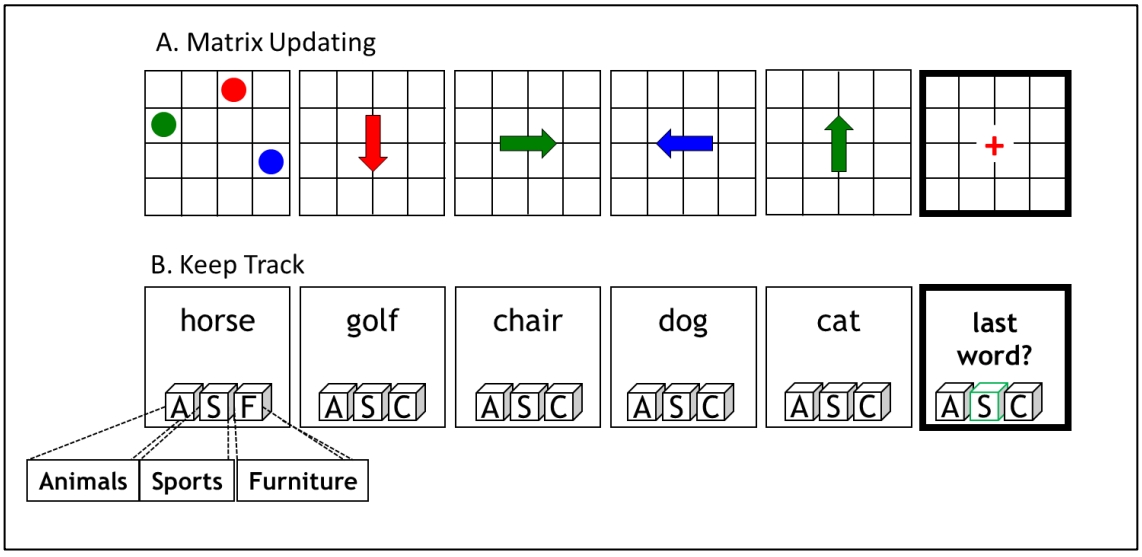

Figure 7.2.1: WMU training tasks, A. Matrix updating, B. Keep track. Images adapted from Flegal, Ragland and Ranganath (2019).

The training sessions took place remotely with the use of two Presentation web license experiment activations allowing the packaged software to run on multiple devices at once. It also enabled delivery of two WMU training versions: 1. a version compatible with a Windows desktop/laptop device (Vista/7/8/10) and 2. a version compatible with iPad/tablet/mobile devices. The Windows version was able to support both MU and KT tasks; the mobile version however was not able to support the KT task due to the keyboard response not being a part of the supported features at the time the pilot was conducted. Both WMU training versions remained active throughout the 8-week intervention period. The experimenter created detailed step-by-step PDF guides and video tutorials for both versions which were accessible online[13] and shared with participants. The experimenter additionally offered individual practice sessions on how to use the Presentation software prior to starting the intervention period, i.e., visits 2-9, if needed. Information on participants' performance and update level reached for each training visit, written out to summary text files when the training tasks were completed, was used on the next training visit for adaptively adjusting the starting update level according to the individual's performance on the final block of the previous training session.

7.2.4 Data Analysis

The anonymised participant data were exported from the CANTAB software to examine performance on the cognitive assessment tests. The output file contained a large amount of information, e.g., participant ID, number of study visit, start and end time of assessment etc., as well as the raw score for all outcome measures and for each test variant. We only selected outcome measures which additionally provided standardised and scaled scores as described in Table 7.2.2. Similarly, we downloaded the output log files created with the Presentation software to examine performance on the WMU tasks for each training session throughout the training period. We focused on extracting the maximum update level reached per training day for the MU and KT tasks as our outcome measure of training performance. Total score on the DEX was calculated by summing up the response values for each question and for each

[13] http://www.sinapse.ac.uk/ipress/wm-training

participant we calculated two scores per visit, i.e., self-rating score and independent-rating score.

Means and standard deviation descriptive measures for the small pilot sample were calculated with the R studio application (Team, 2019) in R software (R Development Core Team, 2020). In more detail, the tidyverse (Wickham et al., 2019), dplyr (Wickham et al., 2021) and ggplot2 (Wickham, 2016) packages were used for data manipulation and visualisation purposes.

7.2.5 Design & procedure

The study involved a total of ten sessions (Figure 7.2.2) which took place remotely with the use of Microsoft (MS) Teams run on the NHS Greater Glasgow & Clyde computer network to ensure data protection and confidentiality. The experimenter sent an electronic calendar invite to participants prior to each study visit and provided instructions on how to access the virtual meeting space. Participants were instructed to use any computer desktop/laptop and/or iPad/tablet/mobile device of preference. For the first and last study visits only, participants were asked to have two devices at hand if possible; one to access the meeting space and another to perform the cognitive tests. The reason for this was to enable the interaction between experimenter and participant during the assessment period to ensure compliance, assist with queries and provide re-assurance between tests. Prior to the first appointment, participants were provided with their unique web link for accessing the CANTAB assessment webpage and were instructed not to click on it before the assessment day.

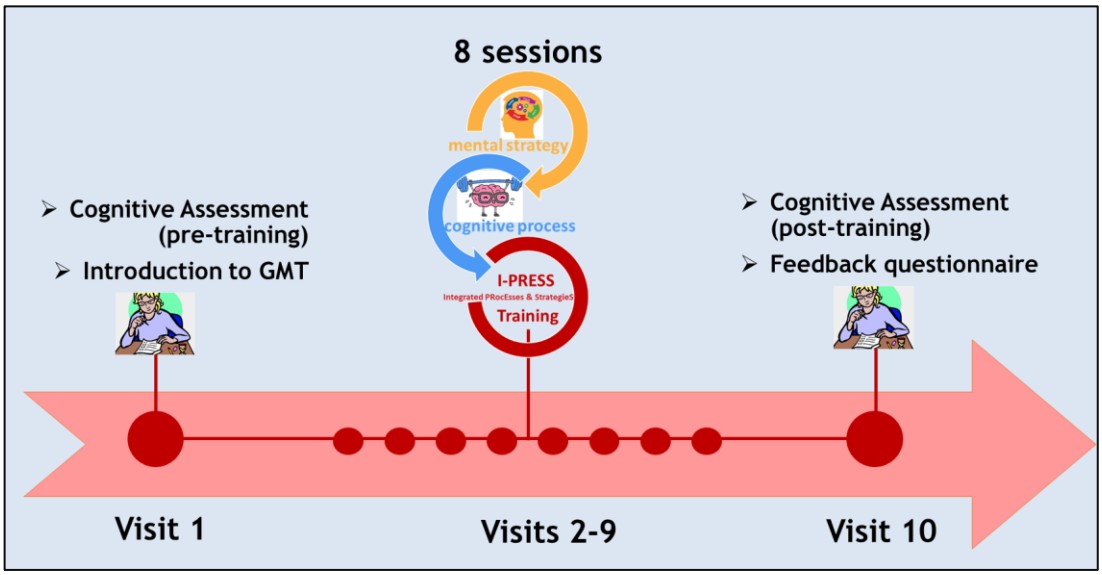

Figure 7.2.2: Study procedure.

At the beginning of the first appointment the experimenter went over the study consent form to ensure participants were informed and in agreement as to what their participation entailed and how their data would be managed. Following that, and after the participants' two-devices setup was in action, they were asked to follow the CANTAB web link and adhere to the software's instructions step by step. Once the participants ensured their device audio was on and their screen was on full screen mode, they were re-directed to the assessment page where the CANTAB software provided clear on-screen and voice-over instructions before each assessment. Participants performed five CANTAB tests (Table 7.2.2) for a total of 35-45 minutes. The experimenter stayed on the MS Teams meeting on mute throughout the assessment period and checked in with participants after completion of each test. Following the end of the assessment battery, participants were instructed to use the device logged in to the MS Teams meeting with the experimenter to continue with the appointment. The experimenter then shared their screen to go over the DEX questionnaire with the participants, i.e., get a self-rating score. The second component of the first visit involved presenting the GMT Module 1, i.e., introducing central concepts such as absent-mindedness, present-mindedness, and providing illustrative examples. The experimenter shared the GMT slides from module 1 and presented the standard material as instructed per GMT manual. In addition, a digital group consent form (Appendix 4.1) was completed to ensure confidentiality and privacy amongst GMT group members before the groups commenced. At the end of the first appointment, the experimenter sent

participants a copy of the study consent form, the digital consent form as well as the DEX questionnaire for a friend/partner/family member to provide their score, i.e., independent ratings.

Prior to the first group GMT session, i.e., Module 2, participants were provided with a hard copy of the GMT material via post, i.e., workbook, bookkeeping tasks, CDs. In addition, between the first and second study visits, the WMU training material was introduced and shared with participants to ensure the Presentation training program was setup before entering the 8-week intervention period. The experimenter noted the type of device each participant would use, i.e., Windows desktop/laptop or iPad/tablet/mobile device and distributed the PDF and video tutorials according to the device used. The first step involved installing and completing the practice trials of the WMU tasks, for participants to familiarise themselves with the nature of the training program and understand the tasks. When everyone in the group had completed the WMU practice trials (individually), the experimenter shared the instruction materials for setting up the full training program, i.e., uninstalling the practice version and downloading the full AT training version.

Study visits 2-9 involved the two main intervention components: the GMT weekly group sessions and the WMU computerised training sessions which participants completed at their own time. Once again, MS Teams was used for scheduling and performing the weekly GMT group sessions. Between group sessions, participants received reminders of the upcoming appointments as well as prompts to complete their GMT assignments and WMU training sessions. All participants were assigned in the WMU AT group and were started at the 3-update level for the MU task and at the 4-update level for the KT task. For each subsequent session, the update level was adaptively adjusted according to the individual's performance on the final block of the previous training session. If participants answered at least four trials correctly, i.e., 80% accuracy criterion after every five trials; then the update level would increase by one in the next five trials, alternatively the update level would decrease.

The final study visit, i.e., visit ten, involved completing the same CANTAB assessments and DEX questionnaire performed in visit one using the same procedure described above. The participants were then provided with a study-

specific feedback questionnaire (Appendix 4.2) and were asked to complete it in their own time to ensure honest feedback without the experimenter's influence. If participants had not provided their feedback one week later, the experimenter sent reminder prompts and as a last resort, an MS Teams meeting was then arranged to go over the feedback questionnaire verbally.

7.2.6 fMRI tasks adapted from (Flegal, Ragland and Ranganath, 2019)

The fMRI protocol consisted of two working memory tasks (a criterion version of the visuospatial MU, which was also part of the WMU training programme, and a spatial n-back), in addition to a task assessing episodic memory, the Object Location (OL) association task. We modified a few task elements from the original study paradigm used with healthy young adults (Flegal, Ragland and Ranganath, 2019) such as prolonging trial duration and reducing task difficulty level, to better suit individuals with ABI.

The criterion MU task was modified from the training task version to an event-related fMRI design with similar trial structure and timing but with a yes/no recognition probe type rather than freely indicating the updated dot location as in the training version (Figure 7.2.3). In the fMRI MU task, the participant needed to respond yes when the updated location of the dot which re-appeared was correct or no if it was incorrect. The MU task consisted of three trial types: 6 updates presented the high updating demand, 3 updates served as the lower updating demand and a maintenance-only baseline where grey arrows were presented, and the recognition probe simply referred to the original location of the coloured dots on that trial. For each trial type, the dependent variable was the proportion of correct trials.

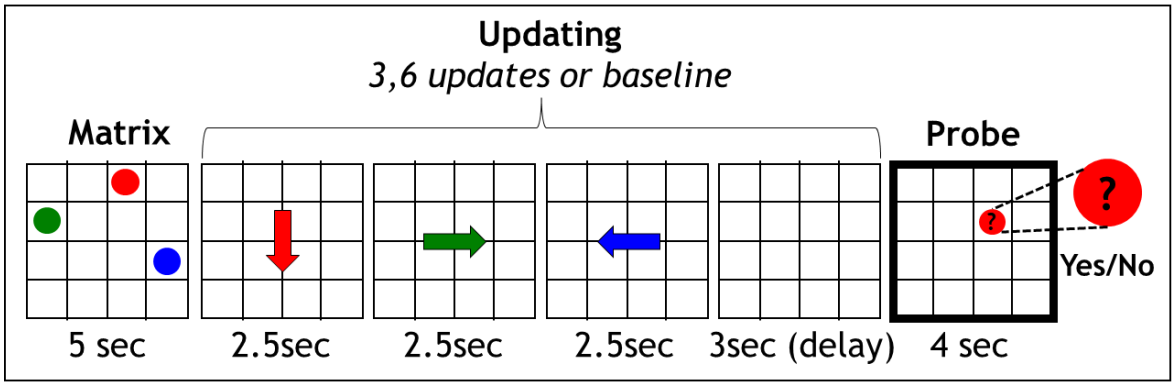

Figure 7.2.3: During each fMRI MU task trial, the matrix stimulus was presented for 5sec followed by either 3/6 coloured or grey arrows appearing for 2500ms and a jittered intertrial interval varying between 2 and 8 sec. The task was divided into four runs of eleven trials each (run duration = 312sec). The Figure was adapted from Flegal, Ragland and Ranganath (2019).

In the n-back task, blue squares appeared sequentially at one of eight locations on a 3x3 matrix with an unseen perimeter for 750ms each with a 2750ms interstimulus interval (ISI) (Figure 7.2.4). The participant had to respond by pressing one button when the current location matched the one presented n trials earlier and a different button when the location did not match. The task consisted of three trial types which were dependent upon the value of n: 2-back, serving as the high updating demand, 1-back, representing a lower updating demand; and 0-back, a baseline condition in which the target location was always the upper left corner of the screen. Overall accuracy served as the dependent variable for each block of trials.

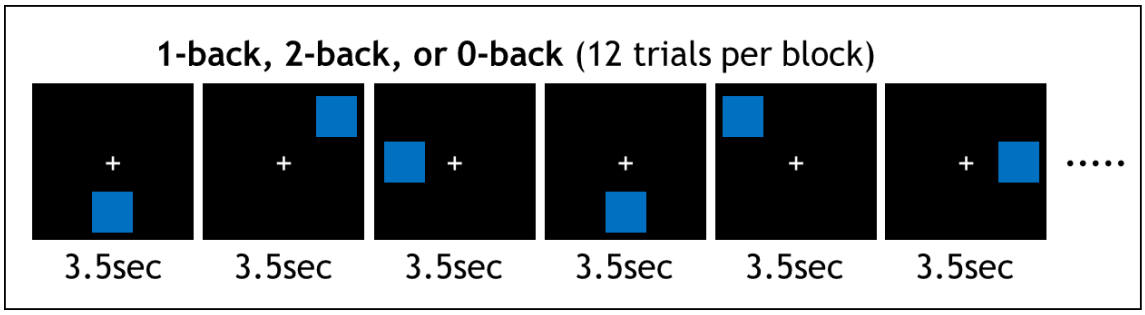

Figure 7.2.4: fMRI n-back trial duration was 3.5sec with a total of 12 trials per block. The task was divided into two runs of nine blocks each (run duration = 473sec). The figure was adapted from Flegal, Ragland and Ranganath (2019).

Object-Location Association is a visual episodic memory task and was based on a paired associate learning paradigm adapted for fMRI testing (de Rover et al., 2011; Gould et al., 2005). The task consisted of an encoding and a subsequent retrieval phase. In the encoding phase, participants were instructed to remember a series of unique kaleidoscope images (“objects”) (Voss et al., 2008) that were presented one at a time for 3.5secs each at variable locations on a 4x4 matrix (Figure 7.2.5). After the encoding phase, there was a set of retrieval trials where one of the cells in which one of the objects had appeared

earlier was highlighted for 6sec. The participant was presented with two options, i.e., a target object and foil, at the bottom of the screen and they had to press a button to indicate which object appeared on that cell location during the encoding period. The OL task consisted of three trial types: 6 associates serving as the high memory load of 6 pairs, 4 associates representing the low memory load of 4 pairs and a baseline condition controlling for motor and perceptual load in absence of any memory load. During the encoding phase for baseline trials, participants were instructed to simply rest with their eyes open whilst four grey squares were presented one at a time; in the retrieval phase another four grey squares appeared sequentially and participants were asked to indicate which half of the matrix each one appeared, i.e, left or right. Proportion of correct trials served as the dependent measure for the OL task.

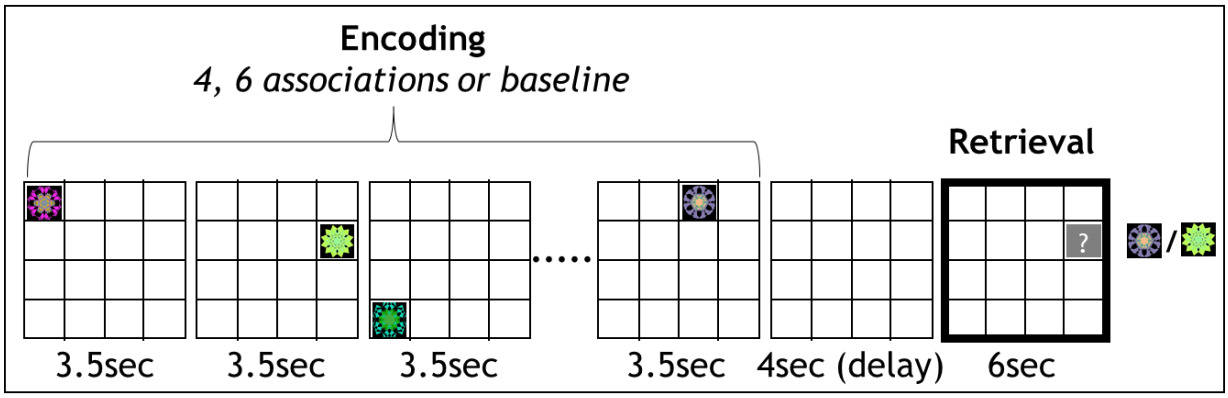

Figure 7.2.5: The OL task was divided into two runs of 6 blocks each (run duration = 358sec). The figure was adapted from Flegal, Ragland and Ranganath (2019).

7.2.7 fMRI pilot: procedure & acquisition

Participant PT002 was invited to attend the MRI appointment serving as a pilot to test the fMRI protocol on an individual with ABI. The appointment took place at the Clinical Research Imaging Facility (CRIF), Queen Elizabeth University Hospital (QEUH) in a 3T Prisma Siemens scanner. At first, PT002 was asked to complete a few rounds of task practice before the scan to become familiar with the task instructions and response type. As soon as the task practice was complete, the experimenter and participant moved to the scanner area. One of the radiographers on site went over the CRIF MRI screening form to ensure the

participant was safe to undergo a scan. Following that, the participant was accompanied to the MR room and positioned into the scanner bore.

During the fMRI session the participant performed four runs of the MU task (21min), two runs of the n-back task (15.7min) and two runs of the OL task (12min). The fMRI tasks were presented using Presentation 20.1 (www. neurobs.com) and task responses were collected using the Nordic Neuro Lab (NNL) fMRI solutions products: the ResponseGrip response collection device and the SyncBox, an MR image and stimulus synchronization device. After completing the fMRI tasks, PT002 remained in the scanner for another 20mins approximately to acquire a set of anatomical images necessary for neuroradiologist reviewing.

fMRI data were acquired with a multi-slice gradient-echo Echo Planar Imaging (EPI) sequence (repetition time [TR]1220 ms; echo time [TE] 24 ms; multi-band factor 2; flip angle 67°; field of view [FOV] 448 x448 matrix; 38 slices; 3.0 mm isotropic voxels). The first four volumes were discarded at each functional run, necessary for signal equilibration. For each MU run, a total number of 261 volumes were collected, 392 volumes for each Spatial N-Back run, and 298 for each OL Association run.

Four kinds of anatomical sequences were acquired at the end of the scanning session. An MP-RAGE sequence (TR 2500 ms; TE 2.88 ms; flip angle 8°; FOV 256 mm; 256 x 256 matrix) was used to obtain high-resolution T1-weighted anatomical images. An axial T2-weighted (TR 5260 ms; TE 103 ms; flip angle 150°; FOV; 240 x 320 matrix), an axial T2-weighted FLAIR (TR 9000 ms; TE83 ms; flip angle 150°; FOV; 250 x 320 matrix) and a SWI (TR 24 ms; TE 20 ms; flip angle 15°; FOV; 192 x 320 matrix) sequences were further acquired for neuroradiologist reviewing.

7.2.8 fMRI data pre-processing and first-level analysis

fMRI task data pre-processing was performed with SPM12 www.fil.ion.ucl.ac.uk/spm/software/spm12/ . The participant's functional images were realigned using a six-parameter rigid body transformation, coregistered to their anatomical image, normalized to MNI (Montreal Neurological Institute) space using affine and nonlinear transformations, and

spatially smoothed using a 6-mm isotropic FWHM Gaussian kernel. The participant's T1-weighted anatomical image was segmented, normalized, and spatially smoothed. BOLD responses for each task were analysed using the general linear model (GLM) in SPM12. Motion parameters estimated at the realignment stage of preprocessing were included in each fMRI task model as covariates of no interest. Covariates of interest were computed by convolving vectors of predicted neural activity with a canonical hemodynamic response function.

MU was analysed in an event-related design where BOLD activation was modelled with separate regressors for matrix, updating and probe task phases as a function of update level (6-updates/3-updates/baseline) and task accuracy (correct/incorrect). First-level analysis was performed using the GLM and a high-pass filter with a 200sec cut-off. Our primary contrast of interest involved BOLD activation during the MU probe task phase on correct 6-update trials vs 3-update trials. The n-back and OL tasks were analyses in block-designs with first-level analysis performed using the GLM and employing a high-pass filter with a 128sec cut-off. For n-back, separate regressors for n-back level (2-back/1-back/0-back) were included in the analysis model and the primary contrast of interest focused on 1- and 2-back blocks Vs. 0-back blocks. For OL, individual regressors modelling the encoding and retrieval task phases as a function of associates level (6-Associates/4-Associates/baseline) were included and the primary contrast of interest focused on the encoding phase in 4-and 6-associates block Vs. baseline blocks.

7.3 Results

7.3.1 Recruitment

Recruitment for the remote iPRESS pilot took place between May and September 2021 from the stroke and brain injury teams at NHS Lanarkshire (Figure 7.3.1). From the total number of participants recruited, we completed visit 1, i.e., performed the cognitive assessments and introductory GMT session, with N=6 and finally enrolled N=5 participants in the iPRESS trial after one participant withdrew due to stress unrelated to the study. Recruitment rate was estimated at N = 1.5 participants per month. This was calculated by dividing the

total number of participants enrolled/consented (N=6) in the study by the number of sites recruiting (N=1), then divided by total number of months the study recruited for (N=4). Three participants were included in the first group which took place between July 6th and September 3rd (2 females), whilst the second group comprised of two participants (2 males) and took place between October 5th and November 30th. Participants in both groups remained in the intervention until completion, whilst one participant dropped out before entering the group intervention and therefore drop-out rate was approximately 17% and calculated as the number of dropouts, N=1, divided by the total number of participants enrolled, N=6.

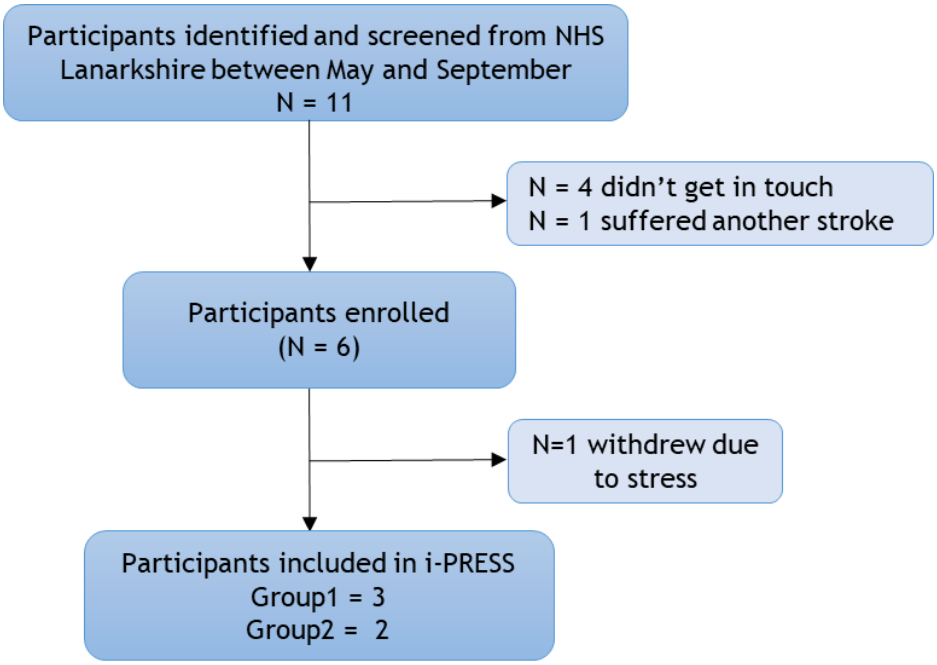

Figure 7.3.1: Recruitment flow between May and September 2021.

7.3.2 Cognitive Assessment

On most occasions the experimenter was able to successfully monitor participants whilst they performed the assessments by staying on the MS Teams meeting on mute as described in the methods section. Nevertheless, in most cases a family member provided technical support to ensure the required setup was in place; no further assistance relating to task completion / instructions was received.

Pre- and post-training scores for each participant on all cognitive assessments are reported in Table 7.3.1. Even though we cannot perform any statistical analyses to evaluate training-related effects on the CANTAB subtests in this small pilot sample, we can identify some post-training changes in raw test scores. For example, participants made fewer errors in the IED subtest post-training whilst they also performed better in the SSP reverse subtest. It appears that the number of SOC problems solved in the minimum amount of moves required also increased post-training. Standardised scores seem to remain stable for the SSP forward and reverse, SWM errors, SOC minimum moves, and IED total errors adjusted test measures, whilst there seems to be a slight increase for the IED total errors and SWM strategy test measures (Figure 7.3.2). Naturally, whether these observed differences are statistically significant cannot be reported at this stage.

Participants' self-reported experience as assessed by the DEX questionnaire -lower score is better- improved post-training for everyone apart from PT006. Scores on the DEX by the independent-rater also improved for PT002 and PT004 whilst the opposite is true for PT001 (Figure 7.3.3). We cannot make any observations for PT005 and PT006 because the independent rater data was not provided.

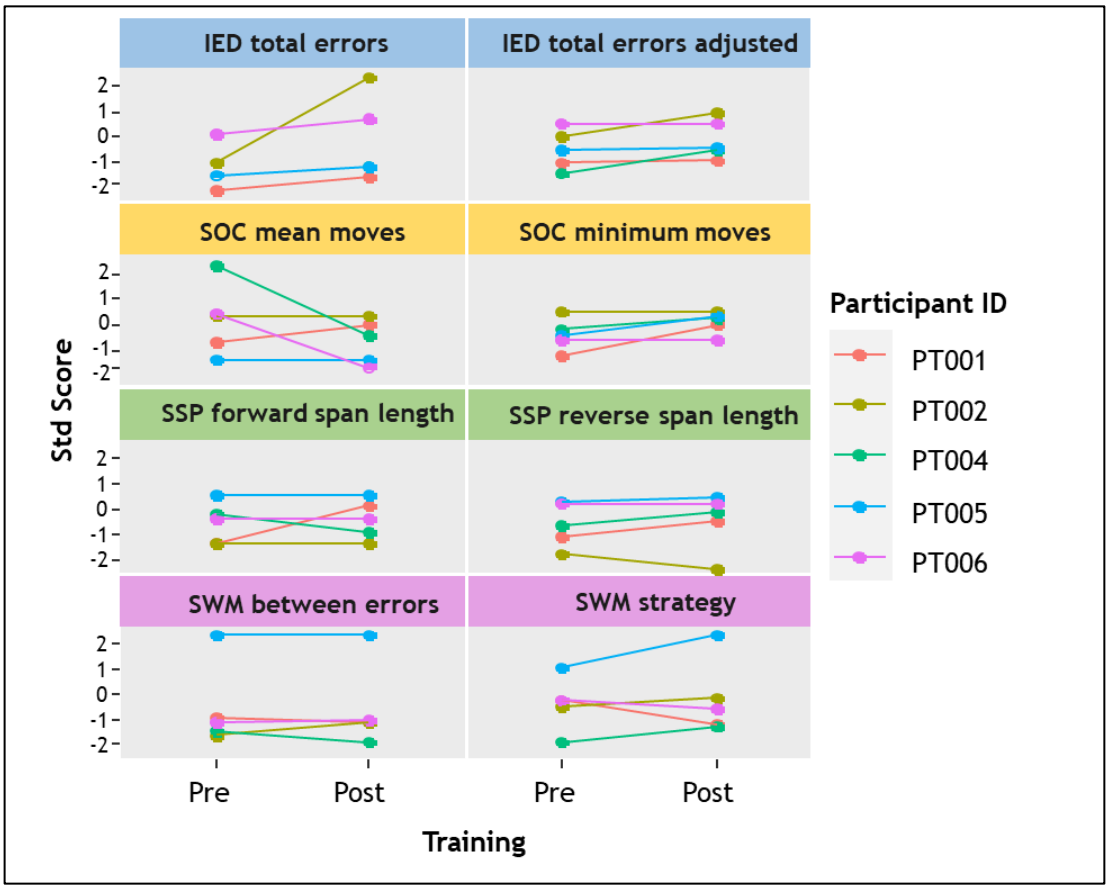

Figure 7.3.2: Standardised scores on the CANTAB test measures pre- and post-training.

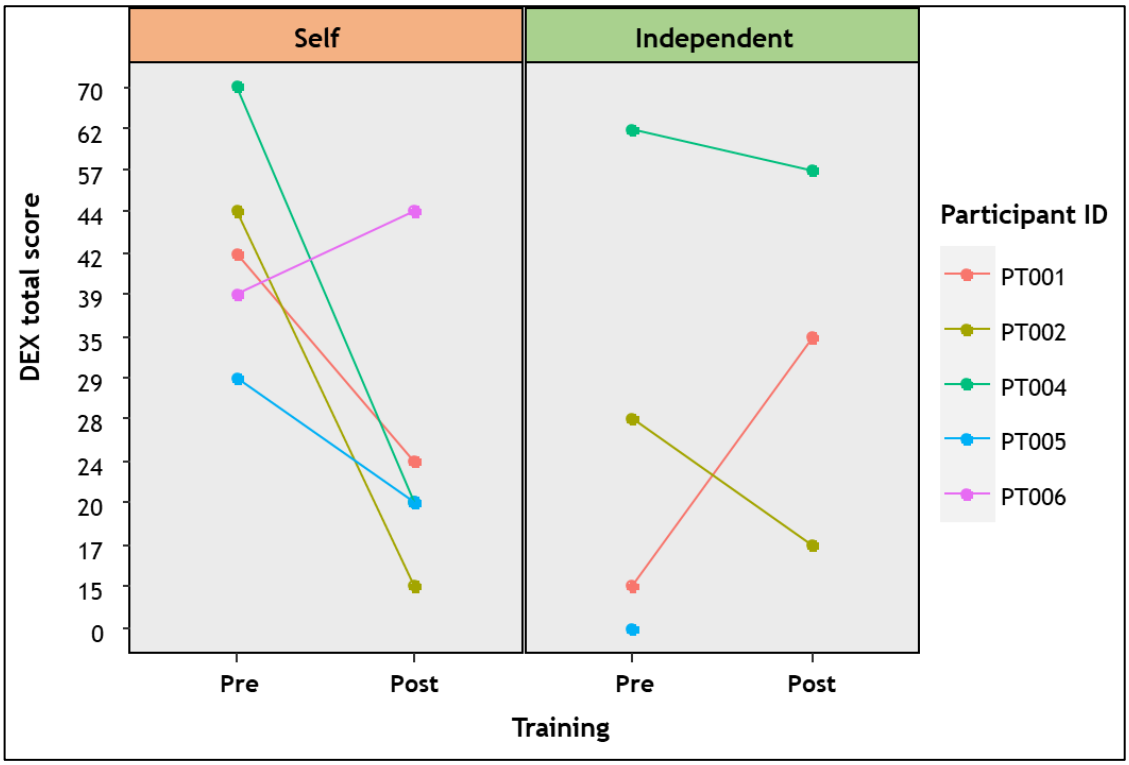

Figure 7.3.3: Scores on the DEX questionnaire pre- and post- iPRESS training. Independent-rater scores are missing for PT006 at both time-points and for PT005 post-training.

7.3.3 Training Program

GMT between-session assignments

Overall participants engaged well with the training despite its online nature. Everyone was able to successfully attend group sessions using the MS Teams software. On the rare occasions a participant could not attend the scheduled group session, the experimenter offered a one-to-one session at a time mutually convenient and additionally provided the module slides that were presented during the session they missed. Attendance was high with only one instance of a participant missing a group session whilst everyone attended their one-to-one introductory appointment. As part of the GMT programme structure, during each session participants were asked to share their entries, experiences and comments relating to their weekly assignments. Participants in both groups completed their assignments successfully apart from PT006 who found it difficult to engage with the training overall despite daily prompts.

WMU training

Participants PT001 and PT002 completed their training on a mobile device, i.e., android tablet/iPad/any android or IOS mobile phone, and therefore only trained on the MU task. Participants PT004 and PT005 downloaded the WMU training on their Windows device and had access to both MU and KT tasks. PT006 was unable to engage with the WMU training despite daily reminders and additional one-to-one tutorial sessions with the experimenter and as a result there is no WMU training data associated with that participant.

Participants were instructed to complete a minimum of 8 training sessions during the intervention period. For the MU task, PT001 and PT002 completed seven training sessions, PT005 completed five, and PT004 performed three sessions in total (Figure 7.3.4). PT002's performance remained constant throughout the training and at a maximum update level of 3-updates (floor performance for this task). PT001 also performed at a constant level, 4-updates for most of the training period but achieving 5-updates on their last training

session. On the contrary, PT005 was improving greatly as training days progressed and reached a maximum level of 23-updates on his final training session. For the KT task, PT004 completed only two training sessions whilst PT005 completed four (Figure 7.3.5). Once again, PT005's performance improved greatly and reached a maximum update level of fourteen on their last training visit. PT004 reached a maximum update level of three on the MU task during his three training visits (floor performance for this task) and an update level of 4 for the KT task (floor performance for this task) for the two sessions he completed.

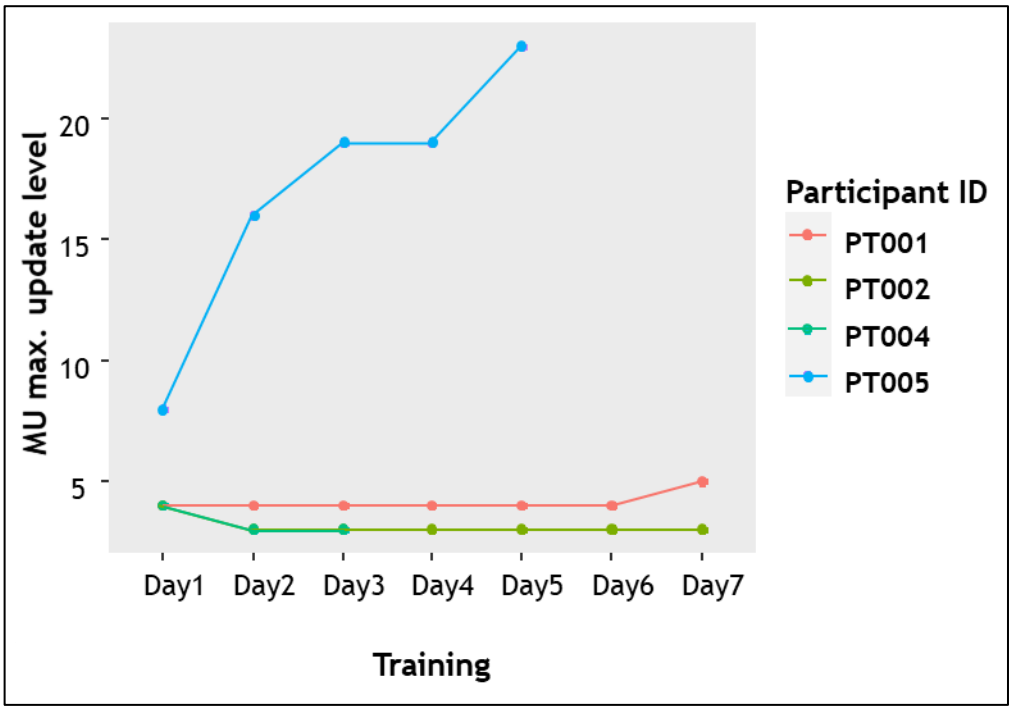

Figure 7.3.4: Matrix updating task - maximum update level achieved per training day.

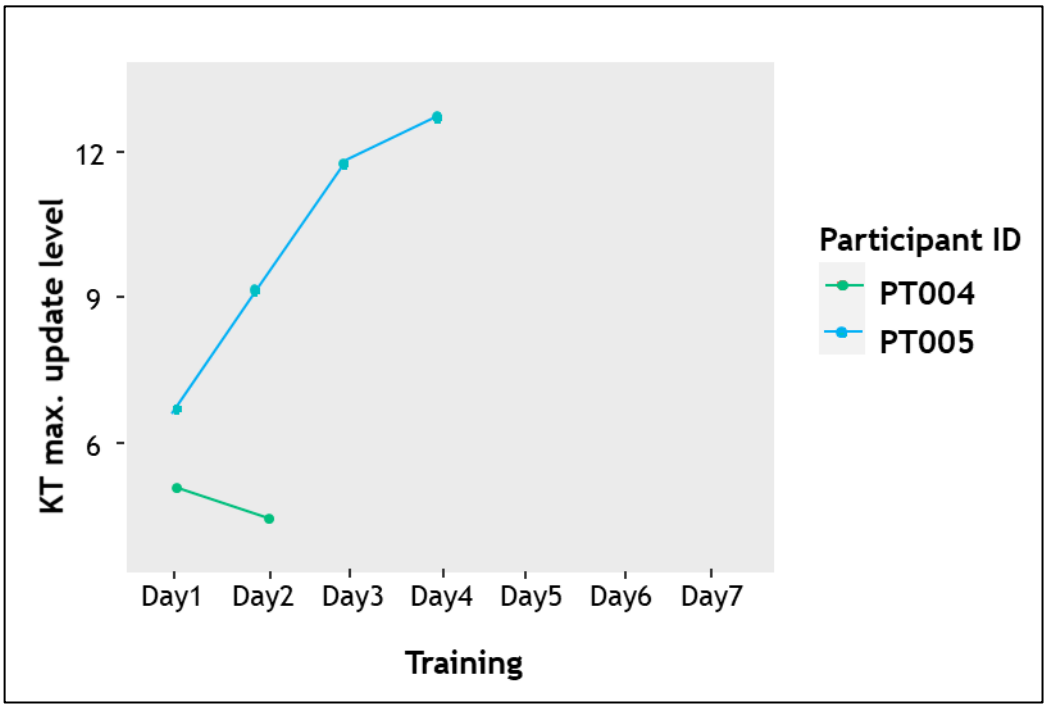

Figure 7.3.5: Keep Track task - maximum number of updates reached per training day. KT was only available on the Windows version of the training; hence performance is depicted for two participants only.

Table 7.3.1: Raw test scores on the CANTAB test measures pre- and post- training.

Participant	Test Measure															
	IED errors total		IED errors adjusted total		SOC mean moves		SOC minimum moves		SSP forward span length		SSP reverse span length		SWM between errors		SWM strategy	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
PT001	33	28	62	59	7.5	7.25	6	9	4	6	4	5	21	24	8	11
PT002	23	0	29	8	7.25	7	9	9	4	4	3	2	27	19	9	8
PT004	-	24	108	55	5.25	7	9	10	6	5	5	6	22	28	12	10
PT005	31	28	66	57	8.5	8.5	8	10	7	7	6	7	0	0	4	2
PT006	5	2	11	11	6	9	8	8	6	6	7	7	19	18	8	9

7.3.4 Participant Feedback

Participants' questionnaire feedback on the iPRESS intervention was very positive overall. The eight questions asked, and Likert scale responses given, are reported in Table 7.3.2. All participants reported that the appointments were convenient, thought it was feasible to remain in the study for 12 weeks and found the group sessions enjoyable. Therefore, everyone stated they would recommend the intervention to another individual with brain injury. In participants' own words and in no particular order:

Question 2

> *"Yes, it was good to meet other people with brain injury who are similar to me."*
>
> *"I would recommend it because of the social aspect."*
>
> *"The training provided by Katerina has helped me immensely and I have already recommended it to another stroke survivor."*

Question 5

> *"Very enjoyable to me, I was looking forward to the sessions. To share a new experience with people that are in a similar position to yourself, you get lots from that. Just listening to others, feeling you are not alone."*
>
> *"That was my first experience of speaking to anybody similar to me and that was very good, I enjoyed it."*
>
> *"Very nice to discuss problems."*
>
> *"I loved my group sessions very much it was good to meet others who were going through similar problems as I was it made me feel less alone on my recovery journey and also from a sociable aspect even though we were online"*

Regarding the feasibility of the WMU training programme, even though ratings were very positive, participants also mention a few difficulties. In more detail about *Question 4.*

> *"As I'm not very tech savvy I did have problems to begin with, but my daughter helped me access the training and also on explaining*

difficulties to Katerina she found ways of making it more simple to access on my own so overall very feasible."

"Overall, it was feasible but for me it was a bit harder to complete."

"It was quite easy to operate and understand as long as you read the instructions properly."

Table 7.3.2: Participants' feedback on iPRESS (see Appendix 4.2 for questionnaire format).

Overall:	**Participant**				
 1 2 3 4 5	**PT001**	**PT002**	**PT004**	**PT005**	**PT006**
1. *How convenient were the appointments?*	1	1	1	1	1
2. *Would you recommend the intervention to someone with ABI?*	1	1	1	1	1
3. *How feasible was it to remain in the study for 12 weeks?*	1	1	1	1	1
4. *How feasible was it to complete the WMU training?*	1	1	1	1	3
5. *How enjoyable were the group sessions?*	1	1	1	1	1
6. *How relevant was the intervention to your situation?*	1	1	1	1	3
7. *Do you feel the intervention contributed to your recovery?*	1	1	1	1	2
8. *Will you continue to use the strategies you learned after the end of the intervention?*	1	1	1	1	2

When questioned about how relevant they thought the intervention was, everyone said it was relevant and mentioned that it improved their understanding of the injury as well as the benefit gained from GMT techniques, i.e., STOP! cycle and breathing exercises.

"It was very beneficial, the breathing exercises, the stop technique, very helpful."

"It helped my understanding of living with an injury."

"Perfect for me, it was exactly what I needed. I would continue making mistakes if I didn't use the stop technique or directions from Katerina."

"I personally found it very relevant as I knew myself the further into the training I got the more I was improving and problems became less stressful."

Only one participant gave a lower rating and stated:

"Breaking the habit of the automatic pilot was both distracting and helpful. I feel like this is a part of me that is gone. I didn't know it was there until it was gone. Doing the training brought that on to me, I noticed it."

Questions 7 and 8 involved a similar theme and once again the comments were very encouraging. Everyone stated they would continue to use the strategies they learned during the training and felt the intervention contributed to their recovery.

Question 7

"It has given me more confidence."

"We talked about things I was unaware of, you don't forget the techniques I learned, they all come back. We use them in relevant situations."

"The course itself helped me understand the limitations of brain injury and seeing that it helped go back in a brand-new world. When you take time to stop it's easier even with limitations, to understand the task and it significantly improves the outcome. The way you feel inside, it changes."

"Absolutely. Problems I was experiencing prior to the training became less stressful and the breathing techniques were particularly useful to me in allowing me to focus more on my left side which after strokes I sort of lost my left side and also these techniques stopped me from getting over stressed."

Question 8

"The strategies are what allow you to return to paid employment. It might not be the same high level as before or with the same speed. By using the techniques, the breathing, stop-state you can

successfully complete a task. It is life-changing, allows you to provide for your family."

"I feel it's like my secret help mechanism, tools only I know about."

"Some of the processes that was brought to me reminded me of processes I knew in the past and that was very useful, so I will try to keep using them"

"I know that the strategies I've learned will be with me for life now as I recognise myself now that without even thinking about it I automatically use them every day like 2nd nature now."

"There will always be daily situations where I will need the stop technique, the breathing exercise, get some fresh air and then continue."

7.3.5 fMRI Pilot

PT002 was diagnosed with a stroke in July 2020 and bilateral parieto-occipital infarcts were visible in the anatomical scans (Figure 7.3.6). The participant was able to remain in the scanner for the total duration of the session lasting 70 minutes and had no trouble performing the fMRI tasks nor making responses on time.

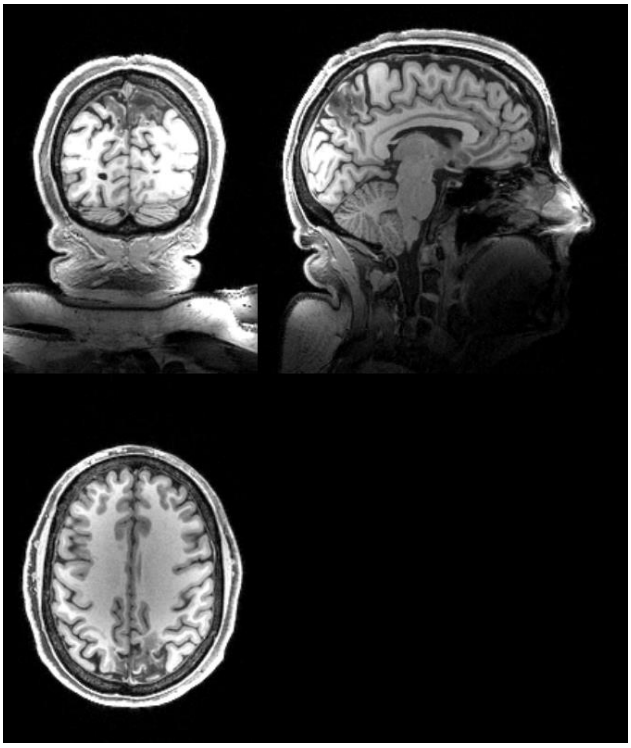

Figure 7.3.6: High resolution T1-weighted anatomical image.

PT002 performed above chance level for most conditions across scanned tasks apart from the 6-updates condition in the MU task and the 4-associates condition in the OL (Table 7.3.3). Interestingly, PT002 performed better in the 6-associates high difficulty condition in the OL compared to the low difficulty condition, and the same was true for the 2-back Vs 0-back in the n-back task.

Our single-subject fMRI analysis showed significant activation in frontoparietal regions of the central executive network and in the right caudate region whilst PT002 performed the MU task, for the correct 3-update trials against correct baseline trials contrast (Figure 7.3.7). A similar pattern was also true for the OL task where bilateral putamen and right hippocampus were active when comparing the 4-associates Vs baseline conditions during the encoding phase. In the n-back task activity was exhibited in right frontal, bilateral occipital and parietal areas when comparing 2-back against 0-back task trials. Similar regions of task-based activation were reported for the MU task in the original study with young adults (Flegal, Ragland and Ranganath 2019) with bilateral striatum (i.e., putamen and caudate nucleus), prefrontal, temporal and parietal areas involved.

Table 7.3.3: PT002's performance on the scanned versions of the Matrix Updating, Object Location association and N-back tasks.

Condition	Mean accuracy	SD
Matrix Updating		
Baseline	0.75	0.32
3-updates	0.63	0.32
6-updates	0.5	0.28
Object Location		
Baseline	1	0
4-associates	0.38	0.25
6-associates	0.62	0.08
N-back		
0-back	0.54	0.15
1-back	0.71	0.09
2-back	0.59	0.19

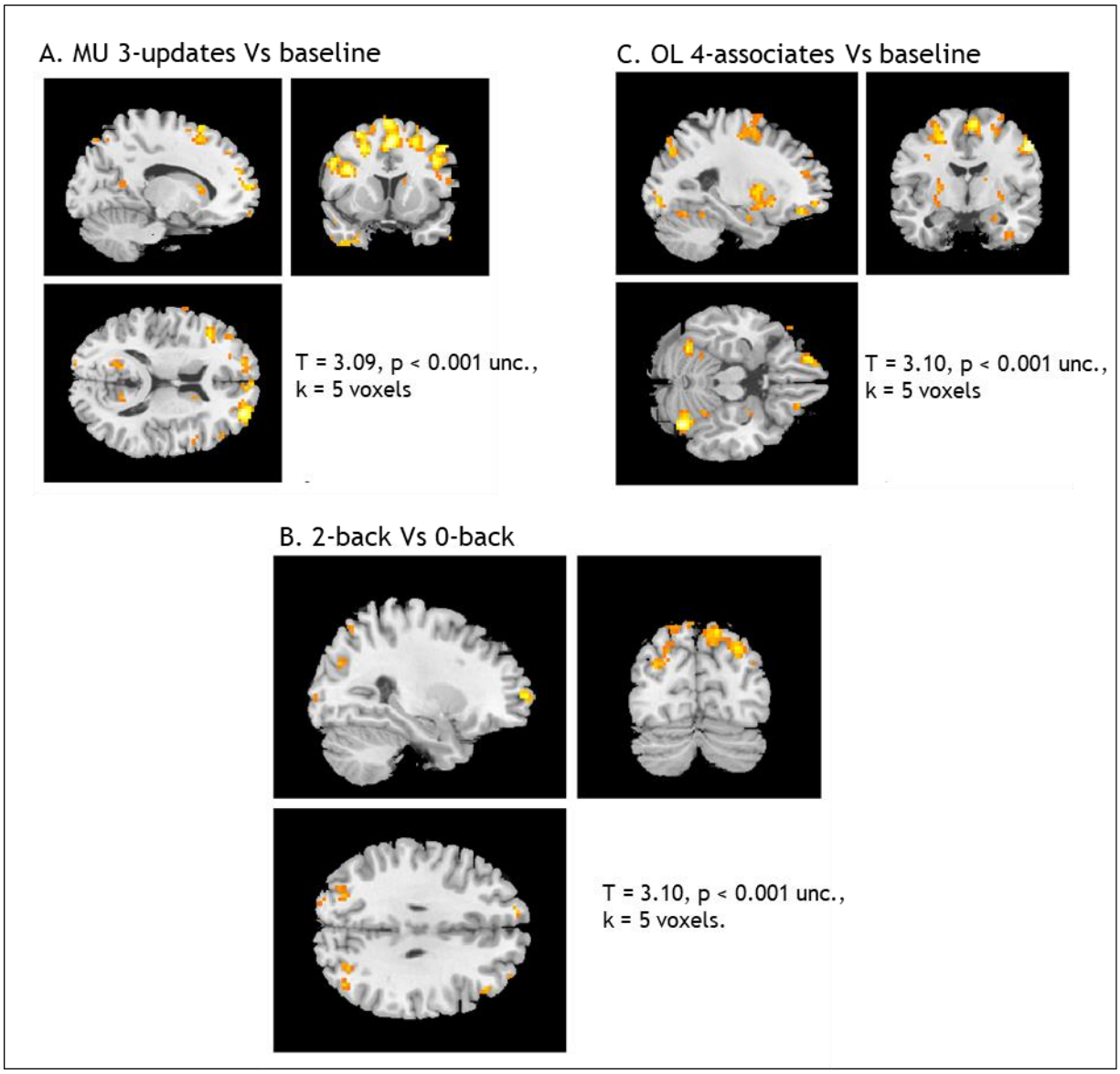

Figure 7.3.7: First-level results from contrasts of interest whilst PT002 performed the A. MU, B. n-back and C. OL tasks.

fMRI Group analysis plan

As described in section 6.6 in Chapter 6, participants are stratified by aetiology of brain injury, i.e. TBI or stroke, in their group assignment, thus counterbalancing group variability in terms of lesion type, size and extent. On a single-level analysis, a participant-specific grey and white matter inclusive mask will be applied to exclude voxels from ventricles and lesioned regions. If standard pre-processing steps do not provide data of high quality due to brain lesions, then automatic lesion-detection software such as LST toolbox in SPM will be used (Schmidt et al., 2012; Khorrampanah et al., 2020). An a-priori region of interest (ROI) analysis approach will be employed based on the original fMRI analysis in healthy young adults (Flegal, Ragland & Ranganath, 2019) reporting

significant group differences in bilateral caudate, putamen and hippocampus. An automatic ROI analysis will be chosen over a manual approach with previous work by Garrison et al. (2015) concluding no differences between the two approaches when studies employ a task interaction design. We hypothesise the patient group analysis will exhibit similar findings to the original study (Flegal, Ragland & Ranganath, 2019) with the AT group exhibiting greater training-related BOLD reductions post-training compared to the NA in all ROIs. Exploratory analysis with masked whole-brain volumes at the group level will investigate whether adaptivity-related activation changes involve additional common brain regions in individuals with ABI.

7.4 Discussion

The present chapter focused on a remotely delivered pilot of the iPRESS intervention. We examined the feasibility of the combined intervention in a small number of participants with ABI and additionally assessed the fMRI protocol on a participant with ABI. Even though small numbers prevented us from conducting statistical analyses, we collected invaluable data on the recruitment rate, suitability of the training program, technical specifications, participant feedback, as well as the suitability and tolerability of the fMRI protocol.

Based on our preliminary data on participants' CANTAB assessments, DEX scores, WMU training performance, low dropout rate, and fMRI pilot session tolerance, we consider the combined intervention to be feasible overall. We do need to consider a few aspects that require modification and/or further improvement, though. First and foremost, our recruitment rate of 1.5 is slower compared to the one reported by (Walters et al., 2017) on their review examining consent, recruitment and retention rates for single and multicentre randomised control trials funded and published by the UK's National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme. This figure is noted solely as a relative measure to facilitate our understanding and not a means of direct comparison. So, even though our recruitment rate seems quite slow, this is to be expected at the beginning of a trial especially if it is taking place amidst a global pandemic. At the same time, this value is based upon recruitment from a single site whilst the study is already established and

will eventually be recruiting from two NHS sites, i.e in NHS Lanarkshire and NHS Greater Glasgow & Clyde. The study dropout rate was low which is promising although this is based on very small numbers and should be interpreted with caution.

Another major aspect of the pilot study involved modifying its components for remote delivery. Performing neuropsychology assessments using CANTAB web-based testing proved to be a suitable alternative with some additional benefits, such as the automated and standardised test administration and scoring as well as secure data encryption and storage. Moving forward, we consider using CANTAB as the standard way of performing cognitive assessment for this study even when delivered in person. Participants engaged well with the GMT group sessions despite the online nature. Participants attended most of the group sessions, they were keen to share their own experiences in the group, demonstrated good effort to complete the GMT assignments both during and between sessions and everyone enjoyed the opportunity to meet others with ABI. For WMU training, however, remote delivery proved more challenging than anticipated. First, we were not able to offer both WMU training tasks in both experiment versions, i.e., Windows and mobile. A downside to this is that not everyone completes the same training protocol overall, in addition to the shorter total training duration for those training on the mobile version compared to the Windows. However, at the same time it does provide the flexibility to include more people in the study since even when participants do not have access to a Windows desktop/laptop, almost everyone has a smartphone mobile device. Another technical complication we experienced had to do with situations where a participant exited the Presentation application before completing the total number of training task blocks. The application did not process this as a complete training session and did not progress the participant on to the next training visit. We therefore came across multiple summary text files with the same visit name for the same participant.

Another set of factors to consider are participants' individual differences in terms of the brain injury, associated cognitive impairments, severity of executive dysfunction, emotional wellbeing, motivation, and how these might interfere with their ability to engage with the training. In this pilot study, even

though PT006 exhibited similar -if not higher- performance on the CANTAB subtests compared to other participants, he was not able to engage with the WMU computerised training at all despite additional one-to-one tutorial meetings and daily text reminders. In terms of the GMT however, he had no trouble accessing the online meetings, attended most group sessions, he was open to discuss how best to try and modify the assignments to suit his abilities. Most importantly, participating in the training brought back awareness of the automatic pilot system. So even in this challenging case, PT006 was still able to gain something from the training and in his own words: "*.. Doing the training brought that on to me, I noticed it.*"

Preliminary data of our fMRI protocol on a participant with ABI showed great promise for studying training-related neural plasticity in individuals with brain injury. PT002's performance on the scanned tasks was well above chance for most conditions, and that is particularly encouraging moving forward. We noted however that the n-back task duration was too long in the scanner setting and decided to modify the paradigm by having 3 runs of 5.3 min duration (rather than 2 runs of 7.88 min); a task length which is similar to the other two scanned tasks. More importantly, the functional activations observed in PT002 were located in brain areas traditionally involved in WM tasks, i.e., in fronto-parietal cortex and the subcortical regions of putamen and caudate. Hippocampal activations were also evident in the OL episodic memory task. These findings are in line with the previous data collected employing the same paradigm on healthy young adults (Flegal, Ragland and Ranganath, 2019) as well as meta-analyses investigating the neural basis of WM (Nee et al., 2013; Rottschy et al., 2012).

7.4.1 Conclusions

This preliminary pilot feasibility study has produced useful results that suggest that the iPRESS study protocol can be implemented, is acceptable to participants and the required data can be collected. The fMRI protocol was well tolerated, and the resulting activations were in line with expectations as well as previous data on the same paradigm with healthy adults. The study has identified a number of minor modifications to the trial delivery procedures that need to be made moving forward. These include adjusting the WMU output file settings to log incomplete training sessions and correctly assign them distinct

visit numbers. Additionally, the fMRI n-back task will be modified to involve three runs of 5.3 min each to make task length more manageable. Our next step will involve evaluating the feasibility of the combined strategy-based GMT and WMU process-based intervention in a larger sample that will additionally allow us to investigate the training-related cognitive and neural changes taking place.

8 General discussion

The research presented in this thesis has been conducted in a series of linked stages. The first stage focused on the cognitive and neural changes evident following working memory training in healthy individuals and the second stage emphasised the transition, development, and evaluation of an integrated intervention involving goal management strategies and working memory process-based training in adults with ABI.

In the first stage, three different methodologies were employed, beginning with a comprehensive systematic review and meta-analysis focusing on WM updating as the trained cognitive process (Chapter two). It was concluded that WM updating training can successfully improve cognition in healthy adults as evidenced by performance on criterion-trained tasks. However, evidence for near transfer of learning was moderate and there was no indication for far transfer of learning to general cognitive domains. Neural findings revealed a relatively homogeneous pattern of fronto-parietal reductions in activation during criterion task performance following training, whilst the training-related pattern of subcortical changes was less clear. Training-related functional activity changes on transfer tasks were less frequently examined but increases in activation were more often involved. The review identified a large gap in the literature relating to: 1. the structural and functional connectivity changes taking place following WM training; 2. the choice of control group and how it can influence study findings; 3. the complexities involved when comparing across studies due to the plethora of research protocols employed; 4. the very low number of studies with neurological samples.

To tackle the first issue, two separate, complementary analyses were conducted investigating the pattern of grey matter volumetric (VBM) changes (Chapter three) and task-based functional connectivity changes (Chapter four) taking place after adaptive WMU training in healthy adults, with fMRI data collected at three time points (i.e., pre-, early- and post-training) across a protocol of 10 training sessions. Both analyses were based upon the original fMRI study conducted by Flegal, Ragland and Ranganath (2019) and focused on a set of a-priori defined subcortical ROIs, i.e., bilateral caudate nuclei, bilateral putamen, and bilateral hippocampi. The VBM analysis did not reveal any training

related changes for any of the ROIs, with additional exploratory whole-brain analyses also exhibiting null findings. The functional connectivity analysis on the other hand found distinct patterns of changes evidenced by data acquired from the scanned criterion and a near transfer task following adaptive WMU training. For the Matrix Updating criterion task, connectivity decreases were evident between the left putamen and right parahippocampal gyrus and cerebellum early-training compared to pre-training, which were subsequently followed by connection decreases between bilateral putamen and right lateral occipital and fusiform gyrus as well as between the right hippocampus and right superior parietal lobule. For the n-back transfer task, connection increases were observed between left caudate and left lateral occipital cortex and precuneus early in the training compared to pre-training. Decreases were also found in the connectivity between the left putamen and left precentral gyrus pre-training to post-training as well as between the left putamen and left supramarginal gyrus pre-training to early-training.

The second stage of this programme of research focused on the transition from research with healthy adults to studies with neurological samples. A critical review was presented discussing key issues in the field of cognitive training with emphasis on WM protocols as well as the importance of employing interdisciplinary methods from the fields of clinical neuropsychology and cognitive neuroscience (Chapter five). The key issues expanded upon involved: 1. the gap between clinical neuropsychology and cognitive neuroscience relating to methods and lack of collaboration; 2. the importance of selecting suitable primary outcome measures and the differences across fields; 3. how each type of control group can serve a distinct purpose for specific study phases; 4. the disproportionate focus placed upon the effect of transfer compared to the effect of training; 5. the remarkable lack of neuroimaging studies with neurological samples. Ways to advance the field were proposed, placing emphasis on preregistering research protocols, conducting systematic reviews, collaboration across fields, and employment of interdisciplinary methods. The next stage involved the development of the protocol with NHS R&D and Research Ethics approval for a cognitive intervention combining the clinically evaluated, strategy-based goal management training with a computerised working memory updating process-based training; the aim was to explore the feasibility and

evaluation of this iPRESS training in adults with ABI (Chapter six). An initial feasibility pilot was conducted on the amended (online) iPRESS version designed to address the issues arising from the COVID-19 pandemic (Chapter seven). The pilot study exhibited promising results with participants engaging well with the online version of the study, able to adhere to the training protocol overall and providing positive feedback. Importantly, the iPRESS fMRI protocol was tested on a participant with ABI, with indications that the protocol may be tolerable and suitable for this population.

8.1 Research implications

Throughout this research several key issues occurred repeatedly that could be placed under two broad categories: 1. those relating to the training-induced plastic changes and 2. those relating to the development of cognitive interventions. Under the first category, key issues included the concepts of flexibility and plasticity as theorised by Lövdén et al. (2010), the timeline of learning, the involvement of fronto-parietal and subcortical regions in relation to WM training as well as the nature of the training-related neural changes. Under the second category, core issues included the assessment of training and transfer effects, the importance of selecting suitable primary outcome measures and employing an appropriate control group in relation to the research question and study phase as well as the benefit of employing complementary analyses and interdisciplinary methods. For this reason, this research work has important implications for the scientific field of training-induced plasticity and for developing cognitive interventions with a focus on WM.

8.1.1 Understanding training-induced plastic changes

The capacity of the brain to restore and compensate in response to brain injury, as well as the experience-induced plastic changes in brain and behaviour, are traditionally considered manifestations of plasticity. Lövdén et al. (2010) introduced the concept of flexibility, i.e., the neural system's capability to improve within the current state of functional supply. In this framework, flexibility is considered synonymous with functional capacity, intelligence, brain functioning and experience, to emphasise the neural system's inherent ability to adapt (within a pre-existing range of functional performance) according to

environmental changes and demands. In this framework, plasticity is then viewed as the capacity for changes in flexibility, i.e., the capacity for changes in the pre-existing range of functional performance. Lövdén et al. (2010) further proposed that a prolonged mismatch between the neural system's functional supply and environmental demands is a necessary condition for plastic changes to occur. Employing adaptive training protocols where task difficulty dynamically adjusts according to the individual's performance and therefore continuously challenges proficiency levels, leads to a prolonged mismatch between functional supply and environmental demands where further neural resources become available, i.e., flexibility, evidently resulting in plastic change, i.e., plasticity.

The complementary analyses on the original fMRI study by Flegal, Ragland and Ranganath (2019) with data collected at three time points, i.e., pre- early- and post- training, together with the systematic review, provide a broad overview of the distinct neural changes taking place following adaptive WMU training as well as the timing at which they occur as evidenced by the scanned criterion task. The very well controlled experimental study design Flegal, Ragland and Ranganath (2019), with both groups engaging in training and the sole difference being the level of task difficulty either adaptively changing to suit performance or staying at a fixed level throughout, provided the opportunity to attribute these training-induced changes to the element of adaptivity specifically. The secondary analysis on the training related changes in grey matter volume and functional connectivity, with a focus on striatal seed ROIs, together with our systematic review of the neuroimaging WM updating training studies provide support for the following hypotheses on the role of the striatum:

- Mediating the effects of WM training and facilitating plasticity (Constantinidis and Klingberg, 2016; Dahlin et al., 2008).

- Being more relevant during the first stages of training (Kühn et al., 2013).

- Acting as a filter allowing only relevant information into WM (McNab and Klingberg, 2008).

These ideas were examined in depth by employing different methodologies and aiming to provide a greater understanding of the neural

mechanisms taking place during WM process-based training. The key research findings were two from the systematic review and meta-analysis: 1. fronto-parietal regions exhibit activity decreases following WMU training; 2. striatal involvement was more often observed in protocols employing highly targeted memory updating tasks as in the case of Flegal, Ragland and Ranganath (2019) and reported a mixture of both increases and decreases; and two from the novel analyses of neuroimaging data: 3. no changes in grey matter volume were observed in striatal ROIs following adaptive WMU training; 4. functional connectivity decreases between striatal areas and the limbic regions were found at the beginning of training and were subsequently followed by decreases with lateral occipital areas whilst no connections with fronto-parietal regions were found. These neural effects were not associated with group differences in performance on scanned tasks.

Based upon these findings, together with previous research on functional connectivity studies reporting increases in frontoparietal networks, it is suggested that striatal and fronto-parietal regions respond differentially to WM process-based training. The fronto-parietal areas appear to be generally involved in the training process regardless of protocol and/or task-specific features whilst striatal areas on the other hand seem to be task- or possibly updating process-specific; that is, they seem to be preferentially involved in protocols employing highly targeted working memory updating tasks. Analysis of fMRI data showed that the neural system was successfully triggered by the adaptivity element of a process-based training protocol, and the neural basis of flexibility lies within areas of the striatum and their associated connections. Taking the timeline of training into consideration and assuming the striatum forms the neural basis of flexibility which precedes plasticity, it was additionally hypothesised that striatal areas are key during the early stages of training. Drawing from the literature of motor learning we could then relate the fast-early learning stage with the concept of flexibility and the subsequent slow-late learning stage with the concept of plasticity. The connectivity decreases between the left putamen and the regions of right cerebellum and parahippocampal gyrus suggested an interplay between them early in the training which then shifts to lateral occipital regions post-training. The cerebellum has close links with the PFC, it

engages in a range of cognitive functions including WM and is thought to serve as an information processing mechanism (Hogan, 2004).

The training related neural processes evident in the studies in this thesis can be summarised as follows. Systematically reviewing fMRI studies training working memory updating (Chapter two) revealed fronto-parietal involvement throughout the training period regardless of the updating task chosen and protocol-specific features, with activity decreases evident by the end of training. This is considered an indication of neural efficiency, i.e., fewer neural resources needed to perform the same task. The same analysis exhibited the involvement of striatal areas in training protocols employing highly targeted memory updating tasks specifically. Striatal areas are hypothesised to form the neural basis of the system's flexibility which can be successfully triggered by continuously adapting the level of task-difficulty and ultimately leading to plastic changes in the system's pre-existing abilities, i.e., mediating the effects of WM training and facilitating plasticity (Constantinidis and Klingberg, 2016). Building on Lövdén et al.'s (2010) framework viewing plasticity as a sluggish capacity, it is further suggested that flexibility precedes plasticity and therefore striatal involvement is more relevant early in the training, i.e., the fast-early stage of learning, consistent with the hypothesis put forward by Kühn et al. (2013). The task-based functional connectivity analysis (Chapter four) revealed reduced connections between striatal regions, primarily left putamen, and areas involved in information processing that have close links to the PFC, at the early stages of training which may be indicative of the striatum's role in filtering out irrelevant information to improve efficiency of WM.

Disentangling the role of the striatum throughout the training period has helped to provide a detailed snapshot of the mechanism, the timing, and task conditions under which training-induced flexibility leading to plasticity might occur; this has important implications for the field of cognitive training and to a greater extent for developing cognitive interventions.

8.1.2 Developing interdisciplinary cognitive interventions

Systematically reviewing the cognitive and neural changes taking place following WM updating training facilitated the development of the novel

integrated goal management strategy and computerised WMU process training and further highlighted the substantial lack of neuroimaging studies with neurological samples in the literature. This subsequently motivated the critical review in an effort to summarise the most pressing issues in the field of cognitive training with a focus on WM processes (Pappa et al., 2021). Staying true to the suggested recommendations described in this review, an interdisciplinary research protocol was developed for individuals with ABI, while collaborating closely with clinical teams across two NHS sites. The novel intervention was designed by employing the most appropriate methodologies from the fields of clinical neuropsychology and cognitive neuroscience to bridge the gap between the two disciplines; examples involve employing a randomised controlled trial (RCT) design in addition to neuroimaging methods. Outcome measures involved both criterion and transfer tasks to examine the size of the training and transfer effects as well as psychometric tasks targeting executive functions and a questionnaire relating to daily living. Additional outcome measures involved the behavioural and neural changes taking place following the iPRESS training thus providing a unique opportunity to investigate the same research questions as in the healthy adult brain. Is the training effect present and is there evidence of transfer? Does the pattern of neural changes match the one exhibited in healthy adults, and does it follow the same timeline? Do striatal and frontoparietal regions play a distinct functional role?

The Covid-19 pandemic notwithstanding, an online version of the iPRESS training protocol was evaluated on adults with ABI. Even though the most prominent novelty of this research study lies in the combination of two different approaches – the clinically evaluated strategy-based goal management training (Levine, Manly and Robertson, 2012) and the adaptive WMU process-based training paradigm (Flegal, Ragland and Ranganath, 2019) – as well as employing neuroimaging methods in adults with ABI, the iPRESS online pilot nevertheless provided an unplanned yet exciting opportunity, i.e., exploring the feasibility of an online intervention for cognitive remediation. The protocol needed to be delivered purely online and therefore substantial amendments were implemented whilst keeping focused on the collaborative, inter-disciplinary and novel nature of this research. Even though the iPRESS pilot was based on a small sample, the findings were promising in that it was feasible to combine these two

approaches, participants engaged with the online format, provided very positive feedback as well as remained in the study for the total duration.

As a result of government restrictions, the neuroimaging component of the pilot study was compromised but recent changes to regulations made it possible to test the fMRI protocol on an individual with ABI, a process which is ongoing. Suitability of the fMRI protocol focused on: task specific features such as difficulty level and presentation rate, task response and overall protocol duration. The participant was able to perform both lower and higher difficulty trial types for the three scanned tasks, i.e., MU, n-back and OL, as well as respond on time whilst keeping missing responses at a minimum. At the same time, she was able to remain in the scanner for the total duration without needing additional breaks unaccounted for by the protocol. Even though based on one participant, there were good indications that the fMRI protocol is tolerable and suitable for individuals with ABI who are able to engage with the working memory training protocol. Finally, the patterns of activations found in the pilot participant were also consistent with those reported in the previous study with healthy adults (Flegal, Ragland and Ranganath, 2019) even though task parameters were modified.

Despite diverging from the original plan, the online iPRESS pilot has important implications for developing cognitive interventions aimed at individuals with a neurological disorder. It provides an alternative possibility, one that can substantially reduce intervention costs e.g., lower staff resources, no travelling expenses, as well as rendering it more accessible to participants and consequently facilitating the sustainability of such an intense intervention long term.

8.2 Future direction

8.2.1 Research on healthy adults

Future research on healthy adults should additionally focus on the training-related neural changes evidenced by scanned transfer tasks. Even though the success of a training regime has more often been evaluated by measuring the existence and size of any transfer effect, rather than the size of

the training effect (Pappa et al., 2020;2021), neuroimaging studies have focused primarily on the neural changes taking place on the scanned criterion task. Researchers have further proposed that the striatum plays a key role in mediating the transfer of learning (Dahlin et al., 2008, 2009; Kühn et al., 2013; Salminen et al., 2016). What does transfer of learning mean in this context though and is it identical to transfer of training? Transfer of learning is tightly linked with the aspect of generality, i.e., an effective cognitive intervention should theoretically be associated with generalised improvements in everyday functioning, maintenance, and competence (Lövdén et al., 2010). Transfer of training on the other hand is viewed as a general assessment tool to measure changes relating to specific aspects of performance rather than assessing generality (Lövdén et al., 2010). This is easier to understand considering task improvements are associated with improvements on various task components, e.g., developing strategies, perceptual expertise etc. rather than with greater efficiency in this process (Lövdén et al., 2010). Despite further subdivision of transfer of training into near and far, i.e., transfer to an untrained task of the same cognitive domain and of a different cognitive domain, respectively, the concept of far transfer is distinct from transfer of learning as described in (Lövdén et al., 2010).

Therefore, improved performance on untrained transfer tasks is better described by the term transfer of training rather than transfer of learning and consequently it could be argued the striatum plays a key role in mediating near/far transfer of training rather than transfer of learning. However, even if the striatum does in fact mediate transfer of training; that implies an aspect of generality which is not supported by viewing transfer of training as a general tool measuring change associated with specific aspects of performance. Taking this into consideration, it is possible that what previous study authors have interpreted as the striatum mediating transfer, is indicative of the striatal areas forming the neural basis of the system's flexibility, i.e., striatum is a key hub representing the neural system's innate capacity to adapt to environmental change by recruiting more neural resources, i.e., mediating the effects of WM training and facilitating subsequent plasticity (Constantinidis and Klingberg, 2016). That is not to say that the striatum does not mediate transfer of learning,

but rather the question of the exact role of the striatum requires further investigation.

The transfer-related neural changes were investigated in the systematic review (chapter two), which found that increases in striatal areas and the inferior frontal gyrus were more often reported, although it should be noted very few studies investigated transfer-related neural changes. Striatal involvement was more often associated when highly targeted WM updating tasks were employed as was the case in two of the three studies mentioned earlier (Dahlin et al., 2008; Kühn et al., 2013). The study reported in Chapter four additionally investigated the training-related functional connectivity changes for the scanned criterion and transfer tasks after adaptive WM updating training with a focus on subcortical ROIs. The analysis exhibited differential patterns of subcortical ROI connections both in terms of the regions involved and the direction of changes over time. In the first case, ROI connections with frontal areas were not observed in the criterion task whilst reduced connections with the precentral gyrus for the transfer task were evident throughout the training period. In the second case, a mixture of connectivity strength increases and decreases were found for the transfer task in contrast to decreases for the criterion task. Functional connectivity analysis can offer valuable insight into the mechanism of learning and training-induced plasticity. It can be approached using many different methods with each analysis providing a unique opportunity to examine the same phenomenon from a different point of view, i.e., subcortical or fronto-parietal focus etc., and at distinct levels of the neural system, i.e., region or network. Moving forward, research on healthy adults should focus on:

- Comparing connectivity patterns between criterion and transfer tasks.
- Comparing connectivity patterns between subcortical and fronto-parietal ROIs.
- Describing the transfer of training by measuring improvement in specific task components.

Exploring these research questions will shed further light into the role of the striatum and associated functional connections in mediating transfer of training. Understanding the neural mechanism of transfer or rather how to best use transfer tasks to measure specific aspects of performance, the key areas involved and the task-specific conditions under which it occurs is critical for plasticity research as well as the development of cognitive interventions for adults with neurological injury. Furthermore, given the fact there were no training-related changes in grey matter volume, future research should employ diffusion MRI methods investigating the changes in structural connectivity and cortical myelination following working memory training.

8.2.2 Research on adults with ABI

As a result of delays and restrictions caused by the Covid-19 pandemic, the nature and size of the feasibility trial was different to the originally planned protocol. Nevertheless, the online group format provided promising preliminary results. In addition to completion of the full iPRESS feasibility pilot study, there are a few key issues to be addressed in the future. The first involves choosing the most suitable control group for each study phase and research question as described in the critical review, (Chapter five), (Pappa et al., 2021). The current WMU training study protocol is designed with the element of adaptivity as the only difference between the experimental and control groups. Another interesting comparison would be to train the experimental group on the combined GMT and adaptive WMU protocol in contrast to a control group training on GMT only. Such study design would capture the added benefit of WMU training. An alternative possibility would be for the experimental group training on the combined GMT and adaptive WMU protocol compared to a control group training on GMT combined with an adaptive training protocol of a different cognitive domain. This design would be ideal for isolating the effect of WM updating training specifically regardless of the element of adaptivity. In each case the training and transfer effects would be explored and evidenced by performance on the scanned tasks, psychometric tests, and everyday functioning questionnaire.

Along the same lines, each control group option would then serve a distinct purpose for investigating the differential neural processes taking place

when focusing on the added benefit of WMU training or the effect of WMU training more generally. The next step would be to investigate the training-related neural mechanism in adults with ABI using the same methods as the ones employed in the healthy adult studies. This would involve examining the location and direction of the functional activity and connectivity changes following training and attempt to answer research questions, e.g., does the ABI sample exhibit the same pattern of fronto-parietal reductions following training? Are striatal regions involved in highly targeted updating task protocols or rather involved more generally? What about the timeline of learning? Naturally, it would be equally interesting to examine the differential patterns of neural changes for the scanned criterion and transfer tasks and their relationship with performance. Once the training-related behavioural and neural changes in adults with ABI are better understood, additional factors potentially affecting responsiveness to training should be examined; a few examples include motivation, pre-training baseline performance, cognitive reserve.

We hope the present study's stepwise transition from research on healthy adults towards individuals with ABI will set a precedent for more studies adopting such approach. The aim is to develop cognitive interventions with a solid scientific background and rationale able to provide a clear enough picture of the cognitive and neural mechanisms taking place during training and are sustainable in the long term. The purpose is to embed and implement such empirically founded interventions within routine clinical practice aiding the recovery and cognitive rehabilitation of individuals with ABI and/or other neurological disorders and ultimately maximising gains in everyday functioning. We are optimistic for more collaborative, interdisciplinary and translational research projects evaluating cognitive interventions targeting patient populations in the future.

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Appendix 1

Table 1.1: PEDro-P Quality Assessment for reviewed studies.

Reference	*Q1*	*Q2*	*Q3*	*Q4*	*Q5*	*Q6*	*Q7*	*Q8*	*Q9*	*Q10*	*Q11*	*Total*	*Quality Rating*
						Healthy Adults							
Aguirre et al. (2019)	1	1	0	1	0	1	0	1	0	0	1	5	fair
Backman et al. (2011)	1	1	0	1	0	0	0	0	0	1	1	4	fair
Backman et al. (2017)	1	1	0	1	0	0	0	1	0	1	1	5	fair
Biel et al. (2020)	1	1	0	1	1	1	0	1	0	1	0	6	good
Buschkuehl et al. (2014)	1	0	0	1	0	1	0	0	0	1	1	4	fair
Clark, Lawlor-Savage and Goghari, (2017)	1	1	1	1	1	1	1	0	0	1	1	8	good
Colom et al.(2016a)	1	0	0	1	0	0	0	0	0	1	0	2	poor
Colom et al. (2016b)	1	0	0	1	0	0	0	0	0	1	0	2	poor
Dahlin et al. (2008)	1	1	0	1	0	0	0	1	0	1	1	4	fair
Emch et al. (2019b)	1	0	0	1	1	0	0	1	0	1	1	5	fair
Finc et al. (2020)	1	1	0	1	1	0	1	1	0	1	1	7	good
Flegal, Ragland and Ranganath (2019)	1	1	1	1	1	1	0	0	0	1	1	7	good
Heinzel et al. (2014)	1	0	0	0	0	0	0	1	1	0	1	3	poor
Heinzel et al. (2016)	1	0	0	1	0	0	0	1	0	1	1	4	fair
Heinzel et al. (2017)	1	0	0	0	0	0	0	1	1	0	1	3	poor
Hempel et al. (2004)	1	0	0	0	0	0	0	0	0	0	1	1	poor
Kuhn et al. (2013)	1	1	0	1	1	1	0	0	0	1	0	5	fair
Lawlor-Savage, Clark and Goghari, 2019 (2019)	1	1	1	1	1	1	1	0	0	1	1	8	good
Miro-Padilla et al. (2020,2018) †	1	1	0	1	0	0	0	0	0	1	1	4	fair

Opitz et al. (2014)	1	0	0	1	0	0	0	0	0	1	1	3	poor
Roman et al. (2016)	1	0	0	1	0	0	0	0	0	1	1	3	poor
Roman et al.(2017)	1	0	0	1	0	0	0	0	0	1	1	3	poor
Salminen et al.(2016)	1	0	0	1	0	0	0	1	0	1	1	4	fair
Schneiders et al. (2011)	1	0	0	1	0	0	0	0	0	1	1	3	poor
Schneiders et al. (2012)	1	0	0	1	0	0	0	0	0	1	1	3	poor
Schweizer et al. (2013)	1	1	0	0	0	1	0	1	0	1	1	5	fair
Thompson, Waskom and Gabrieli (2016) (2016)	1	1	1	1	0	0	0	0	0	1	1	5	fair
Neurological Populations													
Aguirre et al. (2019)	1	1	0	1	0	1	0	1	0	0	1	5	fair
Bonzano et al. (2020)	1	0	0	0	0	0	0	1	0	0	1	2	poor
Leung et al. (2014)	0	0	0	0	0	0	0	1	1	0	0	2	poor
Leung et al. (2016)	1	0	0	0	0	0	0	1	1	0	0	2	poor

Quality Rating: Good: score ≥ 6, Fair: score of 4-5 and Poor: score ≤ 3, **Healthy Adults: Mean:** 4.29, **Median:** 4, **SD:** 1.74, **Neurological Populations: Mean:** 2.75, **Median:** 2, **SD:** 1.50, **Q1** did not count towards the total score. †These studies share the same dataset; **Q1. Eligibility** criteria were specified, **Q2.** Subjects were randomly allocated to interventions (in a crossover study, subjects were randomly allocated an order in which treatments were received), **Q3.** Allocation was concealed, **Q4**. the intervention groups were similar at baseline regarding the most important prognostic indicators, **Q5**. There was blinding of all subjects, **Q6. There** was blinding of all therapists who administered the therapy, **Q7.** There was blinding of all assessors who measured at least one key outcome, **Q8.** Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups, **Q9.** All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat", **Q10.** The results of between-intervention group statistical comparisons are

reported for at least one key outcome, **Q11.** The study provides both point measures and measures of variability for at least one key outcome.

Table 1.2 MRI Functional Connectivity Changes after WMU training in Healthy Adult Studies.

Reference	*Functional Connectivity Changes*	
	Training	***Transfer***
Finc et al. (2020)	*Session by Group comparisons* *Whole-Brain Modularity increases, ns* ($x^2(1)$ = 1.50, p = 0.68). TG showed a higher network modularity (M=3.09) compared to the CG(M=2.87). *Dynamic reorganization of large-scale systems* *Recruitment* - *Frontoparietal System:* ($x^2(3)$ = 9.03, p = 0.028. ↑**Increase in recruitment** for the TG compared to the CG post training. The largest increase was reported for the TG between pre and post-training t(120)= −2.892, p=0.027, Bonferroni-corrected). No significant changes for the CG, t(120)=−1.169, p=1. - *Default mode system,* ns, ($x^2(3)$ =2.66, p =0.48). ↑**Increased** recruitment higher for TG compared to CG, t(165.6)=−3.03, p=0.003). *Integration of systems* - *Frontoparietal with default mode systems*, ($x^2(3)$ =14.25, p=0.0025). ↓***Decrease*** post-training *only found for the TG compared to the CG (*t(120)= 4.37, p=0.0002,). - *Subcortical* with dorsal attention, ventral attention, cingulo-opercular and auditory	-

	systems: ↑**Increase** at early training stages and a ↓**decrease** later on. - *Subcortical with default-mode systems:* initial ↓**decrease** at early training stages and an ↑**increase** at later stages	
Heinzel et al. (2014)	*session by Load comparison* No differences in connectivity changes in the WM network.	-
Thompson, Waskom and Gabrieli (2016)	*Session by Group comparison* ↑**Increased functional connectivity for the TG** was observed for all 4 pairings of prefrontal and parietal ROIs in the 2-back condition ($p < 0.05$, Bonferroni). No changes for 1- or 3-back.	-

Table 1.3: MRI Structural Changes after WMU training in Healthy Adult Studies.

Reference	*Structural Changes*	*Structural Connectivity Changes*
Biel et al. (2020)	*Group by time comparisons, ns* (FWE, p<0.05 whole-brain). No changes in GM volume, myelination and iron levels.	-
*Colom et al. (2014a)***	Voxel-based independent samples t-tests, TG Vs CG post-training. Significant change post-training in L/R temporal lobe. ↓**Decreased volume** in the CG **- Volume preservation** in the TG.	-
Colom et al. (2014b) ***	*Group by Time comparisons* ↑ ***Increased regional grey matter volume*** *for the TG post-training in:* i. L posterior cingulate cortex ii. R cerebellum iii. R temporal lobe	-
Heinzel et al. (2014)	No significant changes in the WM network GM volume after training (t(14)=0.83, p=0.421).	-
Lawlor-Savage, Clark and Goghari, (2019)	*Group By time comparisons, alpha <.001* **No significant effects** for cortical surface area, thickness or volume changes in any of the frontal, parietal lobe regions of interest, in cingulate or insular cortical regions or volume estimates within subcortical regions of interest.	-

	No significant effects for total subcortical GM volumes or total GM volumes.	
*Roman et al. (2016b)***	Mean cortical thickness (CT) and cortical surface area (CSA) were computed at each ROI for the TG and CG before and after training. The standardised change was computed. **ANCOVA, CT differences between TG and CG in:** i. R Ventral frontal cortex ii. R Middle temporal cortex **Minor thickening** for TG. **Minor thinning** for CG. **ANCOVA, CSA differences between TG and CG in:** i. R pas opercularis ii. R posterolateral temporal cortex **Expanding effect** for the TG. **Contracting effect** for the CG.	-
*Roman et al. (2016a)****	Changes more pronounced in the TG compared to the CG in the Sub-Network containing temporal, frontal, parietal, subcortical regions and the insula. **Connectome Topological Properties** Time by Group comparison for the sub-network ↑ **Increase** in **Global efficiency** (**Eg)** for the TG. ↑ **Increase** in **Strength (S)** for the TG. **No change in CG for either Eg or S.**	Network-Based Statistics to identify connectional sub-networks modulated by cognitive training. Changes more pronounced in the TG compared to the CG in the Sub-Network containing temporal, frontal, parietal, subcortical regions and the insula. Most highly connected node in this network was located in the **L middle temporal region** and was highly interconnected with: i. L/R basal forebrain ii. L parahippocampal area iii. L pallidum iv. L supramraginal v. L inferior parietal area vi. R insula

		vii. R accumbens viii. R post central gyrus ix. R pars opercularis ↑ **Increase in Connectivity** for the TG in this network. No changes for CG.

*** These studies shared the same Bx dataset, **Bx:** behavioural, **FWE:** Family-Wise Error, **GM:** Grey Matter.

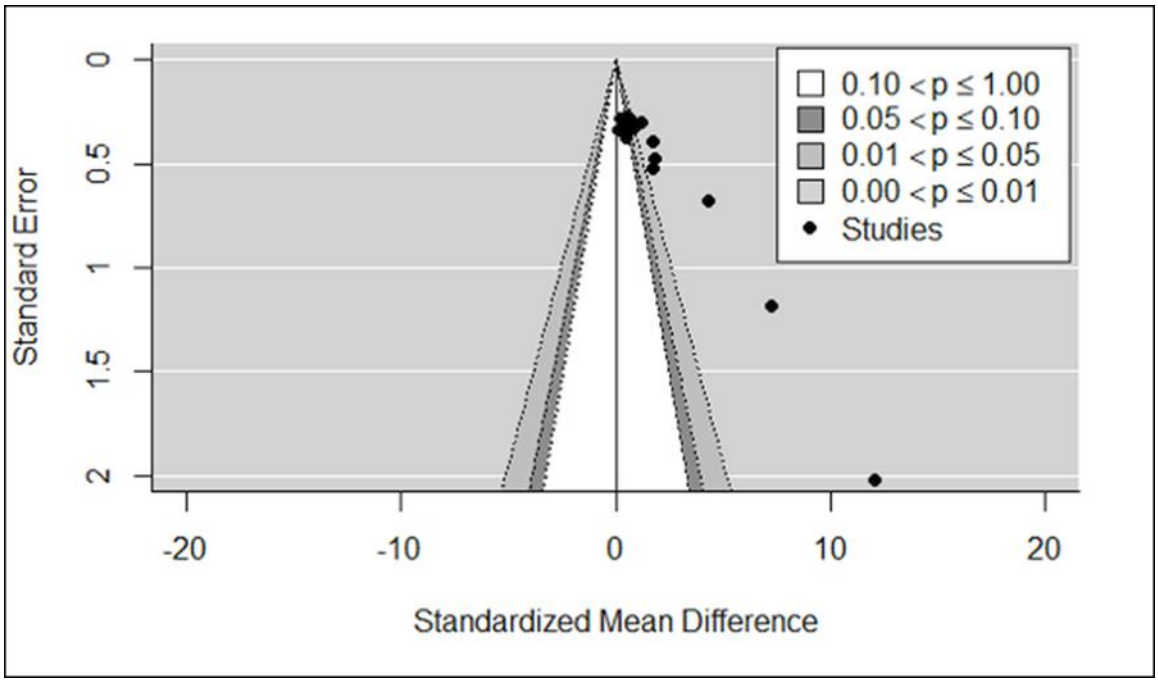

Figure 1.1: Contour-enhanced funnel plot for the overall training effect. The funnel is centered at 0 where the studies concentrating around the midline have no significant effects. The data points falling outside and to the bottom right of the funnel tend to have smaller sample sizes and large variance, in addition to significant and large effect sizes, and thus are more likely to bias the overall effect. The Egger's regression test for funnel plot asymmetry yielded significant results ($z = 9.36$, $p < .0001$) further corroborating the assumption for publication bias.

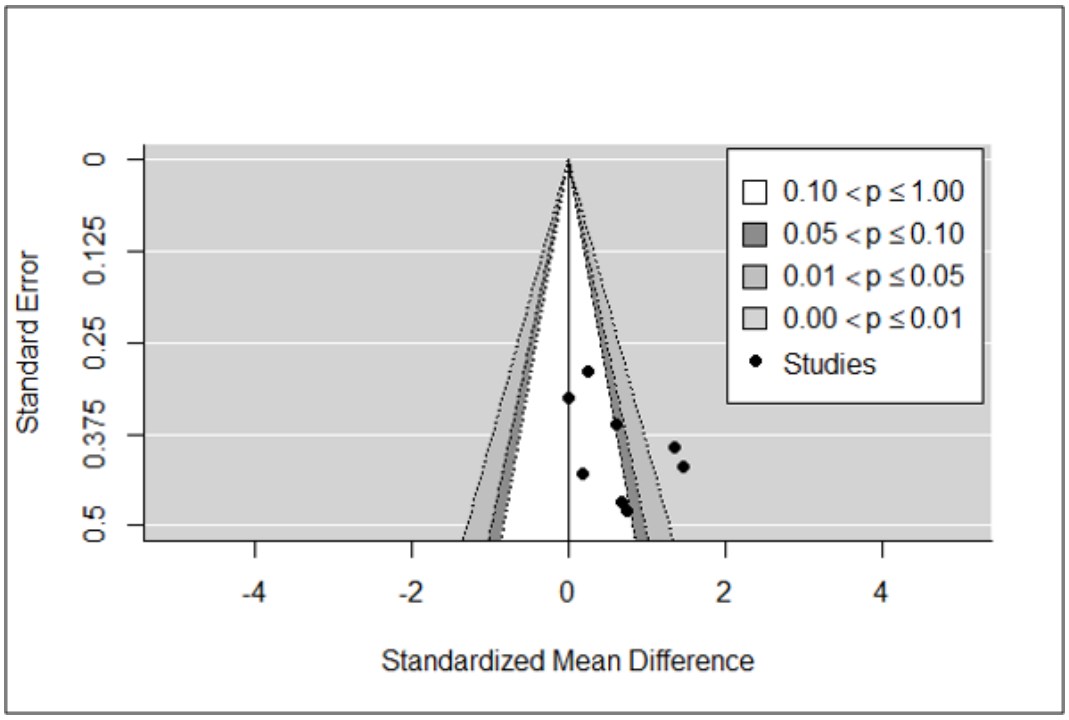

Figure 1.2: Contour-enhanced funnel plot for the near transfer effect. The dispersion of data points in the funnel indicate asymmetry, although the Egger's regression test proved non-significant in this case (z = 1.30, p = 0.19). Only two studies exhibit significant near transfer effects, suggesting that publication bias is unlikely the cause for such asymmetry.

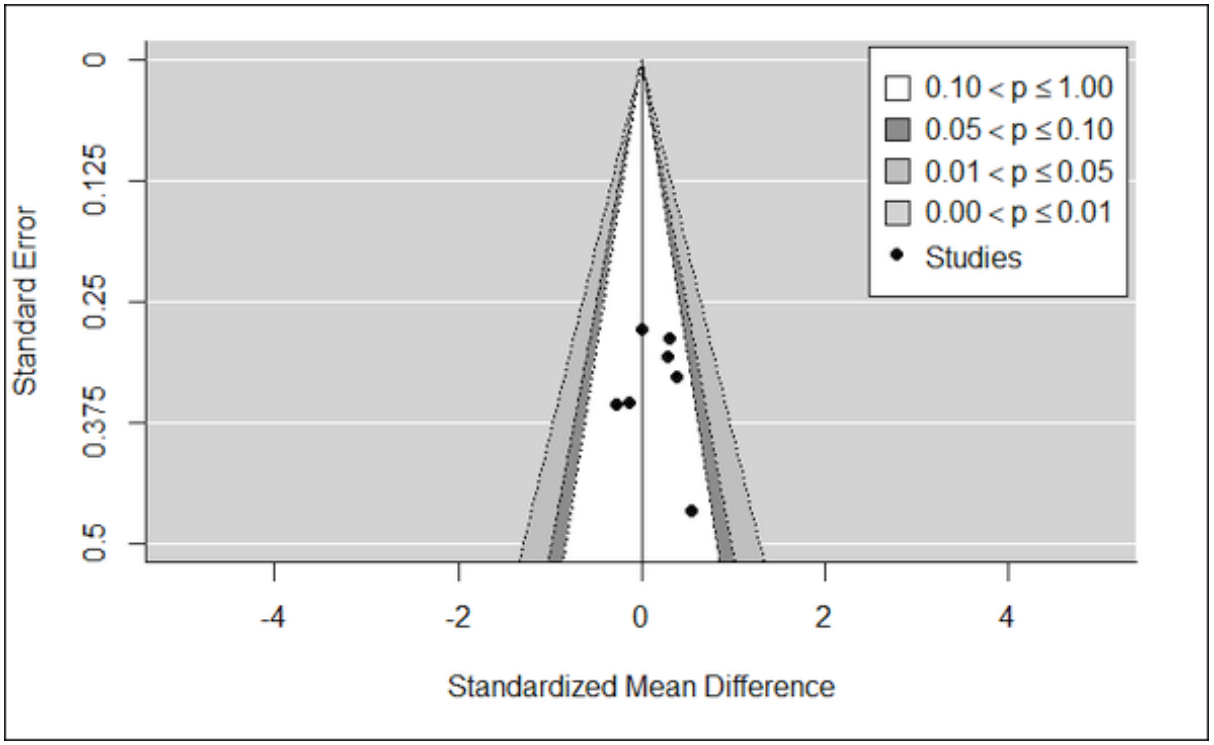

Figure 1.3: Contour-enhanced funnel plot for the far transfer effect. The data points do not indicate asymmetry, however the small number of studies testing for far transfer makes it difficult to draw conclusions. None of the studies exhibited significant effect sizes and the Egger's regression test yielded non-significant results (z = 0.26, p = 0.79).

Appendix 2

Table 2.1: RRC, group by time interaction tests across seeds for both MU and n-back tasks, significant F tests.

Connection	*F test*	*p unc.* *P FDR*
Baseline (0 updates)		
L-R Caudate	F(6,66) =62.23	*<.001* *<.001*
R-L Hippocampus	F(6,66) =55.63	*<.001* *<.001*
L-R Putamen	F(6,66) =49.95	*<.001* *<.001*
L Putamen – L, R Caudate R Putamen, L, R Caudate	F(12,60) =16.68	*<.001* *<.001*
L Putamen – L, R Hippocampus R Putamen, L, R Hippocampus	F(12,60) =3.73	*.003* *.004*
L Caudate– L, R Hippocampus R Caudate- L,R Hippocampus	F(12,60) =1.95	*.046* *.046*
4 updates		
R-L Putamen	F(6,66) =54.40	*<.001* *<.001*
L-R Hippocampus	F(6,66) =48.92	*<.001* *<.001*
R-L Caudate	F(6,66) =48.32	*<.001* *<.001*
L Caudate – L,R Putamen R Caudate, L,R Putamen	F(6,66) =18.79	*<.001* *<.001*
L Putamen – L,R Hippocampus R Putamen, L,R Hippocampus	F(12,60) =2.88*	*.003* *.004*
L Caudate– L,R Hippocampus R Caudate- L Hippocampus	F(12,60) =1.99*	*.041* *.041*
7 updates		
L-R Caudate	F(6,66) =63.59	*<.001* *<.001*
L-R Putamen	F(6,66) =55.39	*<.001* *<.001*
R-L Hippocampus	F(6,66) =51.37	*<.001* *<.001*
L Caudate – L,R Putamen R Caudate, L,R Putamen	F(12,60) =23.5*	*<.001* *<.001*
L Putamen – L,R Hippocampus R Putamen, L,R Hippocampus	F(12,60) =5.83	*<.001* *<.001*

L Caudate– L,R Hippocampus L Caudate- L Hippocampus	F(12,60) =3.66	*<.001* *<.001*
0-back		
L-R Caudate	F(6,66) =76.11	*<.001* *<.001*
L-R Putamen	F(6,66) =65.16	*<.001* *<.001*
L-R Hippocampus	F(6,66) =54.54	*<.001* *<.001*
L Putamen – L,R Caudate R Putamen, L,R Caudate	F(12,60) =11.33	*<.001* *<.001*
L Putamen – L,R Hippocampus R Putamen, L,R Hippocampus	F(12,60) =2.12	*.030* *.034*
2-back		
R-L Putamen	F(6,66) =74.24	*<.001* *<.001*
R-L Caudate	F(6,66) =58.65	*<.001* *<.001*
L-R Hippocampus	F(6,66) =44.76	*<.001* *<.001*
R Caudate – R,L Putamen L Caudate – R, L Putamen	F(12,60) =9.01	*<.001* *<.001*
L Putamen – L,R Hippocampus R Putamen, L,R Hippocampus	F(12,60) =4.72	*<.001* *<.001*
3-back		
R-L Putamen	F(6,66) =67.83	*<.001* *<.001*
R-L Caudate	F(6,66) =55.48	*<.001* *<.001*
L-R Hippocampus	F(6,66) =48.76	*<.001* *<.001*
R Caudate – R,L Putamen L Caudate – R, L Putamen	F(12,60) =15.46	*<.001* *<.001*
L Putamen – L,R Hippocampus R Putamen, L,R Hippocampus	F(12,60) =8.02	*<.001* *<.001*

RRC= ROI-to-ROI connectivity, R= Right, L= Left, unc.= uncorrected, FDR = false discovery rate

Table 2.2: SBC, group by time interaction tests across seeds for both MU and n-back tasks, significant F tests.

Seed ROI	*F statistic*	*Cluster size (MNI coordinates)*	*p unc.*	*p. FDR*
Matrix updating				
Baselines (0 updates)				
Right Caudate	F(6,105) > 4.09, k≥74	k = 65779, (+12 +10 +10)	<.001	<.001
		k = 3602, (-8 -82 -30)	<.001	<.001
		k =2540, (-56 -52 +36)	<.001	<.001
		k = 1777, (-56 -32 -12)	<.001	<.001
		k = 101, (-42 -10-42)	.001	.017
		k = 76, (-30 -22 -30)	.004	.041
		k = 74, (+24 -40 +46)	.005	.041
Left Caudate	F(6,105) > 4.09, k≥72	k = 80611, (-12 +14 +6)	<.001	<.001
		k = 3338, (+60 -22 -18)	<.001	<.001
		k = 1145, (-6 -38 +40)	<.001	<.001

		k = 1039, (0 -62 +4)	*<.001*	*<.000*
		k = 94, (0 -46 -44)	*.002*	*.022*
		k = 87, (0 -10 -26)	*.003*	*.025*
		k = 78, (+22 -68 +48)	*.004*	*.032*
		k = 72, (+28 -40 +48)	*.005*	*.037*
Right Putamen	F(6,105) > 4.09, k≥110	k = 120264, (+24 +10 -2)	*<.001*	*<.001*
		k = 135, (0 -22 -50)	*<.001*	*.007*
Left Putamen	F(6,105) > 4.09, k≥99	k = 79303, (-24 +2 -2)	*<.001*	*<.001*
		k = 139, (-24 -8 +30)	*<.001*	*.006*
		k = 101, (0 -50 -42)	*.001*	*.016*
		k = 99, (-6 +44 +48)	*.002*	*.016*
Right Hippocampus	F(6,105) > 4.09, k≥323	k = 103798, (+28 -20 -18)	*<.001*	*<.001*
		k = 323, (-36 -50 +34)	*<.001*	*<.001*
Left Hippocampus	F(6,105) > 4.09, k≥58	k = 108774, (-24 -20 -18)	*<.001*	*<.001*
		k = 141, (6 -68 +42)	*<.001*	*.003*

		k = 135, (+46 -44 +42)	*<.001*	*.003*
		k = 94, (+34 -82 -38)	*.002*	*.013*
		k = 62, (-26 -52 +34)	*.009*	*.047*
		k = 58, (+40 -70 -48)	*.011*	*.048*
4 updates				
Right Caudate	F(6,105) > 4.09, k≥156	k = 92377, (+12 +16 +4)	*<.001*	*<.001*
		k = 195, (+6 -58 -40)	*<.001*	*.001*
		k = 156, (-6 -8 -26)	*<.001*	*.002*
Left Caudate	F(6,105) > 4.09, k≥475	k = 93789, (-12 +10 +10)	*<.001*	*<.001*
		k = 475, (0 -56 -38)	*<.001*	*<.001*
Right Putamen	F(6,105) > 4.09, k≥91	k = 94402, (+24 +8 0)	*<.001*	*<.001*
		k = 116, (+6 -26 +24)	*.001*	*.016*
		k = 110, (-32 -46 -2)	*.001*	*.016*
		k = 91, (+42 -4 -42)	*.003*	*.027*

Left Putamen	F(6,105) > 4.09, k≥65	k = 96742, (-24 +4 -2)	*<.001*	*<.001*
		k = 105, (-18 -10 +30)	*.002*	*.030*
		k = 86, (+18 -74 +36)	*.004*	*.036*
		k = 78, (-32 -86 -42)	*.005*	*.036*
		k = 76, (-2 -26 +22)	*.006*	*.036*
		k = 75, (+48 -58 -38)	*.006*	*.036*
		k = 65, (-30 -46 0)	*.010*	*.049*
Right Hippocampus	F(6,105) > 4.09, k≥124	k = 111864, (+28 -16 -20)	*<.001*	*<.001*
		k = 287, (+28 +4 +58)	*<.001*	*<.001*
		k = 162, (-44 +28 +30)	*<.001*	*.001*
		k = 124, (+34 -76 -38)	*.001*	*.004*
Left Hippocampus	F(6,105) > 4.09, k≥124	k = 113407, (-24 -20-18)	*<.001*	*<.001*
		k = 534, (+30 -80 -38)	*<.001*	*<.001*
		k = 359, (+30 +4 +58)	*<.001*	*<.001*
		k = 165, (-36 -40 +30)	*<.001*	*<.001*

		k = 157, (+48 +38 +34)	<.001	<.001
		k = 142, (-26 +2 +58)	<.001	<.001
		k = 130, (-30 -80 -38)	<.001	.002
		k = 124, (-44 +28 +30)	.001	.002
7 updates				
Right Caudate	F(6,105) > 4.09, k≥83	k = 97909, (+12 +14 +6)	<.001	<.001
		k = 150, (-30 -50 +4)	<.001	.007
		k = 103, (-14 -50 +76)	.002	.020
		k = 103 (+4 -88 +6)	.002	.020
		k = 83 (+6 -10 -24)	.004	.037
Left Caudate	F(6,105) > 4.09, k≥76	k = 104796, (-12 +10 +10)	<.001	<.001
		k = 159, (-30 -50 0)	<.001	.004
		k = 132, (-2 -44 -30)	.001	.008
		k = 113, (-26 -50 +72)	.001	.012

		k = 76, (+4 -10 -26)	*.006*	*.047*
Right Putamen	F(6,105) > 4.09, k≥135	k = 120264, (+24 +10 -2)	<*.001*	<*.001*
		k = 135, (0 -22 -50)	<*.001*	*.007*
Left Putamen	F(6,105) > 4.09, k≥181	k = 115706, (-20 +8 -2)	<*.001*	<*.001*
		k = 212, (+10 -28 -50)	<*.001*	*.001*
		k = 181, (-30 -16 +24)	<*.001*	*.001*
Right Hippocampus	F(6,105) > 4.09, k≥63	k = 121126, (+28 -22 -14)	<*.001*	<*.001*
		k = 668, (-36 -50 +40)	<*.001*	<*.001*
		k = 282, (-48 +26 +34)	<*.001*	<*.001*
		k = 272, (+28 -82 -38)	<*.001*	<*.001*
		k = 202, (+12 -62 +42)	<*.001*	<*.001*
		k = 180, (+40 +28 +24	<*.001*	*.001*
		k = 171, (-8 -74 +46)	<*.001*	*.001*
		k = 134, (-18 -28 -42)	<*.001*	*.002*

		k = 128, (-30 -80 -38)	*.001*	*.002*
		k = 102, (-36 +50 +18)	*.002*	*.006*
		k = 67, (-30 +8 +64)	*.007*	*.027*
		k = 63, (-8 -64 +66)	*.009*	*.030*
Left Hippocampus	F(6,105) > 4.09, k≥72	k = 120795, (-26 -22 -14)	<*.001*	<*.001*
		k = 1240, (+6 -64 +48)	<*.001*	<*.001*
		k = 523, (+30 -80 -38)	<*.001*	<*.001*
		k = 522, (+42 -40 +36)	<*.001*	<*.001*
		k = 377, (-36 -50 +40)	<*.001*	<*.001*
		k = 308, (+30 +8 +60)	<*.001*	<*.001*
		k = 174, (-30 -80 -38)	<*.001*	<*.001*
		k = 121, (0 -44 -44)	*.001*	*.003*
		k = 90, (+38 -66 +58)	*.003*	*.009*
		k = 72, (-30 +4 +66)	*.006*	*.019*
N -Back				

		0 back		
Right Caudate	F(6,108) > 4.08, k≥61	k = 38247, (+12 +14 +6)	*<.001*	*<.001*
		k = 13605, (+22 -44 +66)	*<.001*	*<.001*
		k = 2027, (+58 -52 +42)	*<.001*	*<.001*
		k = 1299, (+60 -28 +22)	*<.001*	*<.001*
		k = 1059, (-8 -86 -30)	*<.001*	*<.001*
		k = 678, (+60 -20 -14)	*<.001*	*<.001*
		k = 321, (-24 -58 -20)	*<.001*	*<.001*
		k = 299, (+30 -16 -12)	*<.001*	*<.001*
		k = 266, (+42 -32 -26)	*<.001*	*<.001*
		k = 215, (+54 -10 -38)	*<.001*	*<.001*
		k = 209, (-30 -22 -8)	*<.001*	*<.001*
		k = 152, (-60 -60 +34)	*<.001*	*.002*
		k =112, (+6 -8 -26)	*.002*	*.008*
		k = 86, (-2 -4 +46)	*.005*	*.020*

		k = 64, (+36 -14 +4)	*.013*	*.047*
		k = 63, (0 -58 -38)	*.013*	*.047*
		k = 61, (+10 -2 +36)	*.014*	*.048*
Left Caudate	F(6,108) > 4.08, k≥69	k = 41195, (-12 +10 +6)	<*.001*	<*.001*
		k = 17064, (+24 -44 +66)	<*.001*	<*.001*
		k = 2217, (-50 -62 +46)	<*.001*	<*.001*
		k = 1585, (+12 -82 -32)	<*.001*	<*.001*
		k = 835, (+42 +16 +40)	<*.001*	<*.001*
		k = 692, (+56 -62 +40)	<*.001*	<*.001*
		k = 400, (+52 -10 -36)	<*.001*	<*.001*
		k = 264, (-66 -28 +16)	<*.001*	<*.001*
		k = 256, (-24 -58 -20)	<*.001*	<*.001*
		k = 186, (+30 -16 -12)	<*.001*	*.001*
		k = 156, (+12 -26 -36)	<*.001*	*.002*
		k = 155, (+46 +2 +6)	<*.001*	*.002*
		k = 136, (0 -8 -26)	*.001*	*.004*

		k = 115, (-20 -86 -36)	*.002*	*.008*
		k = 109, (+64 -28 -6)	*.002*	*.009*
		k = 91, (-14 -52 +28)	*.004*	*.017*
		k = 83, (+22 -22 +52)	*.006*	*.022*
		k = 69, (+4 -56 -38)	*.011*	*.038*
Right Putamen	F(6,108) > 4.08, k≥75	k = 35475, (+28 +2 -2)	<*.001*	<*.001*
		k = 1703, (-6 -68 +42)	<*.001*	<*.001*
		k = 1327, (-30 -70 +42)	<*.001*	<*.001*
		k = 498, (+40 -68 +40)	<*.001*	<*.001*
		k = 242, (-26 +10 +46)	<*.001*	<*.001*
		k = 190, (+4 -28 +10)	<*.001*	*.001*
		k = 163, (-56 -50 -18)	<*.001*	*.002*
		k =152, (+34 +44 +24)	<*.001*	*.002*
		k = 150, (+24 +14 +42)	<*.001*	*.002*
		k = 75, (-32 +40 +28)	*.007*	*.034*

Left Putamen	F(6,108) > 4.08, k≥70	k = 34265, (-24 +8 0)	<.001	<.001
		k = 2997, (+4 -74 +52)	<.001	<.001
		k = 1464, (-6 +44 +52)	<.001	<.001
		k = 763, (+28 +14 +46)	<.001	<.001
		k = 554, (-18 -64 +28)	<.001	<.001
		k = 334, (+54 -40 -12)	<.001	<.001
		k = 214, (-44 +4 -32)	<.001	<.001
		k = 133, (+18 -50 -20)	.001	.005
		k = 88, (-18 -56 -48)	.004	.023
		k = 70, (+52 +22 +36)	.009	.045
Right Hippocampus	F(6,108) > 4.08, k≥55	k = 68108, (+28 -20 -18)	<.001	<.001
		k = 1750, (-36 -50 +40)	<.001	<.001
		k = 1747, (+46 -44 +36)	<.001	<.001
		k = 1685, (+34 +32 +24)	<.001	<.001
		k = 1411, (-36 +50 +18)	<.001	<.001

		k = 885, (-36 -62 -36)	<.001	<.001
		k = 699, (0 +20 +46)	<.001	<.001
		k = 689, (-38 +32 +30)	<.001	<.001
		k = 608, (+6 -64 +58)	<.001	<.001
		k = 594, (+34 +8 +54)	<.001	<.001
		k = 552, (+24 +58 -14)	<.001	<.001
		k = 504, (+40 -58 -36)	<.001	<.001
		k = 294, (-30 +4 +60)	<.001	<.001
		k = 264, (-50 +14 +4)	<.001	<.001
		k = 192, (+48 +14 +4)	<.001	<.001
		k = 61, (+46 +10 +36)	.015	.035
		k = 59, (-20 -88 +34)	.016	.036
		k = 55, (-44 +4 +36)	.020	.041
Left Hippocampus	F(6,108) > 4.08, k≥11	k = 66904, (-26 -22 -18)	<.001	<.001
		k = 7222, (+34 +32 +24)	<.001	<.001
		k = 3232, (+40 -44 +36)	<.001	<.001

		k = 1839, (-38 -46 +36)	<.001	<.001
		k = 1372, (-36 -62 -36)	<.001	<.001
		k = 942, (-36 +52 +22)	<.001	<.001
		k = 552, (-42 +32 +28)	<.001	<.001
		k = 283, (+40 -56 -36)	<.001	<.001
		k = 277, (-30 +4 +60)	<.001	<.001
		k = 244, (-48 +26 0)	<.001	<.001
		k = 233, (-8 -70 +46)	<.001	<.001
		k = 119, (-30 +22 0)	.001	.004
		2 back		
Right Caudate	F(6,108) > 4.08, k≥63	k = 37861, (+12 +14 +6)	<.001	<.001
		k =14578, (-2 -86 +34)	<.001	<.001
		k =5441, (+54 -50 +46)	<.001	<.001
		k =2657, (-50 -58 +46)	<.001	<.001
		k =954, (-68 -34 -12)	<.001	<.001

		k =934, (-12 -82 -32)	<.001	<.001
		k =360, (+12 -44 +34)	<.001	<.001
		k =227, (+12 -80 -32)	<.001	<.001
		k =177, (+30 -14 -12)	<.001	.001
		k =159, (-30 -14 -14)	<.001	.001
		k =138, (-50-34 +24)	<.001	.002
		k =132, (+34 -68 -36)	.001	.002
		k =109, (+6 -44 -32)	.001	.005
		k =78, (+66 -26 +12)	.005	.019
		k =75, (+40 -8 -2)	.006	.020
		k =64, (+64 -16 +4)	.009	.032
		k =63, (-36 +2 +12)	.010	.032
Left Caudate	F(6,108) > 4.08, k≥61	k = 40717, (-12 4 12)	<.001	<.001
		k = 13523, (-2 -86 36)	<.001	<.001
		k = 4899, (22 -50 58)	<.001	<.001
		k = 3886, (-50 -58 +42)	<.001	<.001

	k = 3066, (58 -52 +46)	<.001	<.001
	k = 2021, (-66 -34 -14)	<.001	<.001
	k = 1263, (60 -34 -12)	<.001	<.001
	k = 927, (30 -68 -36)	<.001	<.001
	k = 190, (60 -2 -8)	<.001	<.001
	k = 184, (-38 -14 +34)	<.001	.001
	k = 163, (+6 -44 -32)	<.001	.001
	k = 158, (+40 -8 -2)	<.001	.001
	k = 154, (-42 -10 +16)	<.001	.001
	k = 151, (16 -46 +34)	<.001	.001
	k = 150, (+54 -14 +46)	<.001	.001
	k = 127, (-12 -82 -32)	.001	.003
	k = 126, (34 -14 -14)	.001	.003
	k = 119, (+52 -26 +24)	.001	.003
	k = 102, (-30 -68 -36)	.002	.006
	k = 98, (-2 -62 +40)	.002	.007

		k = 64, (28 -34 -26)	*.009*	*.031*
		k = 62, (-66 -26 +6)	*.010*	*.033*
		k = 61, (-50 -10 -36)	*.010*	*.033*
Right Putamen	F(6,108) > 4.08, k≥58	k = 42342, (+24 +4 -2)	<*.001*	<*.001*
		k = 1383, (-26 -44 -30)	<*.001*	<*.001*
		k = 587, (-30 -62 34)	<*.001*	<*.001*
		k = 585, (0 -58 +36)	<*.001*	<*.001*
		k = 582, (-44 +20 +34)	<*.001*	<*.001*
		k = 495, (+52 -62 +4)	<*.001*	<*.001*
		k = 396, (+6 +56 -6)	<*.001*	<*.001*
		k = 365, (-30 +10 +52)	<*.001*	<*.001*
		k = 305, (0 +28 +46)	<*.001*	<*.001*
		k = 183, (+12 -82 -36)	<*.001*	*.001*
		k = 130, (+30 +44 +24)	*.001*	*.003*
		k = 116, (+40 -80 -14)	*.001*	*.005*
		k = 107, (+28 +34 -14)	*.001*	*.007*

		k = 102, (-56 -40 -14)	*.002*	*.008*
		k = 90, (+36 -68 +40)	*.003*	*.012*
		k = 83, (+26 +62 -20)	*.004*	*.015*
		k = 81, (+30 +4 -32)	*.004*	*.016*
		k = 76, (+52 +32 -2)	*.005*	*.019*
		k = 58, (+28 -34 -24)	*.013*	*.042*
Left Putamen	F(6,108) > 4.08, k≥80	k = 42391, (-24 +2 +4)	<*.001*	<*.001*
		k = 996, (+30 +14 +46)	<*.001*	<*.001*
		k = 528, (0 -68 +48)	<*.001*	<*.001*
		k = 378, (+4 +28 +46)	<*.001*	<*.001*
		k= 316, (-26 +34 -14)	<*.001*	<*.001*
		k = 311, (-50 +26 +36)	<*.001*	<*.001*
		k = 252, (+12 -62 -20)	<*.001*	<*.001*
		k = 227, (+26 +62 -20)	<*.001*	<*.001*
		k = 220, (+40 -70 +36)	<*.001*	<*.001*
		k = 207, (-30 +8 +48)	<*.001*	<*.001*

		k = 191, (-32 -70 +40)	<.001	<.001
		k = 181, (-36 -64 -42)	<.001	.001
		k = 149, (+48 -62 -2)	<.001	.001
		k = 80, (-36 +2 -38)	.004	.022
Right Hippocampus	F(6,108) > 4.08, k≥49	k = 95371, (+28 -20 -18)	<.001	<.001
		k = 3390, (-44 +26 +30)	<.001	<.001
		k = 2320, (+42 -44 +40)	<.001	<.001
		k = 2117, (-36 +50 -2)	<.001	<.001
		k = 2106, (-38 -50 +40)	<.001	<.001
		k = 1441, (-26 -64 -36)	<.001	<.001
		k = 964, (0 +20 +48)	<.001	<.001
		k = 330, (+30 -62 -36)	<.001	<.001
		k = 257, (+52 +28 -2)	<.001	<.001
		k = 100, (-54 +26 +6)	0.002	0.005
		k = 49, (+22 +16 +30)	0.023	0.047

Left Hippocampus	F(6,108) > 4.08, k≥71	k = 100151, (-24 -22 -18)	*<.001*	*<.001*
		k = 2698, (+42 -44 +40)	*<.001*	*<.001*
		k = 2243, (-48 +26 +30)	*<.001*	*<.001*
		k = 1637, (-38 -50 +40)	*<.001*	*<.001*
		k = 1386, (-26 -68 -32)	*<.001*	*<.001*
		k = 1297, (-32, +58 +10)	*<.001*	*<.001*
		k = 1083, (+6 -64 +48)	*<.001*	*<.001*
		k = 290, (+30 -62 -36)	*<.001*	*<.001*
		k = 269, (+54 +32 0)	*<.001*	*<.001*
		k = 71, (+30 -82 -38)	*0.014*	*0.007*
		3 back		
Right Caudate	F(6,108) > 4.08, k≥69	k = 35855, (+12 +14 +6)	*<.001*	*<.001*
		k = 6231, (+12 -82 +34)	*<.001*	*<.001*
		k = 3722, (+24 -46 +58)	*<.001*	*<.001*

	k = 3595, (+54 -50 +42)	<.001	<.001
	k = 2182, (-56 -44 +48)	<.001	<.001
	k = 1212, (+66 -34 -8)	<.001	<.001
	k = 676, (-32 -64 -36)	<.001	<.001
	k = 381, (-18 -62 -18)	<.001	<.001
	k = 354, (-68 -34 -14)	<.001	<.001
	k = 326, (+58 -2 +4)	<.001	<.001
	k = 221, (+34 -64 -36)	<.001	<.001
	k = 167, (-6 -58 -8)	<.001	.001
	k = 138, (-42 -62 -8)	<.001	.002
	k = 117, (+54 +2 -26)	.001	.005
	k = 111, (-30 -20 -12)	.001	.006
	k = 97, (-30 -80 +4)	.002	.010
	k = 89, (-32 -40 -32)	.003	.013
	k = 80, (+22 -68 +46)	.004	.018
	k = 73, (+4 -38 +42)	.006	.024

		k = 69, (-56 -4 +6)	*.007*	*.027*
Left Caudate	F(6,108) > 4.08, k≥77	k = 32366, (-12 +10 +6)	<*.001*	<*.001*
		k = 8365, (-12 -94 +18)	<*.001*	<*.001*
		k = 3389, (-48 -62 +48)	<*.001*	<*.001*
		k = 1868, (+60 -52 +42)	<*.001*	<*.001*
		k = 1655, (+6 -40 +72)	<*.001*	<*.001*
		k = 1338, (-68 -38 -14)	<*.001*	<*.001*
		k = 497, (+70 -38 -8)	<*.001*	<*.001*
		k = 425, (+34 -64 -32)	<*.001*	<*.001*
		k = 239, (+50 +50 -2)	<*.001*	<*.001*
		k = 108, (-2 -46 -48)	*.001*	*.009*
		k = 85, (-26 +14 -42)	*.004*	*.022*
		k = 77, (-30 -68 -36)	*.005*	*.028*
Right Putamen	F(6,108) > 4.08, k≥51	k = 52796, (+24 +8 0)	<*.001*	<*.001*

	k = 1258, (0 -70 +52)	<.001	<.001
	k = 1122, (-32 -58 +42)	<.001	<.001
	k = 842, (-48 +22 +36)	<.001	<.001
	k = 581, (+6 -82 -32)	<.001	<.001
	k = 434, (+30 -68 -36)	<.001	<.001
	k = 409, (-30 +14 +60)	<.001	<.001
	k = 385, (+10 +22 +42)	<.001	<.001
	k = 312, (+52 +32 -2)	<.001	<.001
	k = 285, (-26 +40 -14)	<.001	<.001
	k = 188, (-14 -62 -24)	<.001	<.001
	k = 154, (+30 +10 +46)	<.001	.001
	k = 142, (-32 +38 +28)	<.001	.001
	k = 138, (+52 +28 +34)	<.001	.001
	k = 108, (+34 +16 -36)	.001	.004
	k = 67, (+30 +44 +24)	.008	.025
	k = 53, (-44 -44 -26)	.016	.048

		k = 52, (-14 -76 +36)	*.017*	*.048*
		k = 51, (+36 -52 +30)	*.018*	*.048*
Left Putamen	F(6,108) > 4.08, k≥60	k = 49407, (-24 +8 -2)	<*.001*	<*.001*
		k = 1034, (+36 +14 +52)	<*.001*	<*.001*
		k = 896, (+4 -74 +54)	<*.001*	<*.001*
		k = 617, (+6 +26 +42)	<*.001*	<*.001*
		k = 571, (-6 -80 -32)	<*.001*	<*.001*
		k = 452, (+40 -50 +34)	<*.001*	<*.001*
		k = 428, (-36 -50 +36)	<*.001*	<*.001*
		k = 389, (-44 +22 +34)	<*.001*	<*.001*
		k = 149, (-32 +38 +28)	<*.001*	*.002*
		k = 124, (+30 +52 0)	*.001*	*.004*
		k = 123, (+52 +32 -2)	*.001*	*.004*
		k = 108, (-30 +14 +58)	*.001*	*.007*
		k = 86, (+30 -58 -38)	*.003*	*.016*
		k = 82, (+24 +34 -14)	*.004*	*.018*

		k =78, (-30 -70 -36)	*.005*	*.020*
		k = 67, (+36 +8 -38)	*.008*	*.032*
		k = 60, (-30 -80 +40)	*.011*	*.042*
Right Hippocampus	F(6,108) > 4.08, k≥60	k = 105000, (+28 -22 -18)	*<.001*	*<.001*
		k = 3440, (-30 +10 +60)	*<.001*	*<.001*
		k = 3108, (+30 +8 +60)	*<.001*	*<.001*
		k = 1265, (+30 -64 -36)	*<.001*	*<.001*
		k = 909, (+30 +56 0)	*<.001*	*<.001*
		k = 825, (-6 +20 +46)	*<.001*	*<.001*
		k = 744, (-32 -62 -36)	*<.001*	*<.001*
		k = 58, (+30 +26 -6)	*0.012*	*0.033*
		k = 56, (-14 -4 +16)	*0.014*	*0.033*
Left Hippocampus	F(6,108) > 4.08, k≥106	k = 103877, (-26 -22 -18)	*<.001*	*<.001*
		k = 4104, (+30 +8 +60)	*<.001*	*<.001*
		k = 2433, (-32 +8 +58)	*<.001*	*<.001*

	k = 1878, (-8 -80 -30)	<.001	<.001
	k = 597, (-32 +62 +4)	<.001	<.001
	k = 491, (+30 -64 -36)	<.001	<.001
	k = 148, (+30 -82 -38)	<.001	.001
	k = 106, (+30 +22 -2)	.001	.004

SBC = Seed-based connectivity, *k = cluster size, unc = uncorrected, FDR = False Discovery Rate, unc.= uncorrected, FDR = false discovery rate*.

Table 2.3: SBC, main effect of time across task conditions and seed ROIs for both MU and n-back scanned tasks.

Main effect of Time						
Seed	***Condition***	***Contrast***	***Cluster size (MNI coordinates)***	***T Statistic***	***p-unc***	***p-FDR***
Matrix Updating						
Right Caudate	Baseline (0 updates)	Post> Early	k = 211, (+22 -34+ 60)	|T(35)|>3.59, k≥116	<.001	.003

			k= 151, (-24 -32 +70)		<.001	.008
			k = 142, (+16 +8 +6)		.001	.008
			k = 133, (-20 +16 0)		.001	.008
			k = 116, (+6 - 46 +70)		.002	.012
Right Caudate	4 updates	Early> Pre	k = 330, (-54 +4 +42)	|T(35)|>3.59, k≥10	<.001	<.001
			k = 123, (0 +2 +60)		.001	.026
			k = 108, (-48 -34 +42)		.002	.031
		Post>Early	k = 171, (+16 +2 +12)	|T(35)|>3.59, k≥133	<.001	.011
			k = 153, (-2 +32 +12)		<.001	.011
			k = 133, (+10 +32 +48)		.001	.014
		Post>Pre	k = 678, (+6 +40 +4)	|T(35)|>3.59, k≥133	<.001	<.001
			k = 482, (+34 +28 -20)		<.001	<.001
			k = 356, (0 +34 +54)		<.001	<.001
			k = 278, (-42 +2 +30)		<.001	<.001

			k = 231, (-6 -22 +40)		<.001	.001
			k = 218, (-26 +28 -26)		<.001	.001
			k = 129, (+22 -2 +58)		.002	.016
Left Caudate	4 updates	Early> Pre	k = 130, (+4 +4 +60)	|T(35)|>3.59, k≥92***	.001	.044
			k = 108, (+52 +10 +24)		.002	.044
			k = 108, (-14 +10 -8)		.002	.044
			k = 94, (+42 +46 +28)		.004	.049
			k = 92, (+30 -62 +54)		.004	.049
		Post>Early	k = 294, (+10 +2 +6)	|T(35)|>3.59, k≥153***	<.001	<.001
			k = 284, (+2 +32 +12)		<.001	<.001
			k = 153, (-2 +28 +54)		.001	.010
		Post>Pre	k = 371, (+6 +38 +4)	|T(35)|>3.59, k≥120***	<.001	<.001
			k = 339, (+34 +26 -20)		<.001	<.001
			k = 122, (-8 +58 +4)		.002	.030

			k = 120, (-8 -52 +30)		*.002*	*.030*
Left Putamen	4 updates	Post>Early	k = 145, (+6 +44 +24)	|T(35)|>3.59, k≥120***	*.001*	*.031*
			k = 120, (-32 -86 -42)		*.002*	*.036*
		Post>Pre	k = 158, (-14 -86 -36)	|T(35)|>3.59, k≥123	*.001*	*.021*
			k = 12, (+54 +34 -16)		*.002*	*.033*
Right Hippocampus	4 updates	Early> Pre	k = 150, (-56 -52 +40)	|T(35)|>3.59, k≥150	<*.001*	*.006*
		Post>Early	k = 496, (-12 -56 +58)	|T(35)|>3.59, k≥84	<*.001*	<*.001*
			k = 496, (+18 -58 +46)		<*.001*	<*.001*
			k = 266, (+22 -2 +48)		<*.001*	<*.001*
			k = 258, (-30 -2 +60)		<*.001*	<*.001*
			k = 237, (-54 -56 +42)		<*.001*	<*.001*
			k = 200, (+40 -82 +10)		<*.001*	*.001*
			k = 159, (+30 -26 +36)		<*.001*	*.003*
			k = 110, (-18 +50 +28)		*.002*	*.015*

			k = 87, (-24 -40 -14)		*.005*	*.033*
			k = 84, (+16 -46 -8)		*.006*	*.034*
		Post>Pre	k = 1268, (+22 -58 +40)	|T(35)|>3.59, k≥141	*<.001*	*<.001*
			k = 300, (+18 -14 -30)		*<.001*	*<.001*
			k = 255, (+24 -2 +52)		*<.001*	*.001*
			k = 141, (-20, -20, -26)		*.001*	*.013*
Left Hippocampus	4 updates	Early> Pre	k = 130, (-56 -52 +40)	|T(35)|>3.59, k≥108	*.001*	*.015*
			k = 86, (+16 -44 +72)		*.004*	*.038*
			k = 78, (+64 -46 +28)		*.006*	*.038*
		Post>Early	k = 944, (+16 -58 +48)	|T(35)|>3.59, k≥111	*<.001*	*<.001*
			k = 385, (-30 -2 +58)		*<.001*	*<.001*
			k = 382, (+30 -4 +52)		*<.001*	*<.001*
			k = 261, (+40 -34 +42)		*<.001*	*<.001*
			k = 203, (+52 +8 +24)		*<.001*	*.001*
			k = 119, (-56 -58 +42)		*.002*	*.015*

			k = 111, (-48 +2 +28)		*.002*	*.017*
			k = 1104, (-38 -28 +64)		<*.001*	<*.001*
			k = 1082, (-24 -16 -18)		<*.001*	<*.001*
			k = 587, (+22 -16 -30)		<*.001*	<*.001*
			k = 494, (+16 -26 +76)		<*.001*	<*.001*
			k = 373, (+54 +22 +22)		<*.001*	<*.001*
		Post>Pre	k = 342, (+54 -40 +42)	|T(35)|>3.59, k≥116	<*.001*	<*.001*
			k = 160, (-8 -44 +78)		*.001*	*.006*
			k = 137, (-12 -70 +42)		*.001*	*.011*
			k = 104, (-36 -44 +34)		*.003*	*.030*
			k = 97, (-42 +4 +22)		*.004*	*.034*
			k = 95, (-54 -40 +34)		*.005*	*.034*
Right Caudate	7 updates	Early> Pre	k = 1330, (+30 -82 +6)		<*.001*	<*.001*
			k = 656, (-2 +4 +60)	|T(35)|>3.59, k≥82	<*.001*	<*.001*
			k = 253 (-42 -78 +42)		<*.001*	*.001*

		k = 251, (+60 -62 +30)		*<.001*	*.001*
		k = 224, (-24 -88 +6)		*<.001*	*.001*
		k = 198, (+30 -44 +42)		*<.001*	*.002*
		k = 185, (-2 +44 0)		*<.001*	*.002*
		k = 156, (-50 -46-30)		*.001*	*.005*
		k = 125, (+46 +8 +22)		*.002*	*.013*
		k = 107 (-54 +2 +46)		*.003*	*.022*
		k = 92, (-50 -70 -18)		*.005*	*.035*
		k = 87, (34 -2 +54)		*.007*	*.038*
		k = 82, (-26 -4 +52)		*.008*	*.043*
	Post>Early	k = 177, (-18 -76 -30)	|T(35)|>3.59, k≥99	*.000*	*.005*
		k = 167 (+10 +4 +10)		*.000*	*.005*
		k = 99, (-8 +4 +4)		*.004*	*.036*
	Post>Pre	k = 1596, (0 +14 +40)	|T(35)|>3.59, k≥98	*<.001*	*<.001*
		k = 1430, (+28 -82 -6)		*<.001*	*<.001*

			k = 1027 (0 +40 +46)		*<.001*	*<.001*
			k = 910, (-44 -4 +52)		*<.001*	*<.001*
			k= 458, (56 -64 +40)		*<.001*	*<.001*
			k = 286, (+30 +22 -20)		*<.001*	*<.001*
			k = 261, (-44 -76 0)		*<.001*	*.001*
			k = 236, (-18 -70 +40)		*<.001*	*.001*
			k = 228, (-2 +44 0)		*<.000*	*.001*
			k = 185, (-48 -34 +42)		*<.001*	*.003*
			k = 128, (+28 -40 +40)		*.001*	*.008*
			k = 121 (-36 +16 +40)		*.002*	*.015*
			k = 100, (+6 +14 +6)		*.002*	*.017*
			k = 98, (+52 +4 +30)		*.005*	*.033*
					.005	*.033*
Left Caudate	7 updates	Early> Pre	k = 825, (+12 +8 +54)	|T(35)|>3.59, k≥123	*<.001*	*<.001*
			k = 486, (-30 -8 +48)		*<.001*	*<.001*
			k = 158, (-50 -46 -30)		*<.001*	*.012*

		k = 157, (+34 -2 +54)		*.001*	*.012*
		k = 129, (+40 -40 +52)		*.002*	*.023*
		k = 123, (+22 -58 +48)		*.002*	*.023*
	Post>Early	k = 281, (+16 +4 +6)	|T(35)|>3.59, k≥157	<*.001*	<*.001*
		k = 157, (-18 +22 +58)		<*.001*	*.007*
	Post>Pre	k = 574, (+16 +4 +52)	|T(35)|>3.59, k≥93	<*.001*	<*.001*
		k = 563, (+34 -82 -6)		<*.001*	<*.001*
		k = 534, (+48 -22 +58)		<*.001*	<*.001*
		k = 488, (+4 +46 +24)		<*.001*	<*.001*
		k = 415, (+42 +34 -18)		<*.001*	<*.001*
		k = 371, (+10 +40 +48)		<*.001*	<*.001*
		k = 282, (-42 -8 +52)		<*.001*	<*.001*
		k = 246, (-12 +46 +48)		<*.001*	*.001*
		k = 224, (-32 +14 +42)		<*.001*	*.001*
		k = 212, (-14 -68 +40)		<*.001*	*.001*

			k = 199, (+4 -40 +58)		*<.001*	*.002*
			k = 196, (+58 -64 +22)		*<.001*	*.002*
			k = 171, (-42 -4 +30)		*.001*	*.003*
			k = 116, (-8 -2 +12)		*.003*	*.016*
			k = 111, (-48 -74 +6)		*.003*	*.018*
			k = 94, (-14 -82 -42)		*.006*	*.029*
			k = 93, (+42 -22 +34)		*.006*	*.029*
Right Hippocampus	7 updates	Post>Early	k = 357, (-20 -16 -20)	|T(35)|>3.59, k≥275	*<.001*	*<.001*
			k = 275, (-36 -88 +4)		*<.001*	*<.001*
		Post>Pre	k = 860, (+54 -38 +36)	|T(35)|>3.59, k≥69	*<.001*	*<.001*
			k = 734, (-20 -16 -24)		*<.001*	*<.001*
			k = 485, (+22 -20 -26)		*<.001*	*<.001*
			k = 389, (+12 -74 +42)		*<.001*	*<.001*
			k = 373, (-12 -76 +48)		*<.001*	*<.001*
			k = 367, (+46 +8 +22)		*<.001*	*<.001*

			k = 336, (+16 -26 +76)		*<.001*	*<.001*
			k = 316, (+34 +2 +52)		*<.001*	*<.001*
			k = 253, (-30 -64 -32)		*<.001*	*<.001*
			k = 249, (-42 +38 +34)		*<.001*	*<.001*
			k = 215, (-30 -88 +6)		*<.001*	*.001*
			k = 206, (+6 +10 +52)		*<.001*	*.001*
			k = 167, (-60 -44 +42)		*<.001*	*.002*
			k = 126, (-36 +44 +18)		*.001*	*.007*
			k = 110, (+36 -88 +22)		*.003*	*.012*
			k = 93, (-36 -2 +52)		*.005*	*.021*
			k = 91, (-14 -46 +4)		*.005*	*.021*
			k = 86, (-2 +8 -14)		*.006*	*.024*
			k = 80, (-36 -50 +40)		*.008*	*.029*
			k = 69, (-12 -44 +78)		*.013*	*.043*
	7 updates	Early> Pre	k = 178, (-60 -46 +46)	|T(35)|>3.59, k≥102	*<.001*	*.009*
			k = 139, (-24 -20 -18)		*.001*	*.017*

		k = 113, (-56 -14 -2)		*.002*	*.029*
		k = 102, (-26 +16 -32)		*.003*	*.033*
	Post>Early	k = 234, (+18 -32 +76)		*<.001*	*.002*
		k = 221, (-30 -32 -18)		*<.001*	*.002*
		k = 155, (+6 -64 +30)	|T(35)|>3.59, k≥120	*.001*	*.011*
		k = 148, (+24 -14 -32)		*.001*	*.011*
		k = 120, (-12 -70 +52)		*.002*	*.023*
Left Hippocampus	Post>Pre	k = 1104, (-38 -28 +64)		*<.001*	*<.001*
		k = 1082, (-24 -16 -18)		*<.001*	*<.001*
		k = 587, (+22 -16 -30)		*<.001*	*<.001*
		k = 494, (+16 -26 +76)	|T(35)|>3.59, k≥95	*<.001*	*<.001*
		k = 373, (+54 +22 +22)		*<.001*	*<.001*
		k = 342, (+54 -40 +42)		*<.001*	*<.001*
		k = 160, (-8 -44 +78)		*.001*	*.006*
		k = 137, (-12 -70 +42)		*.001*	*.011*

			k = 104, (-36 -44 +34)		*.003*	*.030*
			k = 97, (-42 +4 +22)		*.004*	*.034*
			k = 95, (-54 -40 +34)		*.005*	*.034*
			N-Back			
Right Putamen	0-back	Early>Pre	k = 281, (+6 -16 +58)	|T(36)|>3.58, k≥281	<*.001*	<*.001*
		Post>Pre	k = 275, (+22 -34 +58)	|T(36)|>3.58, k≥275	<*.001*	*.001*
Left Caudate	2-back	Early>Pre	k = 148, (-2 -82 +42) k = 106, (+40 -20 +64)	|T(36)|>3.58, k≥106	*.001* *.003*	*.021* *.043*
Right Putamen	2-back	Early>Pre	k = 133, (-62 -16 +22)	|T(36)|>3.58, k≥133,	*.001*	*.034*
Right Hippocampus	2-back	Early>Pre	k = 276, (+42 -68 +40)	|T(36)|>3.58, k≥276	<*.001*	*.001*
		Post>Early	k = 294, (-8 -62 +16)	T(36)|>3.58, k≥115	<*.001*	<*.001*

			k = 115, (+6 +26 -20)		*.002*	*.044*
		Post>Pre	k = 534, (0 +44 -26)	|T (36)|>3.58, k≥97	<*.001*	<*.001*
			k = 166, (+60 -40 +48)		<*.001*	*.008*
			k = 158, (-24 -14 -26)		*.001*	*.008*
			k = 121, (-66 -10 -14)		*.002*	*.020*
			k = 99, (-12 +34 -6)		*.004*	*.032*
			k = 97, (+12 +20 +60)		*.005*	*.032*
Left Hippocampus	2-back	Post>Early	k = 206, (+04 +46 -26)	T(36)|>3.58, k≥206	<*.001*	*.004*
		Post>Pre	k = 530, (+10 +34 0)	T(36)|>3.58, k≥104	<*.001*	<*.001*
			k = 191, (+54 -40 +30)		<*.001*	*.004*
			k = 153, (-24 -16 -24)		*.001*	*.009*
			k = 116, (+24 -14 -26)		*.002*	*.023*
			k = 104, (+12 +16 +64)		*.003*	*.029*

Right Caudate	3-back	Post>Pre		T(36)|>3.58, k≥300		
Left Caudate	3-back	Post>Pre	k = 172, (+6 +62 -8) k = 127, (-50 -50 -30) k = 120, (+40 -70 -8) k = 101, (-2 +28 +48)	T(36)|>3.58, k≥101	*.000* *.001* *.002* *.004*	*.016* *.030* *.030* *.045*
Right Putamen	3-back	Early>Pre	k = 300, (+10 +62 -8)	|T(36)|>3.58, k≥357	<*.001*	<*.001*
Left Putamen	3-back	Early>Pre	k = 376, (-54 +4 +24) k = 205, (-8 +40 -12)	|T(36)|>3.58, k≥205	<*.001* <*.001*	<*.001* *.003*
Right Hippocampus	3-back	Post>Pre	k = 507, (+36 -10 +64) k = 267, (+42 -26 +46) k = 172, (+68 -50 -2) k = 100, (+18 -82 -32)	T(36)|>3.58, k≥91	<*.001* <*.001* <*.001* *.003*	<*.001* *.001* *.006* *.047*

			k = 95, (+48 +14 +46)		*.004*	*.047*
			k = 93, (+48 +32 -2)		*.004*	*.047*
			k = 91, (-24 -74 -32)		*.005*	*.047*
Left Hippocampus	3-back	Post>Pre	k = 134, (-26 -70 -32)	T(36)|>3.58, k≥134	*.001*	*.033*

SBC= Seed-based connectivity analysis, k = cluster size, unc. = uncorrected, FDR = false discovery rate

Appendix 3

3.1 Consent Form

University of Glasgow | College of Medical, Veterinary & Life Sciences

NHS Greater Glasgow and Clyde

IRAS ID: 261172

Centre Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: *Development and Evaluation of a Novel Treatment Intervention for People with Acquired Brain Injury*

Name of Researcher: Miss Katerina Pappa, Professor Jonathan Evans, Dr Kristin Flegal and Dr Satu Baylan.

Please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from University of Glasgow, from regulatory authorities or from the NHS Health boards, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree that my name, contact details and data described in the information sheet will be kept for the purposes of this research project. ☐
5. I agree to the way my data will be collected and processed and that the data will be stored for up to 10 years in University archiving facilities in accordance with relevant Data Protection policies and regulations. ☐
6. I agree to provide my data for future research as detailed in section 11 "Open Brain Data" of the information sheet dated..... (version.....) for the above study. ☐
7. I understand that if I withdraw from the study, my data collected up to that point will be retained and used for the remainder of the study. ☐
8. I agree to my General Practitioner being informed of my participation in the study. ☐

When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes. If they're recruited from the community, how will you access their medical notes?

Version 1.0 16 September 2019

9. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes. If they're recruited from the community, how will you access their medical notes?

3.2 Participant information sheet

University of Glasgow | College of Medical, Veterinary & Life Sciences

NHS Greater Glasgow and Clyde

Participant Information Sheet

Title of Project: *Development and Evaluation of a Novel Treatment Intervention for People with Acquired Brain Injury*

1. Invitation Paragraph

You are being invited to take part in a research study. Before you decide to participate, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If you would like more information on any aspect of the study, please ask us. Take as much time as you need to decide whether or not you wish to take part. If you decide you do wish to take part you will be asked to sign a form (consent form) confirming your willingness to participate and will also be provided with a copy of this form to keep.

2. What is the purpose of this study?

Acquired brain injury (ABI), as a result of a stroke, head injury, tumour etc, may cause difficulties with **memory, concentration, planning, and problem solving.** These difficulties sometimes cause problems with managing everyday tasks, particularly when they involve many steps (such as cooking a meal). Goal management training (GMT) involves teaching people mental strategies to improve their ability to remember the steps in a task, and to stay 'on task' and there is evidence that this can improve performance on complex everyday tasks. **Computerised memory training programmes** that adapt the difficulty level to the performance of the person being trained also hold some promise. **Working memory** is a mental process for keeping and **updating** information in mind, and this is important for planning ahead and solving problems. **Combining GMT and working memory updating (WMU)** training may increase the benefit that could be gained from either of these training programmes alone. We have developed a new combined intervention and want to see if it is acceptable to people with ABI. We also want to use a type of brain scanning, functional magnetic resonance imaging (fMRI), to explore the effect the combined intervention has on brain function. Our aim is to use our findings to **inform clinical treatments for people with ABI.**

3. Why have I been invited to participate?

You are being invited to take part because you have suffered an acquired brain injury (such as a head injury, stroke, or other type of brain injury) and have reported some difficulties with doing everyday tasks that may involve remembering to do things, planning or organisation.

4. Do I have to take part?

No, it is up to you to decide whether or not to take part. Even if you decide to take part, you are still free to withdraw at any time and without giving a reason.

5. What will happen to me if I take part?

We will access your medical records to obtain information about previous brain scans you might have had or details of your brain injury. However, your existing care will not be affected by your decision to take part in the study.

The study has 3 main components.

i. Initial appointments

a. Initial neuropsychology assessment

During your first visit we will ask you to perform some **pen and paper tests to assess memory, planning and problem-solving skills.** We will use a questionnaire to look at everyday functioning and we will also give you an introduction to the training programme. This visit will last approximately two and a half hours. This appointment can also be conducted remotely via a video-call using the internet as a way of mitigating **COVID-19** circumstances.

b. Brain scan

Following that, you will participate in your first brain scanning session, so we can study how your brain responds when you perform memory tasks inside the scanner. The brain scan will take about one and a half hours, although you will not actually be inside the scanner for more than 60 minutes of this time. If you have certain implants or devices in or on your body or certain tattoos (depending on size and location), then you will not be allowed to take part in this study. Additionally, if you suffer from claustrophobia (fear of enclosed spaces), then this study might not be right for you.

When you come for your brain scan, a member of the research team will take you through **a checklist** to make sure that it is safe for you to be scanned. You will then be asked to change into MR-safe clothing and taken into the MRI-room. Once in the MRI-room, you will be positioned on the scanner bed. You will be given earplugs or headphones to reduce the noise made by the scanner. It is important that you are able to stay still during your scan, but if you are uncomfortable, you can ask to stop at any time.

While you are in the scanner we will ask you to perform simple tasks **such as remembering locations of coloured dots or figures you see on a projection screen, and respond by pressing buttons with your fingers**. At all times you will remain in contact with us through the intercom and you will have a buzzer in your hand, in case you want us to stop the scan and come into the scanner room. At the end we will ask you to lie still for a further ten minutes while we acquire a **picture of your brain**.

After your scan, just as a precaution, we ask that study participants not drive for 15 minutes. You will be asked to remain in the Clinical Research Imaging Facility (CRIF), Queen Elizabeth University Hospital (QEUH) with a member of the research team for approximately 15 minutes. A refreshment may be offered while you wait.

Due to the ongoing situation involving **COVID-19** we understand some of you might feel uncomfortable with having a brain scan. Therefore, attending the brain scanning sessions will not be mandatory for entering the study although it is preferrable. Finally, if you intend to complete the brain scan sessions we will ensure that all necessary NHS approved measures and precautions are in place to minimise contact and adhere to social distancing rules.

ii. Intervention

For the next eight weeks, you will be taking part in the **intervention part of the study**. There will be **8 weekly combined GMT and WMU training sessions**. Each GMT session will take two hours while the WMU session will last between one hour and one hour and fifteen minutes. There will be a break between the GMU and WMU training sessions allowing you to have a rest and relax. Sessions will be conducted in a group format – groups will contain two to six participants. If it is not possible for you to complete both training sessions on the same day, alternative options will be offered, i.e. completing the WMU session from home or attending on a different day in the same week. In between the training sessions you will be asked to complete some homework and relaxation exercises. Participants will be offered the option of conducting the **GMT and WMU training sessions remotely via a video-call using the internet** to mitigate **COVID-19** circumstances**.** The **GMT** sessions will continue to be in a group format, while the **WMU** sessions can be completed at one's own time at home.

iii. Follow-up appointments

At the end of the eight-week intervention you will be asked to complete the same pen and paper tests you completed at your initial appointment. This will allow us to assess changes in your performance as a result of the intervention. You will also be asked to undergo a **second brain scan** which will be the same as the first scan you underwent. This appointment can also be conducted remotely via a video-call as a way of mitigating **COVID-19** circumstances.

In between appointments you will receive phone-calls, texts or emails, according to your preference, as reminders of your next sessions.

6. What are the possible benefits of taking part?

We will reimburse you for your travel to the training sessions, and your participation will help us develop a better understanding of the relationship between brain and behaviour. You may also find that the combined training has a positive effect on your thinking skills.

7. Will my GP be informed?

Yes, we will send **a letter to your GP** informing them of your participation and enclosing further information about the study. The **anatomical MRI brain scans** will be transferred to NHS systems and be linked to your **medical file.** Your scans will then be reviewed by a neuroradiologist who will write a report. In the unlikely event that an abnormal finding extending beyond the existing brain injury is detected, we will contact your GP and you will be referred to an appropriate clinician for further investigations. You should be aware that you may then have to disclose such findings in future applications for health-related insurance.

Are there compensation arrangements if something goes wrong?

In the unlikely event of anything untoward happening, NHS insurance applies to the management and conduct of the study. The design of the research will be indemnified by the University of Glasgow. If for any reason you would like to raise a complaint you can contact the NHS Greater Glasgow & Clyde (GG&C) complaints office at: **complaints@ggc.scot.nhs.uk.**

8. Will my taking part in this study be kept confidential and what will happen to my data?

All information that is collected about you during the course of the research will be kept **strictly confidential.** We will be collecting and storing identifiable information from you (such as name and contact details) in order to undertake this study. **This identifiable data will remain on NHS systems** and thus the **NHS GG&C** is responsible for looking after your information and using it properly. **NHS R&D staff may** also require access to the data for **auditing purposes**. Your personal data (name, data collected for safety checks) will be held separately from your brain image data, and your images will be referred to by a code. All images collected from the fMRI scans will be anonymised before any analysis is carried out on them, therefore it will not be possible to identify you from the images in any way. **The anonymised data will be stored on a secure university network.** It is possible that the anonymised data may be used by researchers working within the university for other similar ethically approved research protocols, where the same standards of confidentiality will apply. In all cases your **name will not be used** and your data will be identified only by a digit code.

We will keep personal information about you (and the code) until the project has finished and will not pass this information to a third party without your expressed permission. Should you choose to withdraw from the study, which you are free to do at any time, your data may still be used up until the point of your withdrawal. **The anonymised data will be stored for up to 10 years in University archiving facilities** in accordance with relevant Data Protection policies and regulations.

We will inform you when the study results are published, and the journal article will be shared with you. A summary for readers who are not scientists will also be provided together with the article. In addition, the study findings will be shared with individuals with ABI and their families via local networks. No personally identifiable information about you will be included in these reports and presentations.

9. Who is organising and funding the research?

The research will be organized by **Katerina Pappa, a PhD Candidate** in Psychological Medicine. She is supervised by **Professor Jonathan Evans** and **Dr Satu Baylan,** Institute of Mental Health & Wellbeing, and **Dr Kristin Flegal,** Institute of Neuroscience and Psychology**.** This research is jointly funded by the Neurosciences Foundation and Sackler Foundation.

10. Who has reviewed the study?

The South East Scotland Research Ethics Committee gave the study a favourable ethical opinion. The MRI research environment is overseen by **Tracey Hopkins,** Lead Research Radiographer, CRIF, QEUH.

11. Open Brain Data

We will give public access to all the data from this project through an open online database to allow other researchers to check our analyses, or apply their own. The data we share publicly will not have your name on it, only a code number, so people will not know your name or which data is yours. We will not share any other information that we think might identify you. If you change your mind and withdraw your consent to participate in this study, we will not collect any additional data about you. We will delete your data if you withdraw before it is deposited in the database. However, any data and research results already shared with other investigators cannot be destroyed, withdrawn or recalled. Letting us use and share your data is voluntary. However, you must be willing to share your data in this way to participate in this study.

If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified. However, by using additional data linked to your name (for example brain scans obtained from your medical records), one could potentially associate your images or other information in our database back to you. In addition, a security breach (break in or cyber-attack) might lead to someone being able to link you to your data. This risk is very low because your data are stored in a secure database, and the information about your identity is stored separately from the data themselves, linked only through a code.

12. Data Protection Declaration

NHS GG&C is the sponsor for this study based in Scotland, UK. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NHS GG&C will keep identifiable information about you for ten years after the study has finished, until 2031. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information: https://www.nhsggc.org.uk/patients-and-visitors/faqs/data-protection-privacy/.

13. Contact for Further Information

Miss Katerina Pappa, *PhD Candidate in Psychological Medicine.*
Tel: 0141 451 6863, **Email:** a.pappa.1@research.gla.ac.uk
Institute of Mental Health and Wellbeing, School of Medical Veterinary & Life Sciences.
2nd floor, Imaging Centre of Excellence,
Queen Elizabeth University Hospital, Glasgow, G51 4TF.

Supervisory Team:

Prof Jonathan Evans:	**Tel:** 01412113978,	**Email:** jonathan.evans@glasgow.ac.uk
Dr Kristin Flegal:	**Tel:** 01414516841,	**Email:** kristin.flegal@glasgow.ac.uk
Dr Satu Baylan:	**Tel:** 01414515879,	**Email:** satu.baylan@glasgow.ac.uk

Dr Breda Cullen: **Tel:** 01412113912 **Email:** Breda.Cullen@glasgow.ac.uk
Senior Lecturer in Clinical Psychology, Institute of Mental Health & Wellbeing

Thank you for taking the time to read this information sheet. If you have any questions or would like some more information, please feel free to contact a member of the research team and discuss it with them.
If you would like to discuss the study with an independent member outside of the research team please contact:

3.3 GP Letter

University of Glasgow | College of Medical, Veterinary & Life Sciences

NHS Greater Glasgow and Clyde

Study Title: Development and Evaluation of a Novel Treatment Intervention for People with Acquired Brain Injury

Date

Dear Doctor **Insert: [name]**

Re: **Insert: [Patient Name and DOB]**

I am writing to inform you that your patient has consented to participate in the above research study at the University of Glasgow and has given their consent for us to contact you. This is as small-scale feasibility randomised controlled trial of adult participants who have suffered an Acquired Brain Injury (ABI) and have reported everyday organization and working memory difficulties after their injury. The study involves taking part in an eight week combined mental strategy and cognitive process intervention.

The purpose of this study is to investigate whether it is feasible to combine two types of intervention: 1. A metacognitive mental strategy training called Goal Management Training (GMT) and 2. a process-based Working Memory Updating training (WMU) to improve executive function in people who have suffered an Acquired Brain Injury (ABI). Participants are expected to complete:

i. Two **neuropsychology assessment** sessions (before and after completing the intervention) to conduct tests of cognitive and everyday executive function to assess changes in performance,
ii. Two **functional magnetic resonance imaging (fMRI) sessions** to investigate brain activity while people perform different cognitive tasks inside the scanner before and after the eight weeks of training.
iii. **eight weekly intervention sessions of a combined GMT and WMU training** to improve everyday executive function,

The patient is expected to attend weekly training sessions either at the University of Glasgow premises or the NHS outpatient clinic they were recruited from. Before and after completing the intervention, tests of cognitive and everyday executive function will be conducted and fMRI data will be acquired. The fMRI sessions are taking place at the Clinical Research Imaging Facility (CRIF), Queen Elizabeth University Hospital (QEUH) in a 3T Prisma Siemens scanner.

The MRI anatomical scans will be transferred to NHS PACS and be linked to the patient's medical file. These will be reviewed by a neuro-radiologist, Dr Natasha Fullerton, who will produce a comprehensive report in CRIS for each participant. In cases of an incidental finding extending beyond the existing brain injury, you will be contacted and the patient will additionally be referred to an appropriate clinician for further investigation.

I enclose a copy of the participant information sheet given to your patient. If you would like any further information about the study please contact me at the Imaging Centre of Excellence, Queen Elizabeth University Hospital, Langlands Dr, Glasgow G51 4LB.

Yours Sincerely,

Miss Katerina Pappa, *PhD Candidate in Psychological Medicine, Institute of Mental Health and Wellbeing, School of Medical Veterinary & Life Sciences.*

2nd floor, Imaging Centre of Excellence,
Queen Elizabeth University Hospital, Glasgow, G51 4TF
***Tel:** 0141 451 6863*
***Email:** a.pappa.1@research.gla.ac.uk*

Supervisor
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Encs: Patient Information Sheet, version **(insert version number)** dated **(insert date).**

Appendix 4

4.1 Digital group consent form

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IRAS ID: 261172
Participant Identification Number for this trial:

Title of Project: *Development and Evaluation of a Novel Treatment Intervention for People with Acquired Brain Injury*

DIGITAL GROUP CONSENT FORM

Before the first digital group session, one of the group facilitators will phone to talk through the information in this sheet. They will seek your consent to participate in the digital group sessions. They will have a copy of this sheet and, if you give your verbal consent and agree to each of the below points, they will sign that you have done so.

My Rights:

Choose an item.	I understand that the NHS privacy and confidentiality policies and procedures relating to my personal health information also apply to video conferencing. Personal information will be managed in accordance with current data protection legislation. The study sponsor, NHS GG&C, takes care to ensure personal information is only accessible to authorised people. Staff have a legal and contractual duty to keep personal health information secure and confidential except when there are concerns around safety when information might need to be disclosed.
Choose an item.	I am aware that I can find out more about how current data protection legislation and how my information is processed by visiting the Data Protection Notice at https://www.nhsggc.org.uk/patients-and-visitors/faqs/data-protection-privacy/ or asking one of the group facilitators for a copy of it.
Choose an item.	I understand that the digital group sessions will **NOT** be recorded.
Choose an item.	I understand that all participants are being informed not to record group sessions although NHS GG&C cannot fully guarantee this does not happen, which I also understand.
Choose an item.	I understand that the group facilitators will not allow any other individual who is not directly involved in the group to listen to digital group sessions.
Choose an item.	I understand that the group facilitators will make every effort to engage with, and encourage participation of, all members of the group session. I also understand it is within my rights to choose to just listen and not speak.
Choose an item.	I understand I can withdraw from the group at any time if I want.

My Responsibilities:

Choose an item.	I agree to maintain the confidentiality of other group members while using video conferencing. This means taking reasonable steps to make sure the session is not overheard or seen by anyone not directly involved in the group, by being in a different room from others in the household, and/or using headphones for audio.
Choose an item.	I agree **NOT** to record any video/audio from the group session.
Choose an item.	I agree to otherwise keep personal information of group members confidential.
Choose an item.	I agree to accept directions from the group facilitators to help structure the session, in order to ensure that the learning materials are covered and all participants have an equal chance to speak.
Choose an item.	I will not pass on joining information (link/ passcode/ pin number) to anyone else.
Choose an item.	I agree to contribute to the group in a way which is positive, and which focusses on the here and now and moving forward.

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Choose an item.	I understand that I am expected to be sitting upright (not lying on a bed or sofa) and appropriately dressed during the video sessions.

Statement of consent:

Choose an item.	I understand that I am giving my verbal consent to participate in digital group sessions, thus agreeing to all of the above points, and one of the facilitators is recording this on an exact copy of this form which go into my case file.

Name of Participant Click here to enter text. **Date** Enter a date.

Person completing the form Click here to enter text. **Date** Enter a date.

4.2 Feedback form

University of Glasgow

NHS Greater Glasgow and Clyde

Feedback about Intervention

Title: Development and Evaluation of a Novel Treatment Intervention for People with Acquired Brain Injury

Participant ID:

Date completed ____/____/_____

So that we can evaluate and improve the intervention that you received, we would like you to give feedback of what worked well and what did not. Please circle the numbers that best represent your opinions, and give further details in your own words. There are no right or wrong answers. Please be honest.

1. Overall, how convenient were your appointments (location and time)?

Very convenient **Not at all convenient**
1 2 3 4 5

Please give details:

_____

2. Overall would you recommend the intervention to another individual with acquired brain injury?

Very much **Not at all**
1 2 3 4 5

Please give details:

_____

3. Overall, how feasible was it to remain in the study for 12 weeks?

Very feasible **Not at all feasible**
1 2 3 4 5

Please give details:

_____

4. Overall, how feasible was it to complete the computerised training?

Very feasible **Not at all feasible**
1 2 3 4 5

Please give details:

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5. Overall, how enjoyable did you find the group sessions?

Very enjoyable **Not at all enjoyable**
1 2 3 4 5

Please give details:

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6. Overall, how relevant did you think the intervention was to your situation?

Very relevant **Not at all relevant**
1 2 3 4 5

Please give details:

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7. Do you feel the intervention has contributed to your recovery?

Very much **Not at all**
1 2 3 4 5

Please give details:

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8. Will you continue to use the strategies you learned after the end of the intervention or benefit from it in your everyday life?

Very much **Not at all**
1 2 3 4 5

Please give details:
