Neural correlates of cognitive training in middle-aged adults

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Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: D. Kyriazis

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Abstract

Background

Cognitive training offers a potential approach for the prevention of cognitive decline in later life. Repetition of targeted exercises may improve, or at least preserve, both specific domains and general cognitive abilities by strengthening neural connections and promoting neuroprotective processes within brain networks. Significantly, middle-aged adults have been omitted from the cognitive training literature. Therefore, in a first experiment, we investigated short-term training (1 session) on a perceptual-cognitive-motor task in middle-aged adults. Furthermore, we examined the functional and structural neural correlates of this training. In a second experiment, we tested the effectiveness of longer-term cognitive training (4-6 weeks) in improving overall cognitive function in this age group. In addition, we examined structural and functional brain changes resulting from training.

Methods

Twenty one healthy middle-aged adults between 40 and 50 years old took part in the first experiment. All participants underwent one scanning session during which they completed the perceptual-cognitive-motor task. We compared performance and functional imaging on the pre- and post-training phases of the task. We used diffusion MRI to examine microstructural variation in the brain in relation to training outcome. The diffusion indices included fractional anisotropy (FA), mean diffusivity (MD), neurite density index (NDI), and orientation dispersion index (ODI).

For the second experiment, 40 healthy middle-aged adults between 40 and 50 years of age took part in the study. Participants completed either adaptive cognitive training (experimental condition) or non-adaptive training (active control). We examined performance on trained and untrained (transfer) tasks at pre- and post-training. We also compared functional imaging at pre- and post-training. And finally, we tested for microstructural effects of cognitive training with diffusion imaging.

Results

For experiment 1, we found a significant improvement in performance following training on the task. There were also significant training-induced changes in functional activity in cortical and subcortical brain regions. Furthermore, significant correlations were found between the diffusion indices of FA, MD, and ODI and training outcome. These results indicate that variation in brain structure was related to learning ability.

For experiment 2, we found that both adaptive and non-adaptive groups showed significantly improved performance on the training tasks. In addition, we found improved performance on an untrained task following completion of the training programme.

Increased activity was demonstrated in brain regions following training. And finally, there were training-induced changes in ODI in the frontal pole, indicating a change in brain structure as a result of cognitive training.

Conclusions

We found that short-term and longer-term cognitive training resulted in significant performance improvements in middle-aged adults. Substantial improvements were found for the training tasks, and training gains transferred to an untrained task. Furthermore, functional and structural brain changes occurred as a result of training. Taken together, the findings in this thesis demonstrate considerable cognitive, motor, and neural plasticity in this age group. Therefore, we conclude that cognitive training in middle-aged adults was effective at inducing brain changes and improving cognitive function. This may have a significant potential impact with regards to preventing age-related cognitive decline in later life.

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Acronyms

CSF	Cerebrospinal Fluid
dPFC	Dorsolateral Prefrontal Cortex
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
FDR	False Discovery Rate
fMRI	functional Magnetic Resonance Imaging
IFG	Inferior Frontal Gyrus
M1	Primary Motor Cortex
MD	Mean Diffusivity
MMSE	Mini Mental State Exam
NDI	Neurite Density Index
NODDI	Neurite Orientation Dispersion and Density Imaging
ODI	Orientation Dispersion Index
oPFC	Orbitofrontal Cortex
PAL	Pair-associative Learning
PAR	Pair-associative Retrieval
PCM	Perceptual-cognitive-motor
PFC	Prefrontal Cortex
preSMA	Pre Supplementary Motor Area
RAPM	Raven Advanced Progressive Matrices
ROI	Region of Interest
SMA	Supplementary Motor Area
vPFC	Ventrolateral Prefrontal Cortex

Chapter 1: General introduction

1.1 Cognitive decline in older age

Cognitive decline has been sufficiently evidenced in healthy older adults across several cognitive domains (e.g., attention, working memory, spatial memory, reasoning) (for review see Karbach & Verhaeghen, 2014; Au et al., 2015; Soveri et al., 2017; Pergher et al., 2018). In view of the rapidly increasing elderly population, this is a growing concern for healthcare organisations in the near future (Pergher et al., 2018). As such, the study of cognitive decline during one's life span, and more importantly, what can be done to slow it down, has gained considerable interest from the research community (Pergher et al., 2018).

Negative associations between age and performance on tests for aspects of fluid cognition are well documented (Salthouse, 1991; Kausler, 1994; Lindenberger & Baltes, 1994; Schaie, 1995; Rabbitt, 1997; Verhaeghen & Salthouse, 1997; Salthouse, 2004; Perry et al., 2009; Seidler et al., 2010; Verwey et al., 2010; Verwey et al., 2011). For example, the performance of older adults was found to be lower than that of young adults on tests of reasoning, spatial ability (Salthouse, 1992; Verhaeghen & Salthouse, 1997), and episodic memory (Verhaeghen et al., 1993; Verhaeghen & Salthouse, 1997). Decline has also been shown in working memory (e.g., Baddeley, 1986; Just & Carpenter, 1992; Verhaeghen & Salthouse, 1997; Park & Reuter-Lorenz, 2009; Emch et al., 2019; Pliatsikas et al., 2019). Furthermore, older adults are particularly impaired in associative memory (Iidaka et al., 2001; Sperling et al., 2003; Cowan et al., 2006; Cohn et al., 2008; Shing et al., 2008; Naveh-Benjamin et al., 2009; Edmonds et al., 2012). Attention is also negatively affected by age (Naveh-Benjamin et al., 2005). In addition, there is a basic and relatively pervasive loss in cognitive processing speed with age (Salthouse, 1985; Cerella, 1990; Myerson et al., 1990; Salthouse, 1996). Meta-analysis has shown that this age-related decline is moderately large (Verhaeghen & Salthouse, 1997). These abilities are needed to perform activities of daily living, and therefore there may be a substantial negative impact of cognitive decline on quality of life in older age (Deary et al., 2009).

Research has also demonstrated that there is a decline in motor skill acquisition with age (e.g., Rabbitt, 1997; Li & Lindenberger, 2002; Hedel & Dietz, 2004; Smith et al., 2005; Rieckmann & Bäckman, 2009; Seidler et al., 2010; Bennett et al., 2011; Verwey et

al., 2011; King et al., 2013). For example, Smith et al. (2005) investigated the learning of a novel visuomotor task in adults between 18 and 95 years of age. Participants were split into two groups (18-61 and 62–95 years of age). Motor learning was significantly slower in adults over 62 years of age. The learning of new motor skills, as well as the modification of previously learned skills, is necessary for the performance of everyday activities, and motor skills play a crucial role in all phases of the life span (King et al., 2013). Evidence is mounting that the development and use of complex motor skills decreases with age not only for biomechanical and neuromuscular reasons, but also due to a decline in cognitive functioning (Salthouse, 1996; Rabbitt, 1997; Howard & Howard, 2001; Li & Lindenberger, 2002; Hedel & Dietz, 2004; Howard et al., 2004; Rieckmann & Bäckman, 2009; Seidler et al., 2010; Verwey et al., 2011). Indeed, it has been suggested that motor and cognitive plasticity cannot be seen as being independent from each other (Voelcker-Rehage, 2008). In particular, the early learning phase of motor skill acquisition has been shown to be mainly influenced by cognitive processes to understand the task and prepare strategies (Milton et al., 2004; Kelly & Garavan, 2005).

1.2 Age-related neural changes and cognitive decline

What are the underlying mechanisms of decreased cognitive and motor performance as we age? The aging process is associated with widespread changes in the brain, and these age-related neural changes are thought to substantially contribute to age-related deficits in motor and cognitive functioning (e.g., Cabeza, 2001; Hogan, 2004; Kennedy & Raz, 2005; Paquet et al., 2008; Bäckman et al., 2010; Bennett et al., 2011; King et al., 2013). Evidence linking behavioural deficits to age-associated changes in relevant neural substrates comes from several studies (e.g., Cabeza, 2001; Kaasinen & Rinne, 2002; Raz et al., 2003; Allen et al., 2005; Raz et al., 2005; Bäckman et al., 2006; Bäckman et al., 2010; King et al., 2013). For example, the aging process is associated with decreased volume in the frontal cortex as well as the caudate and putamen (Raz et al., 2003; Allen et al., 2005; Raz et al., 2005), disruptions in the dopaminergic system (Kaasinen & Rinne, 2002; Bäckman et al., 2006, 2010), and degradations in the white matter tracts connecting the striatum to the frontal cortex (Bennett et al., 2011). These age-related neural changes have been associated with learning deficits in older adults (Kennedy & Raz, 2005; Paquet et al., 2008; Bennett et al., 2011).

Furthermore, the prefrontal and mediofrontal cortex, and the frontostriatal network demonstrate the highest age-related decline (for an overview see Cabeza, 2001). For example, using multimodal imaging measures, Giorgio et al. (2010) found extensive reductions in grey matter volume in aging, and reductions were detected earlier in the frontal cortex. In an fMRI study, Dennis and Cabeza (2011) showed that older adults recruited the medial temporal lobe for sequence learning, and this activation was significantly greater, while striatal activity decreased compared with young adults. The cerebellum has also exhibits similar age-related declines as the striatum, at least with respect to reductions in volume (Luft et al., 1999; Raz et al., 2005). In addition, such degradations in the cortico-cerebellar system are thought to substantially contribute to age-associated deficits in motor and cognitive functioning (e.g., Hogan, 2004; King et al., 2013). Moreover, a DTI aging study by Bennett et al. (2011) found that caudate–dorsolateral prefrontal cortex (dPFC) and hippocampus–dPFC tract integrity were related to sequence learning. The caudate–dPFC tract integrity decreased in the older ages, mediating age-related differences in learning. Thus, the slower and/or lower learning gains of older adults may be manifestations of age-related changes in the structure and functioning of the networks subserving different cognitive and motor functions.

Although age-associated neurodegenerative and neurochemical changes are thought to underlie the decline in cognitive and motor performance, compensatory processes in cortical and subcortical functions, e.g., changed activation patterns, de-differentiation (Cabeza, 2001), de-lateralization (Cabeza, 2002; Nyberg et al., 2003), may allow maintenance of performance (and probably learning) level in older adults (Voelcker-Rehage, 2008). In brain-imaging studies, activation seen early in practice involves generic attentional and control areas—prefrontal cortex, anterior cingulate cortex, and posterior parietal cortex are the main areas considered to perform the scaffolding role (together with changes seen in task-specific areas) (Kelly & Garavan, 2005).

1.3 Cognitive plasticity and cognitive training

In general, diminished learning gains are interpreted as a substantial age-related performance loss in older adults, and a reduction in cognitive and motor plasticity (Voelcker-Rehage, 2008). However, several studies have demonstrated that there is

considerable cognitive plasticity up to very old age, and that cognitive training can result in significant performance improvements on the trained tasks (e.g., Singer et al., 2003; Rebok et al., 2007; Basak et al., 2008; Buschkuehl et al., 2008; Voelcker-Rehage, 2008; Borella et al., 2010; Karbach & Schubert, 2013; Karbach & Verhaeghen, 2014). For example, Singer et al. (2003) investigated performance gains after mnemonic training in a sample of participants aged 75 to 101 years old (eight sessions of training in a performance-enhancing mnemonic technique: Method of Loci). It was found that memory plasticity with the Method of Loci is still preserved in very old age, although to a limited degree. In a study by Pfeifer et al. (2014), no significant difference was found between young and older adults on an associative memory task. This is rather atypical in the recognition memory literature, where poorer associative memory performance in older adults is the norm (Sperling et al., 2003; Naveh-Benjamin et al., 2004; Cohn et al., 2008; Naveh-Benjamin et al., 2009; Edmonds et al., 2012). The authors attribute this finding to the effects of the self-paced learning paradigm used in the study. These results are encouraging, as they suggest that when older adults are given sufficient time to train on the task, their associative retrieval becomes non-significantly different from that of young adults (Pfeifer et al., 2014). Owen et al. (2010) reported the results of a six-week online study in which participants (aged 18 to 60) trained several times each week on cognitive tasks designed to improve reasoning, memory, planning, visuospatial skills, and attention. Significant gains were observed in every one of the cognitive tasks that were trained. Thus, with sufficient training, significant improvements have been demonstrated in both young and older adults on trained tasks (e.g., Singer et al., 2003; Basak et al., 2008; Owen et al., 2010; Schmiedek et al., 2010; Karbach & Verhaeghen, 2014; Rebok et al., 2014).

Even without developing Alzheimer's disease, cognitive decline in healthy aging can have real-life consequences, for example, impaired financial and medical decision-making (Moye & Marson, 2007; Agarwal et al., 2009; Boyle et al., 2012; Strenziok et al., 2014). Yet, there is evidence that protective factors against cognitive decline exist, such as educational attainment and multi-lingualism (Yu et al., 1989; Chertkow et al., 2010; Craik et al., 2010; Strenziok et al., 2014). These factors confer some protection against late-life cognitive decline and even against Alzheimer-related pathology (Landau et al.,

2012; Li et al., 2013; Strenziok et al., 2014). This epidemiological evidence suggests benefits to developing cognitive training into a daily activity as a lifestyle intervention against decline in later life (Strenziok et al., 2014).

Two categories of training have emerged with the specific aim of targeting a single cognitive process (process-based training), or multiple cognitive functions (multidomain training) (Lustig et al., 2009). Process-based approaches involve training individual higher-order cognitive functions, such as inhibition, working memory, and attention, and may include training on multiple individual domains with separate tasks. Multidomain approaches, on the other hand, involve training several cognitive functions within the same task. Multidomain programmes are particularly diverse and include videogame training (e.g., Basak et al., 2008), cognitive-social programmes, and exercise training (e.g., Stuss et al., 2007). Multidomain training is considered an optimal context for cognitive interventions because of the variability in task demands, frequent feedback, stimulus variability, and the engaging and motivating nature of the task (Lustig et al., 2009). Positive effects of multidomain training have been repeatedly reported for younger and older adults (Green & Bavelier, 2003; Basak et al., 2008; van Muijden et al., 2012; for a review see Kueider et al., 2012).

Indeed, the importance of healthy cognitive ageing is not limited to clinical populations, and people of all ages can benefit from engaging in cognitively stimulating activities. The concept that brain training may prevent cognitive decline has been emphasised as a potential opportunity for older individuals to maintain or improve their cognitive function. Developing an effective cognitive training programme can therefore have a practical application and large potential impact for use beyond clinical practice, such as in education, and in healthy aging.

1.4 Cognitive function in middle-aged adults

To date, cognitive training has predominantly been used in older adults as a way to improve cognitive functions which have already declined (Kueider et al., 2012; Lampit et al., 2014). However, there is evidence to suggest that systematically engaging in cognitive activities at an earlier age may actually provide a protective effect against

cognitive decline in later life (Akbaraly et al., 2009; Köhncke et al., 2016; Gow et al., 2017; Chan et al., 2018). In particular, middle-aged adults are underrepresented in the cognitive training literature despite increasing general focus on this age group as a crucial period for cognitive decline or stability (Hertzog et al., 2009). For example, Salthouse (2004) demonstrated that many different cognitive variables are affected by increased age and that negative age-cognition relations appear to begin in early and not late adulthood. Specifically, it has been shown that cognitive decline appears to accelerate after the age of 50, but the onset can already be observed before then (Verhaeghen & Salthouse, 1997; Salthouse, 2004). Verhaeghen and Salthouse (1997) conducted a meta-analysis on 91 studies looking at associations between age and cognitive functions such as speed of processing, working memory, episodic memory, reasoning, and spatial ability. To determine whether the magnitude or pattern of the relationships among variables differed across young and older adulthood, they created two subsamples: one consisting of participants between 18 and 50 years of age, the other consisting of participants 51 years old and older. The analyses comparing individuals over and under the age of 50 demonstrated that negative age-cognition relations were stronger in the older group and significantly so for perceptual speed, reasoning ability, and episodic memory. However, it is important to note that there were significant negative age-cognition relations in all variables in the sample ranging from 18 to 50 years of age. These results clearly indicate that although the influences related to age are stronger after 50, sizable associations were evident in both age ranges, indicating that cognitive performance declines with increased age even before 50.

Furthermore, with regards to cognitive training in young adults, it is possible that the impact of training is reduced when the individual is already functioning at their optimal level of fluid intelligence, which is thought to peak in early to mid adulthood (Horn & Cattell, 1967). Therefore, the effects of cognitive training may only become apparent once fluid intelligence, hence general cognitive functioning, has started to decline. The problem with cognitive training in the elderly, however, is that decline is rapid and pathology may have already set in (Deary et al., 2009), thus, intervention becomes less effective or redundant. Indeed, training studies suggest that cognitive plasticity is reduced, although not completely lost in older adulthood, and therefore the

effect of training declines with age (Brehmer et al., 2007; Shing et al., 2008; Schmiedek et al., 2010; Brehmer et al., 2012; von Bastian & Oberauer, 2014; Zinke et al., 2014).

Notably, complex cognitive demands and lifestyle activities in midlife are linked to decreased risk of cognitive decline in later life (Marioni et al., 2012; Suo et al., 2012; Gow et al., 2017; Chan et al., 2018), yet no past studies have looked at the effects of cognitive training in middle-aged adults. For example, Suo and colleagues (2012) found that occupational managerial experience in midlife (ages 31–64) was the largest predictor of hippocampal grey matter atrophy in older age (ages 70 -90). Occupational managerial experience is thought to be representative of complex mental stimulation due to the role's demand for linguistic competency, verbal comprehension, and verbal memory in successful management. Specifically, they found that work-related complex mental stimulation was associated with a diminished rate of grey matter atrophy in the hippocampus some 20 to 30 years later. The authors suggest that cognitive stimulation in midlife initiates a series of neuroplastic events that continue well into older age. In addition, grey matter volume has been found to reach a plateau around 40-50 years of age and steadily decline thereafter (Courchesne et al., 2000). Findings such as these stress the importance of investigating the effects of cognitive training programmes initiated in midlife, and further research with this age group is needed to clarify the underlying neuroprotective mechanisms. Indeed, middle-age might be the optimal time at which to start cognitive training interventions.

1.5 Cognitive training and transfer

Training cognitive processes such as working memory and other executive functions can improve behavioural performance (e.g., Klingberg, 2010; Morrison & Chein, 2011; Hsu et al., 2014; Flegal et al., 2019; Pappa et al., 2020). However, cognitive training research faces criticisms that effects are often limited to the trained tasks, whereas transfer to untrained tasks is inconsistent (Dougherty et al., 2016; Melby-Lervag & Hulme, 2013; Melby-Lervag et al., 2016; Soveri et al., 2017; Flegal et al., 2019; Pappa et al., 2020). Indeed, the ultimate goal of training as an intervention for age-related cognitive decline is transfer to everyday cognitive functioning (Strenziok et al., 2014). If training does not just improve trained-task performance but also broad cognitive abilities, then even small

effects could lead to important benefits for individuals' everyday functioning, as these improvements would generalise to all sorts of cognitive activities (Hertzog et al., 2009; Schmiedek et al., 2010). Moreover, even small delays or reductions of age-associated cognitive decline could substantially prolong individuals' capacity for leading independent lives (Hertzog et al., 2009; Schmiedek et al., 2010). However, if cognitive training effects are restricted to the trained tasks, such benefits would have little practical significance (Schmiedek et al., 2010). Thus, an important issue to consider is whether benefits transfer to untrained tasks testing the same cognitive function as the trained tasks (near transfer), or lead to a general improvement in the level of cognitive functioning and transfer even to tasks measuring different abilities (far transfer).

1.6 Mechanisms underlying transfer

The efficacy of cognitive training with regards to transfer effects is controversial, and progress in the field requires investigation of factors that optimise transfer of training gains (Lustig et al., 2009; Schmiedek et al., 2010; Flegal et al., 2019). While near transfer effects have been widely reported (e.g., Klingberg et al., 2005; Willis et al., 2006; Jaeggi et al., 2008; Mozolic et al., 2009; Schmiedek et al., 2010; Dunning et al., 2013; Karbach & Verhaeghen, 2014; Caeyenberghs et al., 2016; Emch et al., 2019), evidence of far transfer to other more general cognitive domains, is reported less frequently, and regarded more skeptically (Dahlin et al., 2008; Moody, 2009; Owen et al., 2010; Shipstead et al., 2012; Melby-Lervag & Hulme, 2013; Melby-Lervag et al., 2016; Soveri et al., 2017; Flegal et al., 2019). In other words, near transfer occurs readily when trained and untrained tasks are similar, while far transfer to untrained abilities that share few cognitive and perceptual features with the training has been harder to demonstrate (Strenziok et al., 2014). Indeed, one of the most pressing issues for current and future research is how to improve transfer effects, which are often limited in both breadth and effect size (Lustig et al., 2009; Schmiedek et al., 2010; Flegal et al., 2019). Thus, an understanding of the mechanisms that underlie transfer may aid in the development of more effective training programmes.

Cognitive training involves the repeated practice of exercises that target specific cognitive processes, such as attention, memory, and reasoning. The basic rationale is that

the repetitive use of cognitive functions leads to improved efficiency of the brain processes underlying them. Change in cognitive performance as a result of training is known as cognitive plasticity (Jones et al., 2006; Lovden et al., 2010; Pappa et al., 2020), while experience-induced change in the structure and function of the underlying brain systems is referred to as neuroplasticity (Lovden et al., 2010; Gathercole et al., 2019; Pappa et al., 2020). Indeed, the human brain has a large degree of plasticity, i.e., the capacity to adapt to changing demands by altering its structure (Lovden et al., 2010). An explanation for transfer is that the effects observed following training reflect plasticity in the neural system underpinning the particular function that has been trained; training might therefore lead to durable neuronal changes and improved neural efficiency which should extend to other activities that engage the same processes (Westerberg & Klingberg, 2007; Klingberg, 2010; Takeuchi et al., 2010; Astle et al., 2015; Barnes et al., 2016; Caeyenberghs et al., 2016; Salmi et al., 2018; Gathercole et al., 2019).

1.7 Functional plasticity and cognitive training

The nervous system possesses an intrinsic ability to learn and adapt to new experiences throughout life, and this neural plasticity is manifested both functionally and structurally (Pascual-Leone et al., 2005). Functional imaging studies may provide a window into how an intervention is having its effects (Lustig et al., 2009). Two main changes are categorised as a result of training: an increase in activation as measured by the blood oxygen level dependent (BOLD) signal of an area, indicating increased neural activity in that region; or a decrease in activation of an area, indicating either decreased use, or, more likely, an increase in efficiency (Lustig et al, 2009). Neuroimaging studies investigating the effects of well-controlled cognitive training have yielded heterogeneous findings, providing evidence for both training-induced increases and decreases in cortical activity (Lustig et al., 2009; Karbach & Verhaeghen, 2014). These activation changes are thought to reflect shifts in strategy or processing after training, and increased neural efficiency, respectively (Lustig et al., 2009). When training first begins, prefrontal and parietal regions associated with cognitive control, as well as areas associated with the more specific task demands, are found to become more active (Lustig et al., 2009). If the training is successful and results in improved task performance, then subsequent activity in these regions will decrease, indicating increased neural efficiency (Lustig et al., 2009).

Notably, the association of extra activations with good performance occurs in short-term training (i.e., single-session studies), before the task is well-practiced (Braver et al., 2009; Lustig et al., 2009). By contrast, post-training neuroimaging assessments occur after several sessions of training (i.e., longer-term training), when performance has been relatively optimised (Lustig et al., 2009).

In addition to the activation increases and decreases that have been reported, evidence of functional reorganisation, and more complex dynamics of brain activity changes are also found over the course of training (Klingberg, 2010; Morrison & Chein, 2011; Hsu et al., 2014; Flegal et al., 2019). Activation increases in training studies are explained as added recruitment of brain regions or as response strengthening within a cortical region, and are thought to reflect increases in capacity (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020). Activation decreases, on the other hand, are thought to reflect neural efficiency, i.e., fewer resources are needed to perform the same task after training than before training (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020).

1.8 Structural plasticity and cognitive training

In addition to functional changes, the learning of a novel skill also relies upon anatomical changes in the brain (e.g., Draganski et al., 2004; Pascual-Leone et al., 2005; Scholz et al., 2009; Takeuchi et al., 2010; Sagi et al., 2012; Xiao et al., 2016). Experience-dependent functional plasticity can be accompanied by structural changes in both grey and white matter (e.g., Draganski et al., 2004; Scholz et al., 2009). Structural modifications in grey matter could reflect underlying cellular mechanisms including synaptogenesis and dendritic arborisation as shown in animal studies (e.g., Volkmar & Greenough, 1972; Turner & Greenough, 1985; Knott et al., 2002; Xu et al., 2009; Yang et al., 2009). Further evidence from animal studies suggests that white matter modifications as a result of experience could reflect changes in myelination. For example, activity-dependent myelination has been demonstrated in studies by Demerens et al. (1996) and Ishibashi et al. (2006). Exposure to environmental enrichment has been shown to result in a higher number of unmyelinated and myelinated axons, and glial cells (Markham et al.,

2009; Zhao et al., 2012). In an experiment by Hughes et al. (2018), exposure of mice to sensory enrichment dramatically increased the frequency of new oligodendrocyte integration. The authors suggest that this experience-dependent enhancement of myelination may accelerate information transfer in these circuits and strengthen the ability of axons to sustain activity by providing additional metabolic support (Hughes et al., 2018). These processes by which the brain's structure alters in response to the environment may also underlie changes in cognitive and motor performance as a result of training.

With regards specifically to training, changes have been shown in neuron morphology, as measured by dendritic density (Greenough et al., 1985; Withers & Greenough, 1989), and synaptogenesis (Kleim et al., 2002). Moreover, Kleim et al. (2002) have demonstrated that synapse changes were colocalised to the region within which functional alterations were observed following extended motor skill training. They showed that rats trained to reach and grasp food pellets through a slot have significantly more synapses per neuron within layer V of the caudal forelimb area, compared to control animals. Such data indicate that both functional and structural plasticity can occur simultaneously within the same cortical region, and thus shows that morphological changes contribute to the learning of a skilled motor behaviour (Ungerleider et al., 2002). Additional evidence for the role of morphological changes in motor skill learning comes from recent studies in mice that showed blocking the formation of new oligodendrocytes impairs motor learning (McKenzie et al., 2014; Xiao et al., 2016), suggesting that the generation of new myelin is an important form of plasticity used to modify the properties of circuits in the brain (Hughes et al., 2018). For example, McKenzie et al. (2014) knocked out cells responsible for laying down insulating myelin along axons in the brains of adult mice. The mice lacking the myelin-forming oligodendrocytes were less able to learn a new complex motor skill involving running on a wheel with unevenly spaced bars. Furthermore, Gibson et al. (2014) used optogenetic stimulation of the premotor cortex in awake, behaving mice to demonstrate that neuronal activity promotes oligodendrogenesis, and increases myelination within the deep layers of the premotor cortex and subcortical white matter. They were able to show that this neuronal activity–

regulated oligodendrogenesis and myelination is associated with improved motor function of the corresponding limb.

As discussed, invasive procedures in animals are able to detect structural changes following training (e.g., Greenough et al., 1985; Withers & Greenough, 1989; Kleim et al., 2002; Xu et al., 2009; Xiao et al., 2016). In humans, structural effects can be detected *in vivo* by non-invasive techniques such as magnetic resonance imaging (MRI), which can provide invaluable information on neuroplasticity. Indeed, structural imaging techniques have been used to evaluate changes in the brain as a result of motor skill training (e.g., Draganski et al., 2004; Scholz et al., 2009). The structural changes observed in the human brain after extensive training include modifications in grey matter volume and cortical thickness (e.g., Maguire et al., 2000; Draganski et al., 2004, 2006). Draganski et al. (2004) used voxel-based morphometry to investigate region-specific changes in grey matter in participants that received training in a complex visuomotor skill (i.e., juggling). They found that participants in the juggling group demonstrated a significant bilateral expansion in grey matter in the mid-temporal area and overlying the left posterior intraparietal sulcus. In addition, there was a close relationship in these regions between the structural grey matter changes and juggling performance. These findings indicate that training-induced behavioural plasticity is also reflected at a structural level (Draganski et al., 2004).

Diffusion MRI provides unique insight into tissue microstructure and is arguably the most promising candidate for *in vivo* quantification of structural brain changes (Zhang et al., 2012). Alterations in brain microstructures are often the precursors of volumetric changes (Kodiweera et al., 2016). This means that microstructural imaging biomarkers, such as those derived from diffusion MRI, are potentially more sensitive and altered earlier than the structural changes found with traditional volumetric analyses using T1-weighted voxel-based morphometry (Kodiweera et al., 2016). Currently, the standard diffusion MRI technique is diffusion tensor imaging (DTI) (Basser et al., 1994). DTI is sensitive to the displacement and hindrance of water molecules resulting from local tissue boundaries (Scholz et al., 2009; Lerner et al, 2014). DTI provides simple markers, such as mean diffusivity (MD) and fractional anisotropy (FA), which are widely used as measures of microstructure in the brain and serve respectively as indices of tissue

density, and fibre organisation/directionality (Pierpaoli & Basser, 1996). The structural remodelling of brain tissue leads to a change in its water diffusion properties (i.e., a change in the tissue boundaries leads to a change in the displacement and hindrance of water molecules, which can be measured with DTI) (Assaf & Pasternak, 2008; Barazany et al., 2009; Blumenfeld-Katzir et al., 2011; Sagi et al., 2012). These changes in diffusion properties are thought to be the result of an increase in tissue density (due to, for example, reshaping of neuronal or glial processes), or enhancement of tissue organisation (for example, strengthening of axonal or dendritic processes) (Assaf & Pasternak, 2008; Sagi et al., 2012).

Although conventional diffusion MRI techniques such as DTI have been widely used as an indicator of white matter integrity in studies of ageing and training (e.g., Engvig et al., 2012, Lovden et al., 2010; Metzler-Baddeley et al., 2017), the DTI model has two key limitations. First, diffusion indices such as FA and MD are average measurements across a voxel from multiple different compartments, including both intracellular and extracellular spaces that are likely to have varying shapes, orientations, and diffusivities (Kodiweera et al., 2016). Therefore, DTI is sensitive to tissue microstructure but lacks specificity for individual tissue features (Pierpaoli et al., 1996; Zhang et al., 2012; Jones et al., 2013). Hence, a change in these measurements cannot be attributed to specific changes in tissue microstructure (Pierpaoli et al., 1996; Zhang et al., 2012; Jones et al., 2013; Jelescu et al., 2016). For example, a reduction in FA may be caused by a reduction in neurite density, an increase in the dispersion of neurite orientation distribution, as well as various other tissue changes (Beaulieu, 2009; Zhang et al., 2012). Second, the diffusion indices assume fibre bundles are parallel, and thus are inaccurate in microstructural environments containing crossing fibres as found in areas of complex axonal or dendritic architecture (Jeurissen et al., 2013; Jones et al., 2013; Vos et al., 2012). Indeed, crossing fibres are thought to occur in around 90% of the brain's white matter (Jeurissen et al., 2013). More recently developed models of diffusion MRI are designed to overcome these issues.

Neurite orientation dispersion and density imaging (NODDI) is a form of diffusion MRI that can be used to estimate the microstructural complexity of dendrites and axons

(Zhang et al., 2012). Zhang et al. (2012) proposed a model of microstructure consisting of individual compartments for three different tissue environments: intraneurite, extraneurite, and cerebrospinal fluid (CSF). The NODDI model separates the signal arising from these three different tissue environments: intracellular (characterised by restricted diffusion), extracellular (characterised by hindered diffusion), and CSF (characterised by unrestricted diffusion) (Figure 1.1). Significantly, it is an improvement on other diffusion MRI techniques due to the ability to differentiate between these three different (and more specific) microstructural indices. For example, results have demonstrated that NODDI generates sensible measures of neurite density and orientation dispersion, thereby disentangling two key contributing factors to FA and enabling the analysis of each factor individually (Zhang et al., 2012). This means that NODDI indices are less ambiguous microstructural interpretations, in addition to being more likely to detect small-scale changes as a result of cognitive training than alternative structural MRI techniques.

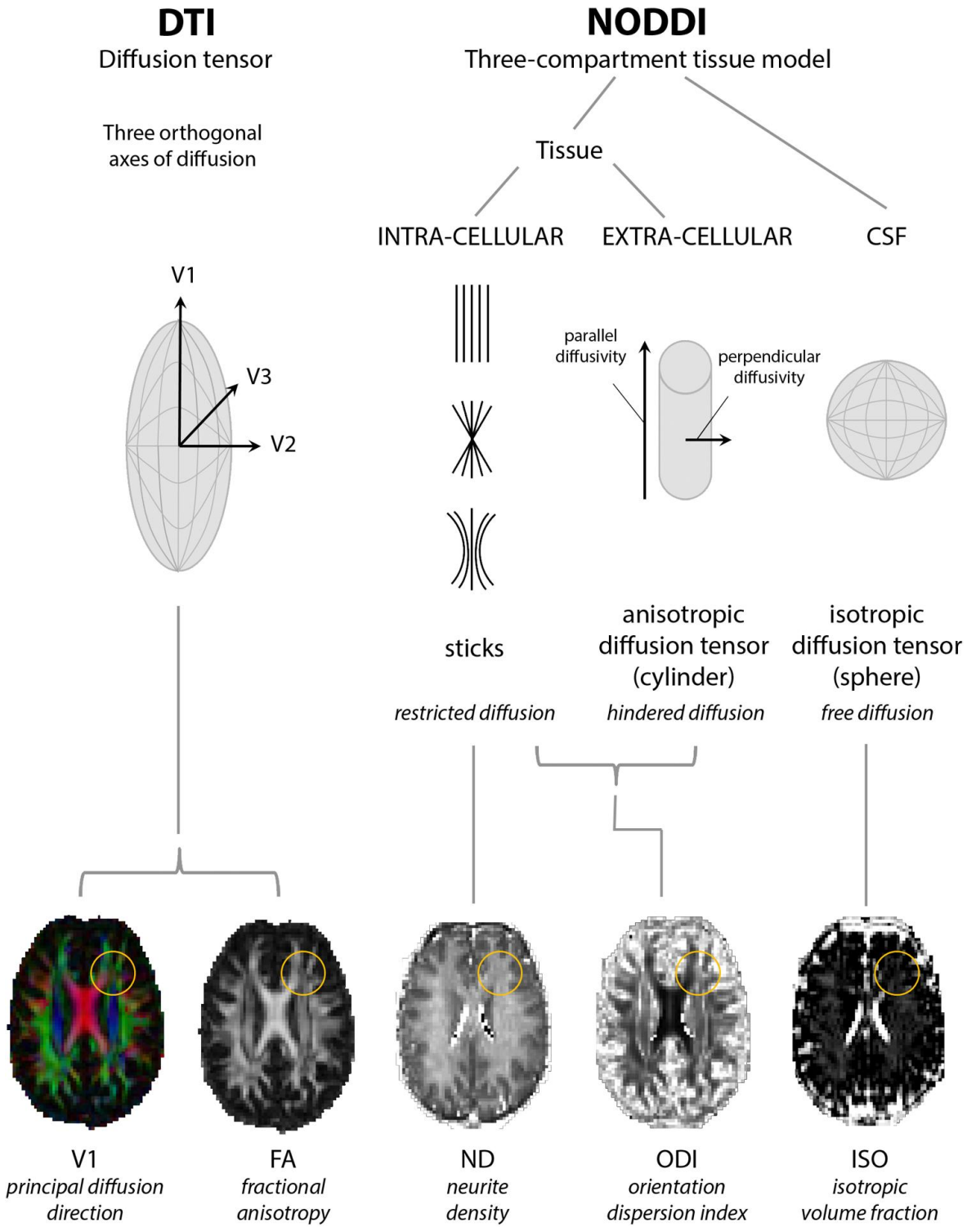


Figure 1.1. The NODDI technique and how it differs from traditional DTI. In DTI, a diffusion tensor models three orthogonal axes of diffusion (V1, V2, V3), from which FA and MD can be estimated. NODDI models diffusion according to three compartments: restricted diffusion in the intracellular compartment, hindered diffusion in the extracellular compartment, and free diffusion in CSF. From this model, parameter maps representing the neurite density index (NDI) and orientation dispersion index (ODI) can be estimated. Yellow circles highlight a region where changes in FA can be accompanied by changes in both NDI and ODI. From Rae et al., 2017.

1.9 Experiment 1: Perceptual-cognitive-motor training in middle-aged adults

In a first experiment, we investigated the functional and structural correlates of short-term training on a novel and complex perceptual-cognitive-motor task in healthy middle-aged adults (40-50 years old). As discussed, middle-age might be the optimal time at which to start training interventions, given that cognitive function, motor skill learning ability, and grey matter volume appear to start declining around this age (e.g., Gershon, 1978; Courchesne et al., 2000; Voelcker-Rehage & Wilimczik, 2006; Janacsek et al., 2012). Indeed, training in the elderly may be less effective as decline is rapid and pathology may have already set in (Deary et al., 2009), whereas the impact of training in young adults may be reduced when the individual is already functioning at their optimal level. As such, we sought to investigate training in middle-aged adults. This is the first study to examine neuroplasticity in a complex perceptual-cognitive-motor task in this age group.

The perceptual-cognitive-motor (PCM) task that we used in our study was adapted from Bennett and colleagues (2018). It is a computer-based task that requires the continuous identification of relevant from irrelevant stimuli, planning and selection of appropriate actions from more than one available option, and the execution of actions under time constraints. Successful completion of the PCM task requires motor as well as cognitive processes (including decision making, working memory, attention, and pattern recognition). Motor skill acquisition in particular is thought to be the integrative product of multiple functions and neural mechanisms, each contributing to a different aspect of learning (Hikosaka et al., 2002). Therefore, motor skill training might be a promising avenue to prevent decline in later life. Consequently, we decided to use the PCM task as it is multidomain, including motor, cognitive, and perceptual elements, and this form of training has been shown to be particularly effective in improving cognitive function (e.g., Green & Bavelier, 2003; Basak et al., 2008; Lustig et al., 2009; van Muijden et al., 2012).

Motor skill training has been extensively studied in young adults and is thought to follow several distinct stages including an early, fast learning stage in which considerable improvement in performance can be seen within a single training session; and a later, slow learning stage in which further gains can be observed across several sessions of practice (e.g., Nudo et al., 1996; Karni et al., 1998; Ungerleider et al., 2002; Doyon et al.,

2003; Krakauer et al., 2005; King et al., 2013). In addition, the neural substrates underlying motor skill learning have been extensively characterised (for reviews see: Grafton et al., 1995; Ungerleider et al., 2002; Doyon et al., 2003; Penhune & Steele, 2012; King et al., 2013). The brain regions involved in motor skill learning differ depending on whether it is the early or late phase of training, and on the nature of the cognitive processes required (e.g., learning by trial and error, implicit learning, etc.) (Doyon et al., 2003; Coynel et al., 2010).

The early, fast learning phase of motor skill acquisition (i.e., session 1) elicits widespread activation in subcortical areas (basal ganglia, cerebellum, hippocampus), as well as relevant cortical areas (supplementary motor area: SMA, preSMA, primary motor cortex: M1, premotor cortex, anterior cingulate, inferior parietal regions, and dorsolateral prefrontal cortex: dPFC) (e.g., Sakai et al., 1998; Doyon & Ungerleider, 2002; Ungerleider et al., 2002; Floyer-Lea & Matthews, 2005; Albouy et al., 2008; Albouy et al., 2012). The pattern of activation in these different structures changes as a function of learning (King et al., 2013). For example, activity in the striatum increases while activity in the cerebellum decreases with training (Grafton et al., 1994; Grafton et al., 1995; Doyon et al., 1996; Penhune & Doyon, 2002; Ungerleider et al., 2002; Doyon et al., 2003). The cerebellum is especially critical for early motor sequence learning, not only for error detection and correction, but also for the acquisition of sequence knowledge (e.g., Seidler et al., 2002; Tamás Kincses et al., 2008; Doyon et al., 2009; Steele & Penhune, 2010; King et al., 2013). Cerebellar activity decreases with practice and may become undetectable when the sequential movements are well learned (Grafton et al., 1994; for review, see Doyon & Ungerleider, 2002). Notably, researchers have also reported striatal activations in the early phase of motor sequence learning, when participants have to rely more strongly on the use of cognitive strategies and working memory (Jenkins et al., 1994; Jueptner et al., 1997; Toni et al., 1998; Ungerleider et al., 2002). Further, the ability to perform complex problems has been shown to be initially supported by extensive attentional and strategic resources, which engage a prefrontal, orbitofrontal, and anterior cingulate network (Minati & Sigala, 2013). With practice, these resources are gradually replaced by access to long term working memory for familiar material, which engages predominantly occipital and medial temporal areas (Minati & Sigala, 2013). Regions such

as the sensorimotor territory of the basal ganglia, ventrolateral prefrontal cortex (vPFC), intraparietal sulcus, precuneus, and inferior parietal area, show increased activation during later stages of motor sequence learning, while the cerebellum, anterior cingulate, premotor cortex, and inferior parietal regions, show significant reductions in activity (Doyon, 1997; Sakai et al., 1998; Doyon & Ungerleider, 2002; Ungerleider et al., 2002; Doyon et al., 2003; Lehéricy et al., 2005; King et al., 2013). Therefore, distinct cerebellar–basal ganglia–cortical networks are engaged during the early and late phases of motor skill training, and different regions are involved depending on the cognitive processes required (Coynel et al., 2010; King et al., 2013).

Doyon and Ungerleider (2002) have proposed a framework for interpreting this complex pattern of brain activation underlying motor skill learning. At the heart of this framework operate two loop circuits, a cortico-striatal and a cortico-cerebellar system, which are both recruited and operate in parallel during the fast learning stage (Figure 1.2). Specifically, early in the learning phase the following structures are recruited: the striatum, cerebellum, motor cortical regions (e.g., premotor cortex, SMA, preSMA, anterior cingulate), as well as prefrontal and parietal areas. Dynamic interactions between these structures are believed to be critical for establishing the motor routines necessary for learning new skilled motor behaviours (Doyon & Ungerleider, 2002; Ungerleider et al., 2002; Doyon et al., 2003; Doyon & Benali, 2005).

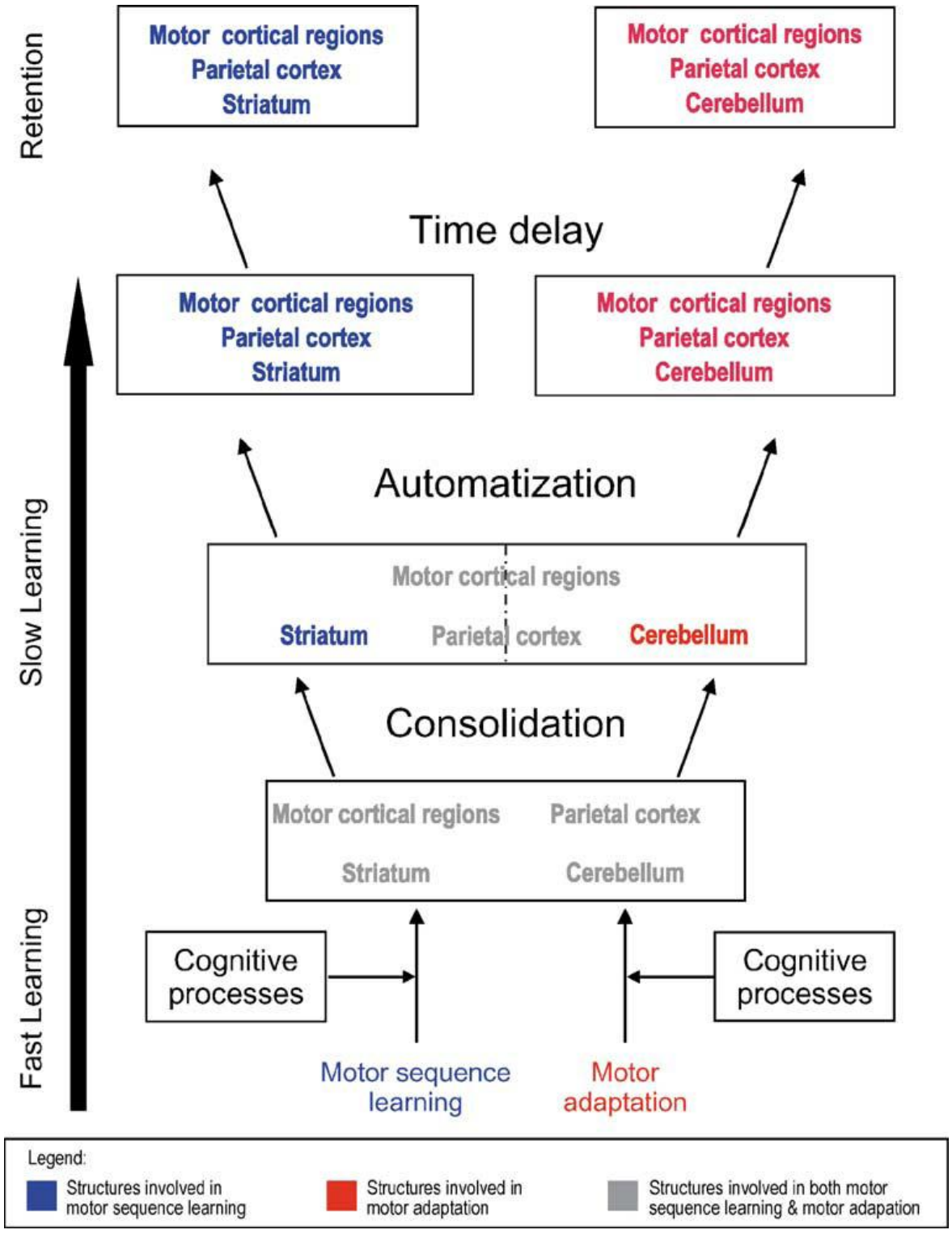


Figure 1.2. Model of motor skill learning. Cortico-striatal and cortico-cerebellar systems are both recruited during the fast learning stage of motor skill training. Both motor sequence and motor adaptation tasks recruit similar cerebral structures early in the learning phase: the striatum, cerebellum, motor cortical regions (e.g., premotor cortex, SMA, pre-SMA, anterior cingulate), as well as prefrontal and parietal areas. As learning progresses after consolidation in the slow learning phase, however, representational changes can be observed. From Doyon et al., 2003.

Similarly, in a model proposed by Hikosaka et al. (2002), two loop circuits are recruited which specialise in learning spatial and motor features of sequences independently, and in different coordinates (Figure 1.3). Learning spatial coordinates is supported by a frontoparietal-associative striatum-cerebellar circuit, while learning motor coordinates is supported by an M1-sensorimotor striatum-cerebellar circuit. For example, for simple reaching to a visual target, the target position is first coded in spatial coordinates — centred around the eye, head, or object — and then converted to motor coordinates — such as joint angles or muscle forces. The Hikosaka et al. model suggests that this coordinate transformation process depends on the SMA, pre-SMA, and premotor cortices. Importantly, it is argued that learning spatial coordinates is usually explicit and faster as it may be accompanied by increased attention or working memory, putatively involving prefrontal and parietal cortical regions (Miller & Cohen, 2001). By contrast, motor coordinates are usually processed implicitly and require minimum attention, therefore they are slowly acquired during learning. Both models share the view that motor skill learning involves interactions between distinct cortical and subcortical structures, crucial for the unique cognitive and control demands associated with skill acquisition (Doyon & Ungerleider, 2002; Hikosaka et al., 2002).

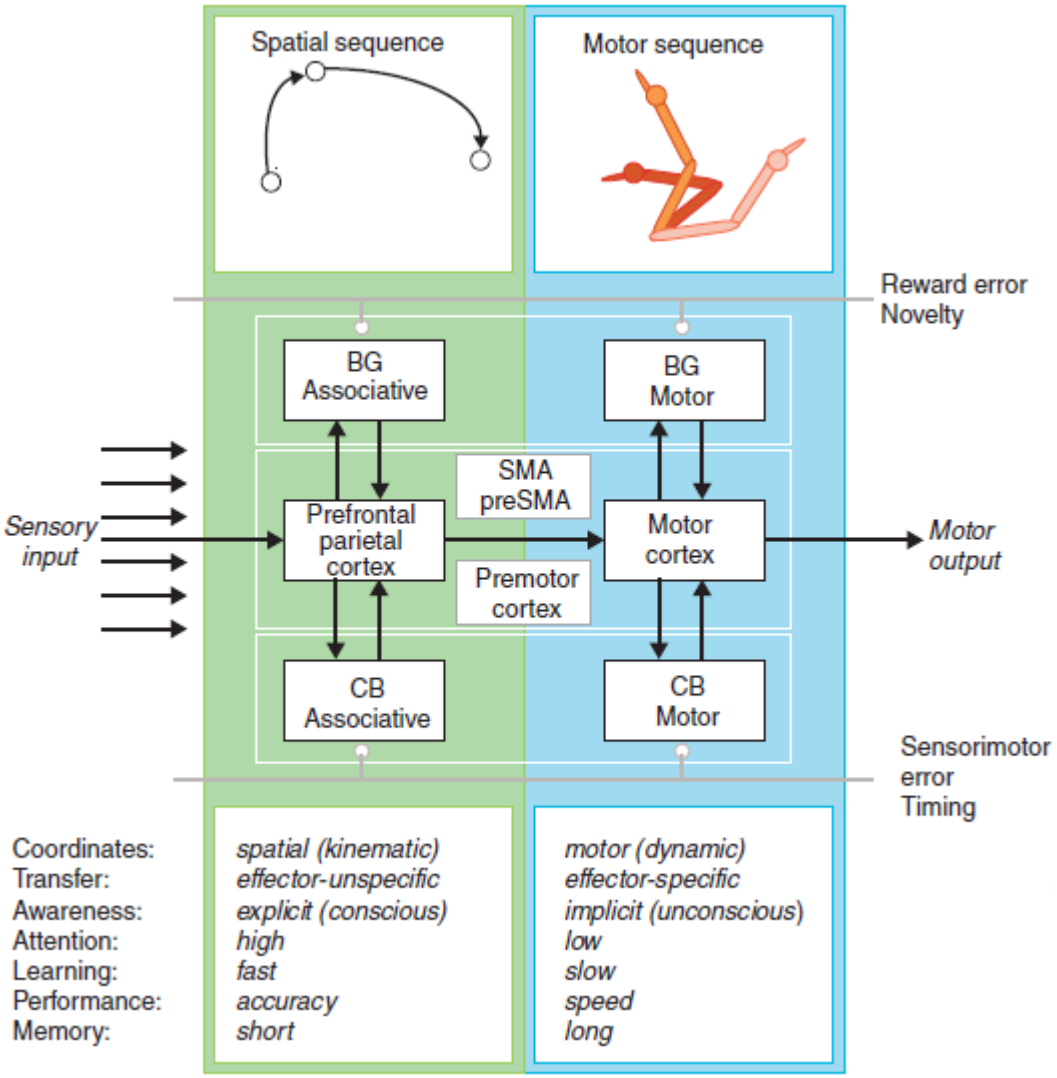


Figure 1.3. Scheme of motor skill learning. A sequence of movements is represented in spatial coordinates and motor coordinates. The left side of the figure is characteristic of the spatial sequence, the right side is characteristic of the motor sequence. Learning spatial coordinates is supported by a frontoparietal-associative striatum-cerebellar circuit, while learning motor coordinates is supported by an M1-sensorimotor striatum-cerebellar circuit. The coordinate transformation process depends on the SMA, pre-SMA, and premotor cortices. Spatial sequences are usually processed explicitly and therefore quickly acquired, but require maximum attention. Motor sequences are usually processed implicitly and therefore slowly acquired, but require minimum attention. BG = basal ganglia and CB = cerebellum. From Hikosaka et al., 2002.

For the current experiment, we sought to characterise functional plasticity at the early stage of training, and as such, we used functional magnetic resonance imaging (fMRI) to investigate changes in activation over 1 session of practice. Therefore, we expected training-induced increases in activity in cognitive and motor networks as per the

early learning phase of motor skill acquisition in the Doyon and Ungerleider (2002) and Hikosaka et al. (2002) models. Specifically, we expected PCM learning to be supported by increased activity in the striatum, cerebellum, hippocampus, parahippocampus, SMA, preSMA, M1, premotor cortex, anterior cingulate, dPFC, orbitofrontal cortex (oPFC), and inferior parietal cortex. In addition, we sought to link functional plasticity as a result of training, with underlying structure. Diffusion imaging provides a promising opportunity to image the structural underpinnings associated with learning and task performance. Thus, we used both DTI and NODDI to analyse microstructural variation in grey and white matter in relation to training outcome.

1.10 Experiment 2: Working memory, attention, and executive function training in middle-aged adults

In a second experiment, we tested the effectiveness of longer-term cognitive training (4-6 weeks) in improving overall cognitive function in healthy middle-aged adults (40-50 years old). This age group are not performing at their peak, but still have time to implement lifestyle changes and training programmes that may improve their cognitive resilience and quality of life in older age. In addition, we examined how the brain responds to this training and investigated any resulting structural and functional brain changes. This is the first study to examine longer-term cognitive training and neuroplasticity in middle-aged adults.

The cognitive training programme in this study included several tasks targeting working memory, attention, and other executive functions, such as inhibition. Working memory provides temporary storage and manipulation of information essential for complex cognitive tasks such as language comprehension, learning, and reasoning (Baddeley, 1992). The classic working memory model consists of three components: an attentional control system or “central executive”, responsible for the regulation of cognitive processes, i.e., executive functions; a visuospatial sketchpad which manipulates visual images; and a phonological loop which manipulates speech-based information (Baddeley, 1992; Miyake et al., 2000). Furthermore, 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; and 3.

working memory updating, i.e., modifying the content of working memory according to incoming information (Miyake et al., 2000; Nee et al., 2013; Pappa et al., 2020). Therefore, we aimed to target these particular processes in our training programme with a view to improving broad cognitive abilities, thus increasing the probability of transfer to untrained tasks.

Substantial benefits of working memory training have been widely reported (e.g., Klingberg et al., 2005; Jaeggi et al., 2008; Schmiedek et al., 2010; Dunning et al., 2013; Caeyenberghs et al., 2016; Emch et al., 2019). For example, Caeyenberghs et al. (2016) compared adaptive working memory training to non-adaptive training in younger adults aged 19-40 years old. Adaptive working memory training led to significant improvement on untrained working memory tasks (near transfer), and generalisation to tasks of reasoning and inhibition (far transfer), compared to the non-adaptive group. Recent work by Emch and colleagues (2019) used an adaptive verbal working memory training (N-back task) in adults aged 50–65 years old. The active control group performed a non-adaptive low-level of the same verbal working memory training (fixed level of 1-back task). They found significant near transfer to another verbal working memory task (HAWIE-R digit span forward task) in the adaptive group compared to the active control, indicating that the training generally improved performance in this cognitive domain (far transfer effects were not tested for in this study). Indeed, working memory training gains have been found at all ages from the preschool years through to late adulthood (Wass et al., 2012; Melby-Lervag & Hulme, 2013; Sonuga-Barke et al., 2013; Karbach & Verhaeghen, 2014; Gathercole et al., 2019). Thus, working memory training may lead to fundamental improvements in a cognitive system critical for everyday functioning across the lifespan (Baltes et al., 1999; Schmiedek et al., 2010; Gathercole et al., 2019).

Studies targeting attention that require participants to inhibit interference or switch attention have also produced reliable results (e.g., Willis et al., 2006; Bherer et al., 2008; Mozolic et al., 2009). For example, Mozolic and colleagues (2009) investigated the effects of a cognitive training intervention aimed at helping individuals suppress irrelevant auditory and visual stimuli. Participants received 8 weeks of either the attention training programme or an educational lecture control programme. Participants

in the intervention programme showed significantly larger improvements than the control group in untrained domains such as processing speed and dual-task completion, demonstrating the utility of attention training for improving cognitive function.

Furthermore, Mowszowski et al. (2016) showed that executive function training including planning, reasoning, and problem-solving resulted in maintained improvements up to ten years, with accompanying evidence of far transfer to general cognitive abilities. Willis et al. (2006) showed that training conferred sustained benefit in cognitive function for participants. Specifically, episodic memory, speed of processing, and divided attention training predominantly enhanced performance in these specific functions (near transfer), while improvements associated with executive function training generalised to other cognitive domains (far transfer). Moreover, these effects were maintained 5 years after the initiation of the intervention. Therefore, given that attention, executive function, and working memory training seem to be particularly beneficial and can result in widespread transfer (Schmiedek et al., 2010; Karbach & Verhaeghen, 2014; Pappa et al., 2020), we focused on a training intervention that targets these domains.

To measure transfer of training-related cognitive improvements, we used the Raven Advanced Progressive Matrices (RAPM: Raven & Court, 1998), an associative learning task (PAL), an associative memory task (PAR), and a working memory task (N-back). The RAPM was used to investigate far transfer by measuring each participant's fluid intelligence before and after cognitive training. Fluid intelligence refers to the ability to solve novel reasoning problems independently of previously acquired knowledge (Cattell, 1963; Jaeggi et al., 2008). It is critical for a wide variety of cognitive activities, and is considered one of the most important factors in learning (Cattell, 1963; Jaeggi et al., 2008). Previous research has demonstrated that fluid ability can benefit from cognitive training (e.g., Basak et al., 2008; Jaeggi et al., 2008; Stine-Morrow et al., 2008; Karbach & Kray, 2009; Buschkuehl & Jaeggi, 2010; Strenziok et al., 2014). For example, Jaeggi and colleagues (2008) showed that intense training with a demanding working memory task (dual N-back, spatial and verbal) led to generalised improvements of fluid intelligence as measured by the RAPM. In the Jaeggi et al. (2008) study, transfer resulted even though

the trained task (dual N-back) was very different from the intelligence test itself (RAPM) (i.e., far transfer).

Pair-associative learning (PAL) and pair-associative retrieval (PAR) tasks were used to measure far and near transfer effects, respectively. Associative learning refers to the binding of objects commonly seen together in the environment to become linked in our mind (Curtis & D'Esposito, 2003; Ranganath, 2006; Ciaramelli et al., 2008; Albright, 2012; Pfeifer et al., 2014, 2016). Associative memory involves the retrieval of the associated objects from memory to guide future behaviour, and draws on multiple cognitive mechanisms that include bottom-up perception and top-down imagery, as well as attention, and working memory (Curtis & D'Esposito, 2003; Ranganath, 2006; Ciaramelli et al., 2008; Albright, 2012; Pfeifer et al., 2014, 2016). The result of these processes is an experience of declarative memory, i.e., the conscious recollection of associated stimuli or events that constitute our factual knowledge (semantic memory), or personal experiences (episodic memory) (Curtis & D'Esposito, 2003; Ranganath, 2006; Ciaramelli et al., 2008; Albright, 2012; Pfeifer et al., 2014, 2016). There are previous reports of transfer to associative memory from cognitive training (Schmiedek et al., 2010; Rudebeck et al., 2012; Toril et al., 2016; Flegal et al., 2019). For example, Flegal and colleagues (2019) used an adaptive working memory training programme and found transfer to an untrained associative memory task (Object-Location Association task).

The N-back task was used to measure training-induced near transfer effects. The N-back was originally developed by Kirchner (1958) as a visuospatial task, and by Mackworth (1959) as a visual letter task, for measuring working memory. The task involves various cognitive processes, such as working memory updating, which includes the encoding of incoming stimuli, the monitoring, maintenance, and updating of the sequence to store the last *N* elements, and stimulus matching (matching the current stimulus to the one presented *N* positions back in the sequence) (Jaeggi et al., 2010; Schmiedek et al., 2014; Pergher et al., 2018; Pappa et al., 2020). In addition, it involves a number of core executive functions besides working memory, such as inhibitory control and cognitive flexibility, problem solving, decision making, and selective attention (Kane & Engle, 2002; Pergher et al., 2018). Thus, the N-back task was selected as a test of near

transfer as it includes the working memory, attention, and inhibition components of the cognitive training programme used in this study.

In addition to investigating the behavioural effects of cognitive training, we assessed training-induced functional changes. The N-back and PAR transfer tasks were selected for task-based fMRI. The N-back task has been shown to consistently activate regions involved in working memory (i.e., fronto-parieto-cerebellar circuitry and subcortical regions such the striatum) (Wager & Smith, 2003; Owen et al., 2005; Rottschy et al., 2012; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019). Key regions forming the neural basis of working memory comprise the vPFC; dPFC; frontal pole; posterior parietal cortex; inferior temporal cortex; striatum; and cerebellum (Curtis & D'Esposito, 2003; Wager & Smith, 2003; Ranganath et al., 2004; Ranganath, 2006; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019; Pappa et al., 2020). In addition, the PAR task also engages the working memory regions discussed above (Wager & Smith, 2003; Owen et al., 2005; Rottschy et al., 2012; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019). Thus, the working memory training in our programme was expected to engage these areas, thereby inducing functional plasticity that would translate to an improvement on untrained tasks that require the same processes (i.e., the N-back and PAR tasks). We therefore expected training-related changes in activity in vPFC, dPFC, frontal pole, superior parietal cortex, inferior parietal cortex, inferior temporal cortex, striatum, and cerebellum during performance of the N-back and PAR tasks.

To further investigate the neural mechanisms involved in transfer of training gains, we used the NODDI technique in addition to traditional DTI. Thus, we examined the underlying microstructural alterations that may occur following cognitive training, thought to indicate experience-dependent plasticity. Indeed, it's suggested that cognitive training results in durable changes in neural infrastructure supporting transfer of training (Schmiedek et al., 2010; Strenziok et al., 2014). If cognitive training can enhance cognitive resilience and improve, maintain, or reduce decline in cognitive function, this could potentially have an enormous public health impact (Gates & Sachdev, 2014; Corbett et al., 2015). An understanding of the neural mechanisms underlying training-induced

plasticity that may drive improvement in task performance, could aid in the development of effective cognitive training programmes.

This thesis aimed to investigate how the brain responds to cognitive training in healthy middle-aged adults, with a view to improving cognitive function and potentially preventing age-related decline in later life. We sought to characterise both functional and structural neuroplasticity as a result of training with task-based fMRI, and diffusion-weighted MRI. If cognitive training results in improved cognitive function, then significant gains in performance should be observed for the training tasks. Specifically, we should see improvements on the PCM training task in the first experiment, and on the working memory, attention, and inhibition training tasks in the second experiment. Furthermore, if training results in an improvement in the general cognitive functioning of middle-aged adults, then we should observe significantly improved performance on the transfer tasks. We also predicted both structural and functional brain changes as a result of training, indicating neuroplastic events that may underlie improved cognitive function and successful transfer of training gains to untrained tasks. If cognitive training is effective at inducing brain changes and improving broad cognitive abilities in middle-aged adults, then this may be an important step towards designing large-scale interventions that can have a positive impact on healthy cognitive ageing.

Chapter 2: Methods

2.1 Perceptual-cognitive-motor training in middle-aged adults: Behavioural and MRI experiment (Chapter 3)

The aim of this experiment was to investigate the functional and structural correlates of short-term training on a novel and complex perceptual-cognitive-motor task in healthy middle-aged adults (40-50 years old). We sought to characterise functional plasticity at the early stage of training, and as such, we used functional magnetic resonance imaging (fMRI) to investigate changes in activation over 1 session (160 trials = 31 minutes of training). In addition, we sought to link functional plasticity as a result of training, with underlying structure. Thus, we used both DTI and NODDI to analyse microstructural variation in grey and white matter in relation to training outcome.

2.1.1 Participants

A sample size calculation was performed using the G*Power calculator v. 3.1.9.2 (Faul et al., 2007). The sample size calculation for the current study was based on the effect size results of Uji, Bennett, Hayes, and Ford (unpublished data) demonstrating that practice at the perceptual-cognitive-motor task led to improved performance for the training group with a large effect size of $\eta_p^2 = .49$. The current study was therefore powered to detect a large effect size ($t = 1.73$) and required a total sample size of 21. Twenty one participants would allow the study to detect differences at a significance level of 0.05 with a 95% probability. Twenty-two middle-aged adults between 40 and 50 years old took part in this experiment after giving informed, written consent. Participants were compensated for their time. They were recruited from the University of Brighton and from the local community using e-mail advertisement and via posters in the local area. All participants had normal or corrected-to-normal vision and were right–hand dominant. The participants had no history of psychiatric or neurological illness, or brain injury. Participants also had no history of alcohol or drug use disorders. Participants were not taking prescribed medications at the time of the experiment. All participants were carefully screened for MRI contraindications, such as pacemakers, metal within the body, or claustrophobia. Due to low task-engagement during the session, one participant was excluded, leaving 21 participants in the final sample (female: $n = 11$; age: $M = 44.67$ years, $SD = 3.23$) in a within-subjects study design. The mean number of years of education for

the sample was 18.24 (*SD* = 2.72). The study was reviewed and approved by the Brighton and Sussex Medical School Research Governance and Ethics Committee.

2.1.2 Procedure

All participants underwent one MRI scanning session. Participants received written instructions for the perceptual-cognitive-motor task (Appendix I, pg. 278) and saw an example of the task on a computer screen just prior to starting the scanning session. Participants then underwent the scanning procedure (Figure 2.1), during which they first habituated to the scanner and MRI computer mouse used for the task by completing 8 practice trials (~1min) of the perceptual-cognitive-motor task. They used a fibre-optic MRI-compatible mouse (FOM-2B-10B, NAtA technologies, Canada) to control the white cursor on the screen, such that it reached the red target while avoiding the green objects. They then completed 80 trials (~15min) of the task in a pre-training phase while undergoing fMRI scanning. Following this, they completed 72 trials during a training phase while undergoing structural and diffusion scanning. The training phase was divided into two parts: 24 trials (~6min) were completed during a T1 structural scan, and 48 trials (~9min) were completed during a NODDI/DTI scan. Finally, they repeated 80 trials (~15min) of the task during a post-training phase while undergoing fMRI scanning.

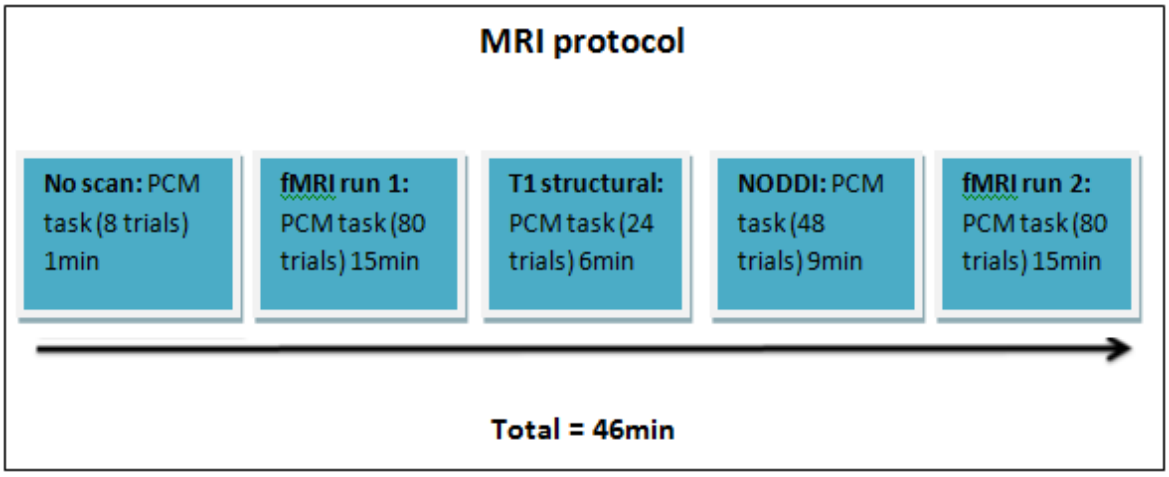


Figure 2.1. MRI protocol: participants completed 8 practice trials of the PCM task (no scan, 1min), followed by 80 trials (fMRI scan, 15min), then 24 trials (T1 scan, 6min), then 48 trials (NODDI/DTI scan, 9min), and finally, they completed 80 trials (fMRI scan, 15min).

Perceptual-cognitive-motor task

The perceptual-cognitive-motor (PCM) task (Figure 2.2) was adapted from Bennett and colleagues (2018). It is novel and computer-based, requiring participants to move a cursor to a target while avoiding random moving objects, and requires the selection of appropriate actions to execute from more than one available option.

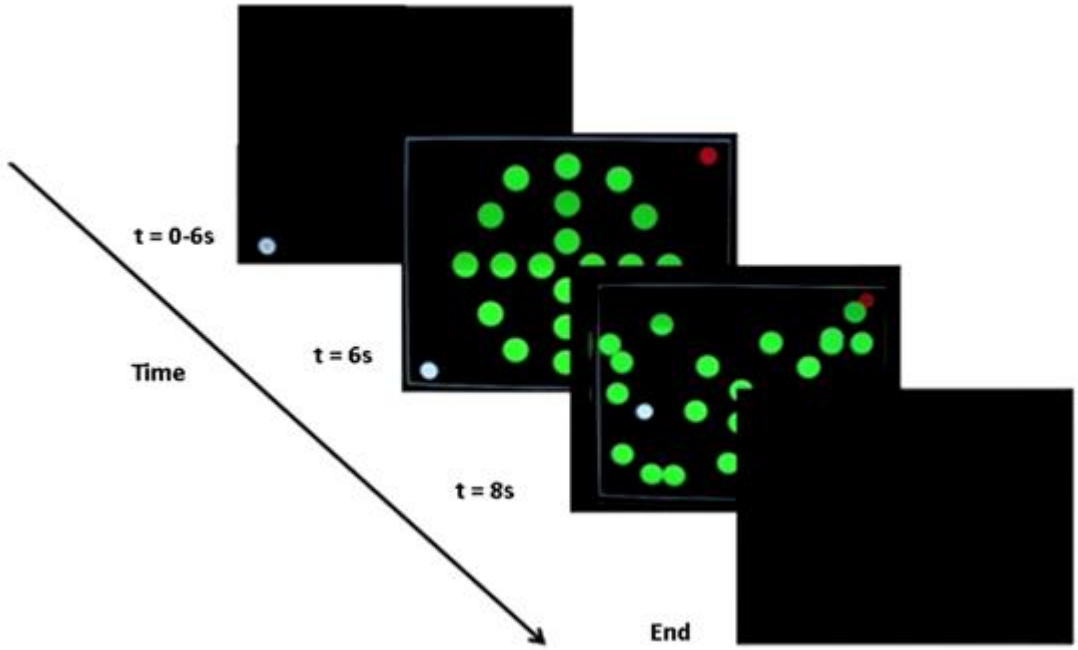


Figure 2.2. PCM task: the goal is to move the white cursor to the red target while avoiding a number of green circles that move around on the screen. The onsets of each phase of the trial are shown; t denotes time in the trial. Adapted from Bennett et al., 2018.

The task goal was for participants on each trial to move the cursor (represented by a white circle on the screen) from the bottom corner of the computer screen to a red circle target located in the diagonal corner of the screen. The white cursor would appear in either the bottom left or bottom right of the screen. The starting positions of the white cursor changed pseudo-randomly from trial-to-trial, but with an equal number of these two possible starting positions across the experiment. To achieve the task goal, participants had to move the white cursor to the red target while avoiding a number of

green objects (*N* = 20 circles) that were moving around the screen on pseudo-randomised linear trajectories. After 6s the group of 20 green circles (2x diameter of the white cursor) appeared onscreen. When the green objects started their linear movement (after 8s), participants were able to move the white cursor freely on the screen with the goal of reaching the red target. The green objects moved around on the screen with pre-programmed linear trajectories. There were four different movement patterns for the green objects that each began with the same start positions. A total of eight movement patterns across the two starting positions were created by mirroring the original four movement patterns relative to either of the two starting positions of the white cursor in an attempt to have equal task difficulty on each starting position. Participants were unaware of either the gain relationship of the white cursor movement or the number of different movement patterns of the green objects. If the white cursor touched one of the green objects, the trial ended and was deemed unsuccessful. If the white cursor reached the red target, the trial ended and was recorded as successful. Participants were not restricted in their response times in each trial, therefore each trial time was recorded, and the experiment continued until all trials had been completed. The MRI-compatible computer mouse was held by participants in their right hand and was moved on an MRI-compatible tray and mouse pad to control the cursor location on the computer screen.

2.1.3 MRI data acquisition

fMRI

Imaging data were collected using a Siemens Magnetom Avanto 1.5-T MRI scanner (Siemens, Erlangen, Germany) with a 32-channel phased-array head coil, tuned to 66.6 MHz. The PCM task was presented on an in-bore rear projection screen, at a viewing distance of approximately 45 cm, subtending 5° of visual angle. Stimuli were delivered using Cogent 2000 v1.32 running under MATLAB R2015a (The MathWorks, Inc., Natick, MA). Time-course series of the two runs were acquired using a T2*-weighted echo planar imaging (EPI) sequence, obtaining 354 volumes during run 1 of the PCM task (pre-training) and 354 volumes during run 2 of the PCM task (post-training). Each volume consisted of 34 axial slices oriented 30° to the AC–PC line and covering the whole brain. Slices were acquired bottom–up in the sequential mode. The following functional imaging

parameters were used: repetition time (TR) = 2520 ms, echo time (TE) = 43 ms, flip angle = 90°, matrix = 64 × 64, field of view (FoV) = 192×192 mm, slice thickness = 3.0 mm with a 20% gap, resulting in 3.0 mm isotropic voxels.

Structural T1

A whole-brain, high-resolution T1-weighted 3D structural image was obtained using a magnetisation-prepared gradient-echo sequence, consisting of 192 contiguous axial slices (TR = 2730 ms, TE = 3.57 ms, flip angle = 7°, matrix = 256 × 240, FoV = 256 × 240 mm, 1.0 mm isotropic voxel size). The T1-weighted image was used as an anatomical reference for each participant's functional data.

Diffusion MRI

Multi-shell diffusion-weighted data were acquired with single-shot, twice-refocused pulse gradient spin-echo EPI using multiband (MB) acceleration factor 2. Sixty axial slices oriented in parallel to the AC–PC line and covering the whole brain were acquired with the following parameters: TR = 4036 ms, TE = 95 ms, matrix size = 96 x 96, FoV = 240 x 240 mm, 2.5 mm isotropic voxel size. Two b-value shells were acquired, b = 800 and 2000 s/mm^2 with 30 and 60 non-collinear diffusion-weighted directions, respectively. The images included a total of 9 non-diffusion-weighted volumes (b = 0). Further images with b = 0 were acquired in the opposite phase encoding direction in order to estimate and correct for susceptibility induced distortions.

2.1.4 Data analysis

2.1.4.1 Behavioural data analysis

Statistical Package for the Social Sciences (SPSS IBM V. 22 for Windows) was used for analyses. Tests of assumptions were conducted to check that the chosen statistical analyses were appropriate for our data. The dependent variable was the number of successful trials in which the cursor reached the red target in the pre- and post-training phase. Number of successful trials on the PCM task was analysed using a paired samples t-test comparing pre- and post-training performance. Statistical significance was set at $p < .05$ (two-tailed). Cohen's *d* was used as an effect size measure (Cohen, 1992). Cohen's *d*

can be interpreted as: *d* = .20 (small effect); *d* = .50 (medium effect); and *d* =.80 (large effect).

2.1.4.2 fMRI analyses

Preprocessing

We compared functional imaging during the pre-training and post-training phase. We used SPM12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; www.fil.ion.ucl.ac.uk/spm) running under MATLAB R2015a for data preprocessing and statistical analyses. Preprocessing of functional images included slice time correction to the middle slice, spatial realignment to the first image, and unwarping. The T1-weighted structural image was coregistered to the mean functional image and subsequently segmented to obtain normalisation parameters based on the standard Montreal Neurological Institute (MNI) template. The normalisation parameters obtained from segmentation were used to transform each participant's functional images and the bias-corrected structural image into MNI space. Voxel sizes of the functional and structural images were retained during normalisation, and the normalised functional images were spatially smoothed using an 8mm full-width-half-maximum (FWHM) Gaussian kernel.

First-level analysis

Statistical analyses were performed using the general linear model. The response function was modelled relative to the onsets and durations of each trial, using a canonical hemodynamic response function (HRF) available in SPM12. At the single-subject analysis, the model was composed of the 2 fMRI runs (Pre-training and Post-training). Each run included 2 regressors representing the onset and duration of successful trials and unsuccessful trials. Thus, for fMRI run 1 there were two conditions: Pre-training _Successful trials and Pre-training_Unsuccessful trials, and for fMRI run 2 there were two conditions: Post-training_Successful trials and Post-training_Unsuccessful trials, resulting in 4 regressors of interest. There were 6 regressors of no interest representing motion-related variance for each fMRI run. A high-pass filter was applied with a period of 128 seconds to remove low-frequency signals relating to scanner drift and/or physiological noise.

Second-level analyses

Results of the single-subject analysis were taken to second level to examine activation differences following training in regions of interest (ROI). In addition, we tested whether performing more accurately (Successful vs Unsuccessful trials) was associated with activations in particular brain areas. The subject-specific beta images of Pre-training and Post-training Successful and Unsuccessful trials (i.e., Pre-training_Successful, Pre-training_Unsuccessful, Post-training_Successful, Post-training_Unsuccessful) were entered into separate 2 × 2 repeated measures ANOVAs for each ROI using the full factorial design specification in SPM12. Testing phase (Pre-training, Post-training) and Trial Performance (Successful, Unsuccessful) were entered as within-subject factors to look for differences in brain activation for successfully vs. unsuccessfully performed trials during the pre- and post-training phases. All main and interaction effects derived from the ANOVAs are reported using a statistical significance of $p < .05$ after False Discovery Rate (FDR) correction for multiple comparisons at the cluster level, clusters formed using $p < .001$ (Genovese et al., 2002; Chumbley & Friston, 2009). Significant clusters for all analyses were localised according to the Anatomy toolbox (v 2.2b, Eickhoff et al., 2005).

We computed normalised difference scores for the PCM task, such that Difference Score = (Post-training score - Pre-training score) / (Post-training score + Pre-training score). Higher difference scores indicate a bigger training gain. Correlations were run between the difference scores and activity in the ROIs using the contrasts Pre-training > Post-training and Post-training > Pre-training, i.e., all trials were included regardless of whether successful or unsuccessful. We used the MarsBaR (MARSeille Boîte À Région d'Intérêt) 0.44 toolbox for SPM (Brett et al., 2002) to extract the mean percent change in beta values of each ROI for the contrasts Pre-training > Post-training and Post-training > Pre-training, and correlated this with the difference scores using an in-house script run in MATLAB R2015a.

ROIs were selected based on the models for motor skill learning by Hikosaka et al. (2002) and Doyon and Ungerleider (2002). These models include the striatum, cerebellum, premotor cortex, SMA, preSMA, M1, anterior cingulate, as well as prefrontal

and parietal areas. In addition, we included the hippocampus as increases in activity have been demonstrated in this region for both the early and later stages of motor training (Schendan et al., 2003; Albouy et al., 2008; Fernández-Seara et al., 2009; Gheysen et al., 2010; King et al., 2013). And finally, the parahippocampal cortex was included as it is highly engaged during visuospatial processing (van Strien et al., 2009; Aminoff et al., 2013; Hohenfeld et al., 2020), a key aspect of the PCM task. We specified 12 anatomical ROIs bilaterally: striatum (including caudate and putamen), cerebellum, hippocampus, parahippocampus, SMA, preSMA, M1, premotor cortex, anterior cingulate, dPFC, oPFC, and inferior parietal cortex. The precuneus and vPFC were selected to serve as control regions. We did not expect to see a change in activity in these areas as they show increased activation during later stages of motor skill learning (Doyon, 1997; Sakai et al., 1998; Doyon & Ungerleider, 2002; Ungerleider et al., 2002; Doyon et al., 2003; Lehéricy et al., 2005; King et al., 2013). All ROI masks were from the WFU PickAtlas v2.4 (Maldjian et al., 2003; http://www.nitrc.org/projects/wfu_pickatlas/).

2.1.4.3 Diffusion MRI analyses

Preprocessing

We used diffusion imaging to examine microstructural differences in grey and white matter in relation to training outcome. Diffusion-weighted data sets were analysed to produce the NODDI indices of neurite density index (NDI) and orientation dispersion index (ODI). In addition, the diffusion tensor imaging (DTI) indices of fractional anisotropy (FA) and mean diffusivity (MD) were obtained.

The diffusion images were first corrected for movement and eddy current distortions using FMRIB software library (FSL, version 5.0.7, Oxford, UK). Eddy current distortions were estimated and corrected for using FSL's topup tool. Data were preprocessed using the NODDI MATLAB toolbox (Zhang et al., 2012; http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDImatlab) which yielded maps of NDI and ODI for each participant. Diffusion tensors were fitted using DTIFIT in FSL, providing output maps of FA and MD. All maps were normalised to the MNI space using the

Advanced Normalization Tools (ANTs, version 2.1.0; http://stnava.github.io/ANTs). Images were spatially smoothed using a 5mm FWHM Gaussian kernel.

Statistical analyses

To quantify the relationship between performance and brain microstructure, 4 simple regression analyses were performed in SPM12. Correlations were run between the PCM difference scores and the DTI indices of FA and MD, and the NODDI indices of NDI and ODI. The whole-brain voxel-wise analyses were conducted using a simple regression (converted to t-contrast) procedure. We entered participants' diffusion maps into separate one-sample t-tests for FA, MD, NDI, ODI, and included difference scores as a covariate. As we explicitly modelled a constant regressor as the first column of the design matrix, we ran the contrasts 0 1 to check for positive correlations and 0 -1 to check for negative correlations between each index and difference scores. A statistical significance threshold of $p < .05$ FDR-corrected at the cluster level was used, after clusters were formed with an uncorrected $p < .001$.

2.2 Working memory, attention, and executive function training in middle-aged adults: Behavioural experiment (Chapter 4)

The aim of this experiment was to test the effectiveness of cognitive training in healthy middle-aged adults (40-50 years old). We compared the training condition to an active control treatment. Participants in the experimental condition completed an adaptive cognitive training programme, while the active control group completed a non-adaptive version of the same training. To test for training-related improvements in cognitive function we examined performance on the training tasks. In addition, to assess whether training gains transferred to untrained abilities we examined performance on transfer tasks.

2.2.1 Participants

The sample size for this experiment was based on a study by Caeyenberghs et al. (2016) that examined transfer effects following working memory training in 40 younger adults (*M* age = 26.5 years). Therefore, we aimed to have a minimum of 40 participants in the present experiment. Participants were recruited from the Universities of Sussex and Brighton, as well as from the local community. This was carried out using volunteer databases available to researchers, e-mail advertisement, social media, and via posters in local shopping and leisure centres. A total of 53 middle-aged adults were recruited for this study. Participants were pseudo-randomly assigned to either the experimental or control group, with the provision to match the groups for age, sex, handedness, and education level. All participants were blind to the group they were assigned to. However, the experimenter was not blind to group assignment. Participants had normal or corrected-to-normal vision. The participants had no history of psychiatric or neurological illness, or brain injury. Participants also had no history of alcohol or drug use disorders. Participants were not taking prescribed medications at the time of the experiment. They were carefully screened for MRI contraindications, such as pacemakers, metal contamination, or claustrophobia. Written informed consent was obtained under a protocol approved by the Brighton and Sussex Medical School Research Governance and Ethics Committee. Participants were compensated for their time. Three participants were excluded from further analysis due to failure to complete the training programme. Three

were excluded as they were unable to complete the first MRI scanning session. A further 6 withdrew before the first MRI session as a substantial time commitment was required for the study. And 1 participant was excluded due to an incidental finding during the MRI scan. Thus, a total of 40 participants (28 females, 12 males) between 40 and 50 years of age (*M* = 44.97 years, *SD* = 3.07) were included for analysis. Of these, 20 were part of the adaptive (experimental) training group (14 females, 6 males; *M* age = 44.15 years, *SD* = 2.94), and 20 were part of the non-adaptive (control) training group (14 females, 6 males; *M* age = 45.80 years, *SD* = 3.04). The mean number of years of education for the adaptive group was 17.30 (*SD* = 3.80). The mean number of years of education for the non-adaptive group was 17.15 (*SD* = 3.10). There were 18 right handed participants in the adaptive group, and 19 in the non-adaptive group.

2.2.2 Procedure

To investigate whether regular cognitive training leads to overall improvement in cognitive function in middle-aged adults, we used a mixed design with group (cognitive training, active control) as a between-subjects factor, transfer task as a within-subjects factor (RAPM, PAL, PAR, N-back), and session (pre-training, post-training) as a within-subjects factor. We compared cognitive training to an active control treatment to ensure that any effects observed in the cognitive training group could not be attributed to simple test-retest effects (typically performing better the second time, regardless of training), or the fact that the trained participants would have more attention paid to them (i.e., the Hawthorne effect: Landsberger, 1958), or higher expectations of themselves due to the training (Collie et al., 2003; McCarney et al., 2007; Green & Bavelier, 2012). To make sure that training conditions were the same for both groups, participants in the experimental condition completed an adaptive cognitive training programme, while the active control group completed a non-adaptive version of the same training. For participants assigned to the adaptive group, the training dynamically changed relative to performance, thus keeping task demands challenging and at a high level of difficulty. For participants in the non-adaptive group, task difficulty was lower and remained within a constant limited range over the entirety of training, regardless of the participant's performance. Cognitive function and transfer effects were assessed using a fluid intelligence test: RAPM (far

transfer), a paired associative learning task: PAL (far transfer), a paired associative memory task: PAR (near transfer), and a working memory task: N-back (near transfer). Participants in both the experimental and control groups received the same detailed written instructions for all the tasks (Appendices II, III, and IV, pgs. 279, 281, and 284).

All participants came in for an introductory session lasting about an hour, during which the study and MRI scanning were described in detail. They received instructions for the N-back task and a demonstration of the task on the computer. And finally, they completed the baseline RAPM test. Following this, participants came in for the first scanning session and further baseline testing. Participants first learned a set of 8 paired associates (PAL) and were then tested on them during a memory task in the scanner (PAR). Following which they completed the N-back task, also in the scanner. Participants then completed 12 sessions of either the adaptive or non-adaptive training over 4-6 weeks (2-3 sessions per week). Post training, participants again completed the RAPM, PAL, PAR, and N-back tasks (with different stimuli to reduce practice effects) to measure possible changes in cognitive ability and transfer. See Figure 2.3 for procedure overview.

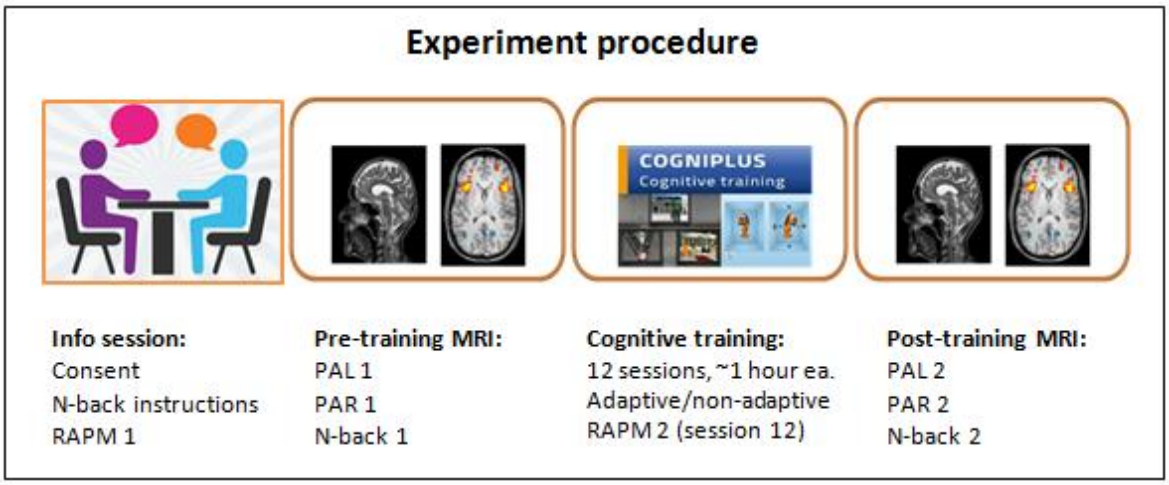


Figure 2.3. Experiment procedure: participants attended an information session during which they received instructions for the N-back task and completed the baseline RAPM test. Participants then came in for the first scanning session and further baseline testing (PAL, PAR, and N-back tasks). Following this they completed 12 sessions of either the adaptive or non-adaptive training. At the end of the final training session, they completed the post-training RAPM test. Finally,

participants came in for the post-training MRI session, during which they completed the PAL, PAR, and N-back tasks.

Cognitive training tasks

We used CogniPlus software (SCHUHFRIED GmbH, Austria) for the cognitive training programme (Figure 2.4). The training programme consisted of 5 computer-based exercises that aimed to train working memory, attention, and executive function. Each task was 10min long and total training time per session was 50min. Training for all participants was completed individually on a computer in a quiet room. All training was carried out in the laboratory to ensure each session was fully completed and to provide assistance should the participants require it. Both the adaptive and non-adaptive groups completed the same tasks. For participants assigned to the adaptive group, the difficulty of the task dynamically changed relative to performance within task blocks (increasing or decreasing dependent on >75% correct performance). Participants in the adaptive group began each session where they left off in the previous session, i.e., a participant's level was stored for each task at the end of each session, and they started from that level in the next session rather than from the beginning. For participants in the non-adaptive group, task difficulty remained within a constant limited range over the entirety of training, regardless of the participant's performance. Participants in the non-adaptive group started each session from the beginning. The training tasks were: Divided Attention (DIVID), Spatial Coding (CODING), Spatial Updating (DATEUP), Response Inhibition (HIBIT-R), and Mental Rotation - Spatial Processing (ROTATE). Each is discussed in more detail below.

Divided Attention (DIVID)

The DIVID task trained divided attention; the ability to perform multiple tasks simultaneously (Sturm, W., SCHUHFRIED GmbH). This is an important ability in daily life where multiple streams of information across modalities (or aspects of the environment) must be monitored. The divided attention task exemplified this by placing the participant in the role of a security officer at an airport. Participants simultaneously observed a range of scenes on several control monitors, such as sliding doors at the entrance, a ticket

counter, and luggage conveyor, as well as audio announcements (Figure 2.4A). Their task was to deal with problems as they occurred in different monitors by pressing a response key as quickly as possible. If they failed to react promptly to a problem or a relevant announcement, the scenes on the monitors froze, and the correct monitor was highlighted until the reaction button was pushed.

Spatial Coding (CODING)

CODING is an exercise that trained visuospatial working memory (Schellig, D., Schuri, U., Sturm, W., SCHUHFRIED GmbH). Participants were shown a series of vehicles driving onto a bridge with multiple traffic lanes (Figure 2.4B). Once the vehicles drove over the bridge they disappeared from the participant's view. When the vehicles reappeared, one of them might have changed position relative to the others. It was the participant's job to identify which of the vehicles had moved. This involved comparing the new arrangement of the vehicles with the previously stored layout of their original arrangement and identifying any differences. As the task becomes more difficult, the number of cars that change position increases.

Updating - Spatial (DATEUP)

The DATEUP task trained the executive updating function of spatial working memory, whereby memory contents were renewed in a controlled and goal-directed manner (Schellig, D., Schuri, U., Sturm, W., SCHUHFRIED GmbH). Participants watched different types of butterflies in a natural setting as they flew over meadows and sandy ground (Figure 2.4C). Throughout the task, one butterfly lands and another starts its flight until eventually, at irregular intervals, the participant is asked a question. Depending on the difficulty level, the participant must highlight one or more butterflies in a specific order, such as the last but one butterfly, the last three butterflies, or the last of each of three different butterfly types.

Response Inhibition (HIBIT-R)

The HIBIT-R task trained the executive ability to suppress unwanted reactions (response inhibition) (Weisbrod, M., Kaiser, S., Pfüller, U., Roesch-Ely, D., Aschenbrenner,

S., SCHUHFRIED GmbH). The training programme primarily works with Stop Signal and Go/No-go tasks. Participants assumed the role of a post-office employee and sorted letters and packages as quickly and accurately as possible (Figure 2.4D). There were four different tasks in which the participant was asked to pay attention to specific cues (e.g., whether there is a stamp) that indicated when they needed to react and when they did not. Additionally, participants were able to co-design their own course of training such that following successful completion of a task, the participant could decide whether they would like to continue the current task or switch to a different one. Thus, they could choose between tasks themselves and design the programme to keep it individually motivating and maximise engagement.

Mental Rotation - Spatial Processing (ROTATE)

The ROTATE exercise trained spatial processing ability (Sommer, M., Heidinger, C., SCHUHFRIED GmbH). Two types of task were presented alternately. In the change of perspective task, the participants saw an object on the right-hand side of the screen surrounded by cameras. The task was to identify which camera was used to take the picture shown on the left side of the screen (Figure 2.4E). The second type of task was a rotation task. The screen showed symbolic axes of rotation, called “rotation rods”, which could be used to rotate the object in space. Participants had to decide which rod needed to be used to rotate the object on the right of the screen in order to match the picture on the left side.

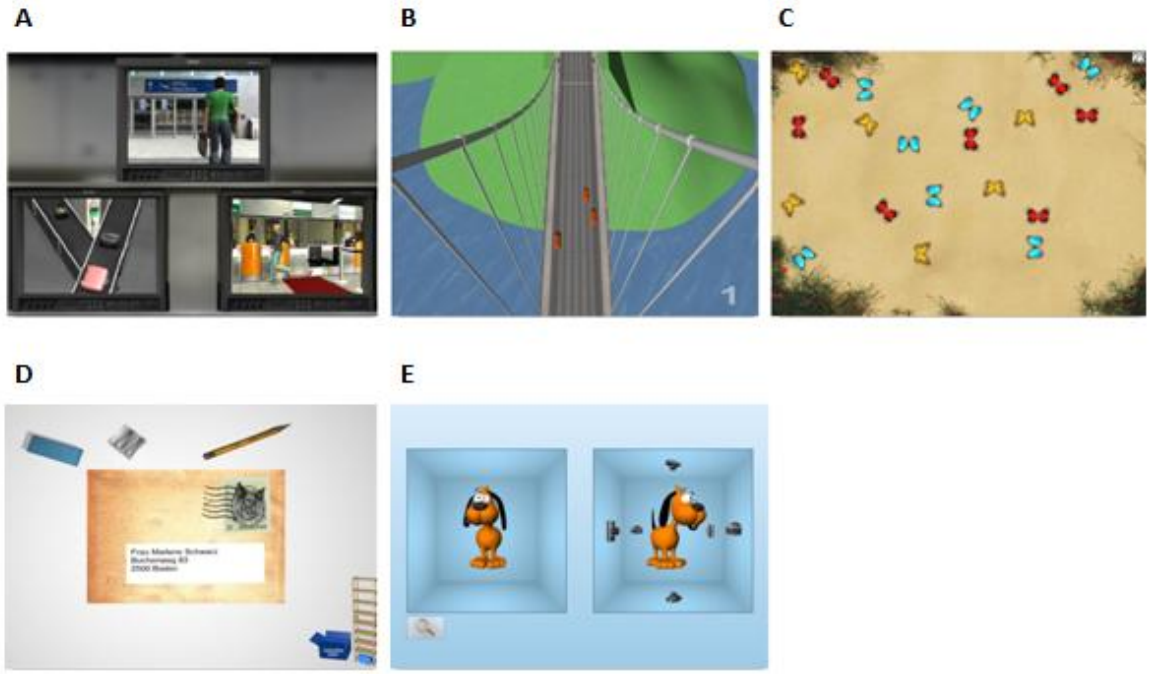


Figure 2.4. Cognitive training tasks used for adaptive and non-adaptive training (CogniPlus, SCHUHFRIED GmbH). A) Divided attention task. B) Spatial coding task. C) Spatial updating task. D) Response inhibition task. E) Mental rotation - spatial processing task.

Cognitive assessment and transfer tasks

In the pre- and post-training sessions, 4 working memory and executive function tasks were used to measure cognitive improvement and transfer effects associated with training. The transfer tasks were: RAPM (far transfer), PAL (far transfer), PAR (near transfer), and N-back (near transfer). Stimuli for PAL, PAR, and N-back were delivered using Cogent 2000 v1.32 running under MATLAB R2015a (The MathWorks, Inc., Natick, MA). The RAPM was administered as a pen and paper test.

RAPM

To investigate far transfer effects, an adapted short version of the Raven Advanced Progressive Matrices (RAPM; Raven & Court, 1998) Set 2 was used to measure each participant's general intelligence before and after cognitive training (see Figure 2.5 for an example question). The RAPM consists of a range of nonverbal problems, whereby participants must identify the missing piece of a 3x3 array of patterns by inferring the

rules that determine the patterns found in each row and column. It is therefore designed to test abstract reasoning and thus directly estimate a person's level of fluid intelligence or general cognitive ability. Participants were given instructions for this task, but no specific guidance on how each puzzle might be solved (e.g., they were told to look for which picture completed the pattern, but not what the specific patterns might involve). The 36-item RAPM was split into two tests of equal difficulty, based on previous findings regarding difficulty in a study by Jaeggi et al. (2014). We used Jaeggi et al.'s (2014) 18-item versions of the test, whereby version B was administered in session one and version A was administered in session two. For both tests, participants were given 10 minutes to complete as many of the questions as they could. Scores were calculated as the total number of correct responses and ranged from 0-18.

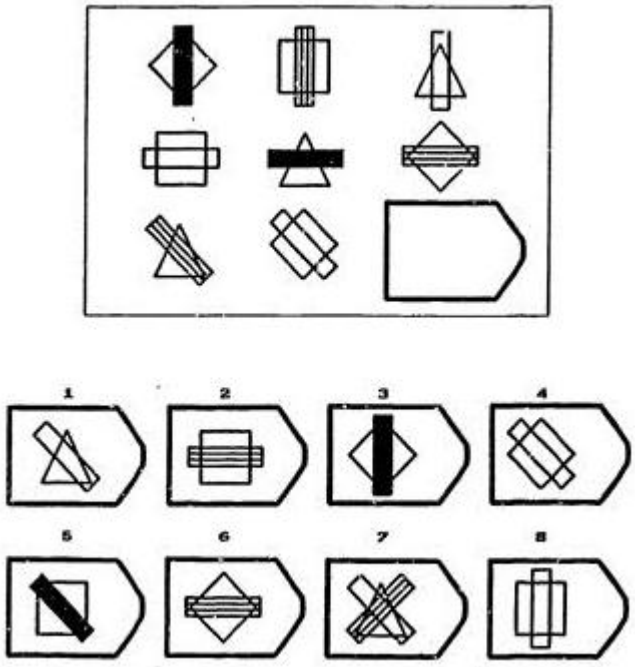


Figure 2.5. Example from the RAPM test. The test consists of a range of nonverbal problems; the task is to find the missing piece of a 3x3 array of patterns by inferring the rules that determine the patterns found in each row and column.

PAL and PAR

Pair-associative learning (PAL) and pair-associative retrieval (PAR) tasks were used to measure far and near transfer effects, respectively. Adapted from Pfeifer et al. (2016), this computer-based task initially involved the participant learning a set of 8 achromatic fractal pair-associates (Figures 2.6 and 2.7) during the learning phase (PAL), outside of the scanner. Participants were explicitly informed that they would be given a memory test on these stimuli during scanning. They were asked to memorise the correct combination of pair-associates for the subsequent memory test to take place in the scanner (retrieval phase, PAR). Firstly, each of the 8 pair-associates was randomly presented once at the centre of a computer screen for 4s, and participants were instructed to remember the correct association of the pairs. The presentation was followed by a trial-and-error learning task. Each trial began with a fixation cross presented for 1s, followed by a cue picture presented at the top of the screen and 4 possible matching target pictures below (Figure 2.8A). The targets were taken from the stimulus set of the 8 pair-associates and one target was always a match (i.e., the correct pair-associate). Participants were asked to indicate which of the 4 targets belonged with the cue, by using different keyboard responses for each target. They had a maximum of 3s to make a response. Following the response, visual feedback appeared below the pictures for 2s, indicating whether or not the matching target had been identified correctly or incorrectly (green tick or red cross, respectively). Sixteen Runs were required in the learning phase and each Run contained 8 trials, such that participants received a score out of 8 at the end of each of the 16 runs (displayed onscreen). Cue and target shapes of all pair-associates were presented interchangeably during learning: a stimulus that had been presented as the cue in one Run constituted the target in the following Run. The task lasted approximately 13 min. Scores were calculated as the total number of correct responses (i.e., correct identification of the target pair-associate in each trial) and therefore ranged from 0-128.

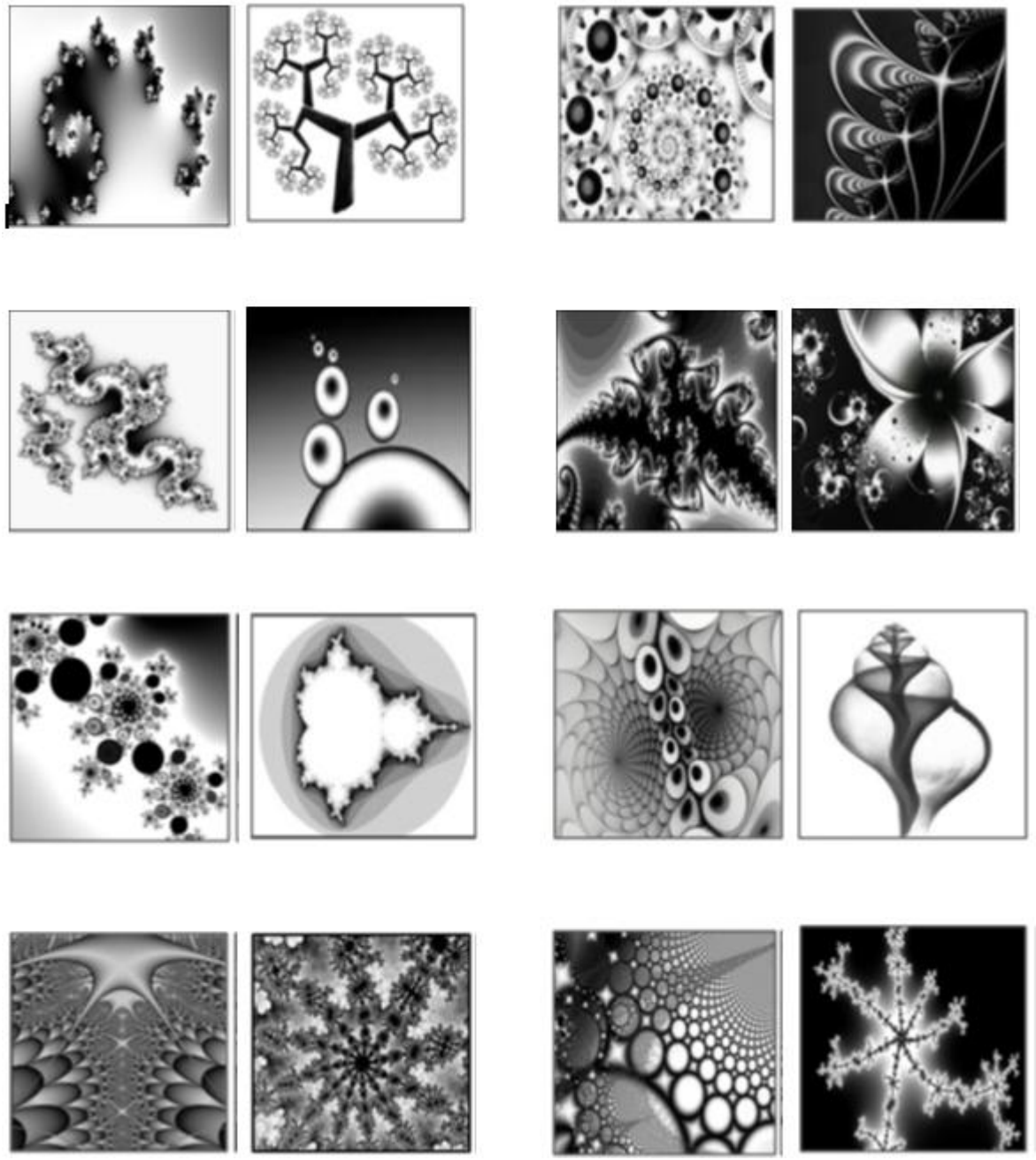


Figure 2.6. The 8 achromatic fractal pair-associates used for the pre-training PAL and PAR tasks (adapted from Pfeifer et al., 2016).

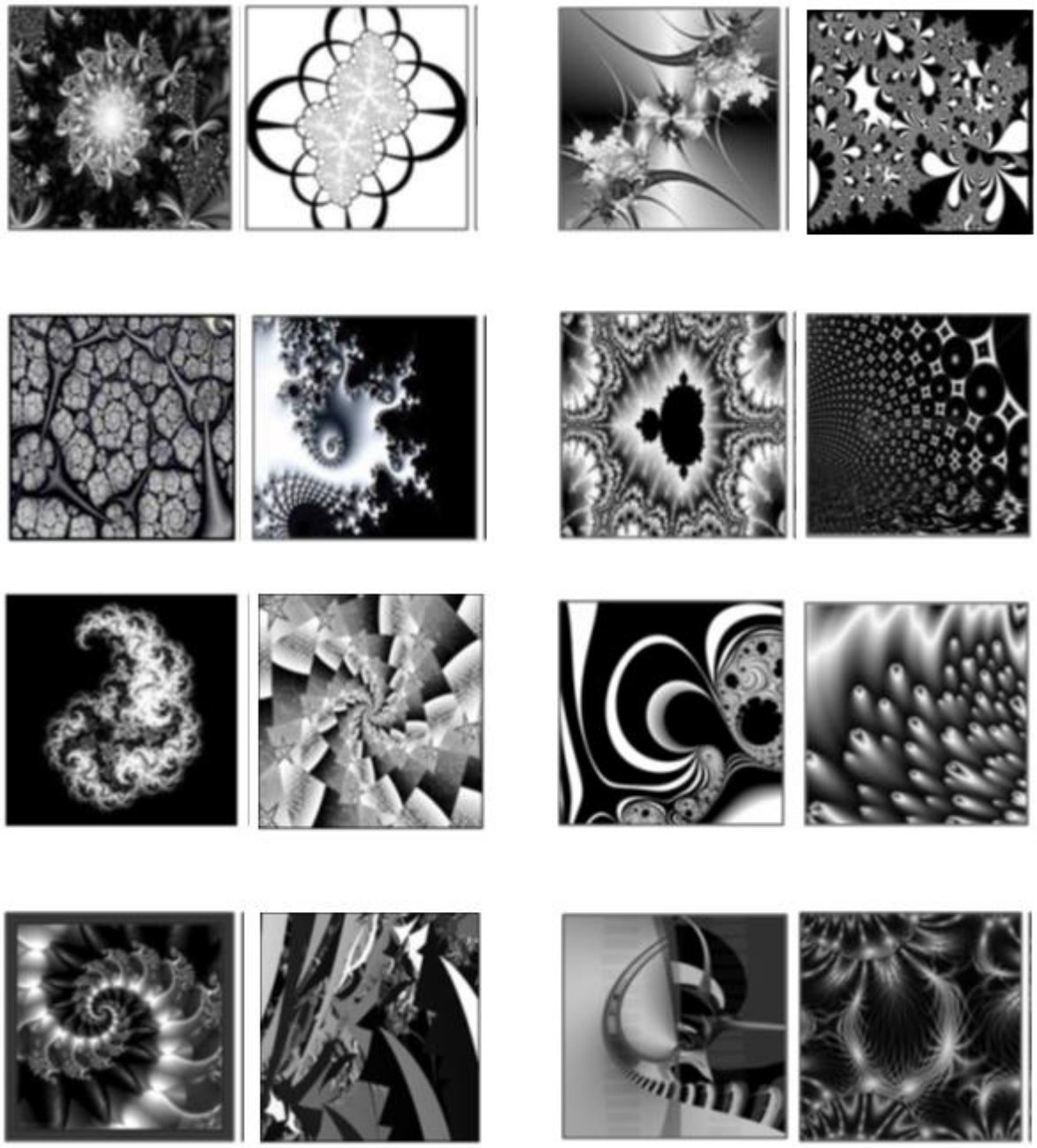


Figure 2.7. The 8 achromatic fractal pair-associates used for the post-training PAL and PAR tasks (adapted from Pfeifer et al., 2016).

Following the associative learning task, participants completed the retrieval phase in the scanner. For the PAR task (Figure 2.8B), a cue picture was presented at the centre of the screen (1s), during which participants were asked to use the cue to retrieve the matching pair-associate (associative retrieval). During the delay period (8s), participants were required to hold the retrieved picture in mind (working memory). Finally, the target presentation (1s) comprised the associative recognition stage, where participants were asked to recognise the target as the matching or non-matching pair-associate. Following target presentation, a response window appeared and stayed on screen for a maximum of 3 seconds, during which participants were asked to press button 1 to indicate the target was a match, or button 2 to indicate the target was a non-match. The button-presses were followed by a variable intertrial interval (ITI) of 6 – 10s before the next trial (pseudo-randomised, biased towards 8 and 10s). No feedback was provided on the accuracy of the participants' responses. The task was about 13 minutes long. There were a total of 40 trials (8 pairs, presented 5 times). Scores were measured as the total combined number of Hits (i.e., correct match) and Correct Rejections (i.e., correct non-match). If they chose non-match when a target was a match, this was recorded as a Miss. If they chose match when the target was a non-match, this was recorded as a False Alarm. Scores ranged from 0-40.

For the PAR task, the cue and target images were presented interchangeably throughout the trials. On 60% of the trials, the cue pictures were followed by a matching target, constituting 24 match trials and 16 non-match trials. In this sense, lure stimuli were non-matching images from the same set of the 8 pair-associates rather than trial unique stimuli. Using recombinations of same-set stimuli constitutes a more powerful test of associative memory, requiring participants to retrieve the intact combination of pair-associates out of equally familiar stimuli rather than rejecting lures on the basis of their novelty (Mayes et al., 2007; Pfeifer et al., 2016). The minimum trial distance between match and non-match trials was 1 (i.e., a match trial could immediately follow a non-match trial and vice versa), and the maximum trial distance was five (i.e., a non-match trial could follow 4 presentations of match-trials). The PAR task was always presented before the N-back task in order to avoid retroactive interference effects on associative memory.

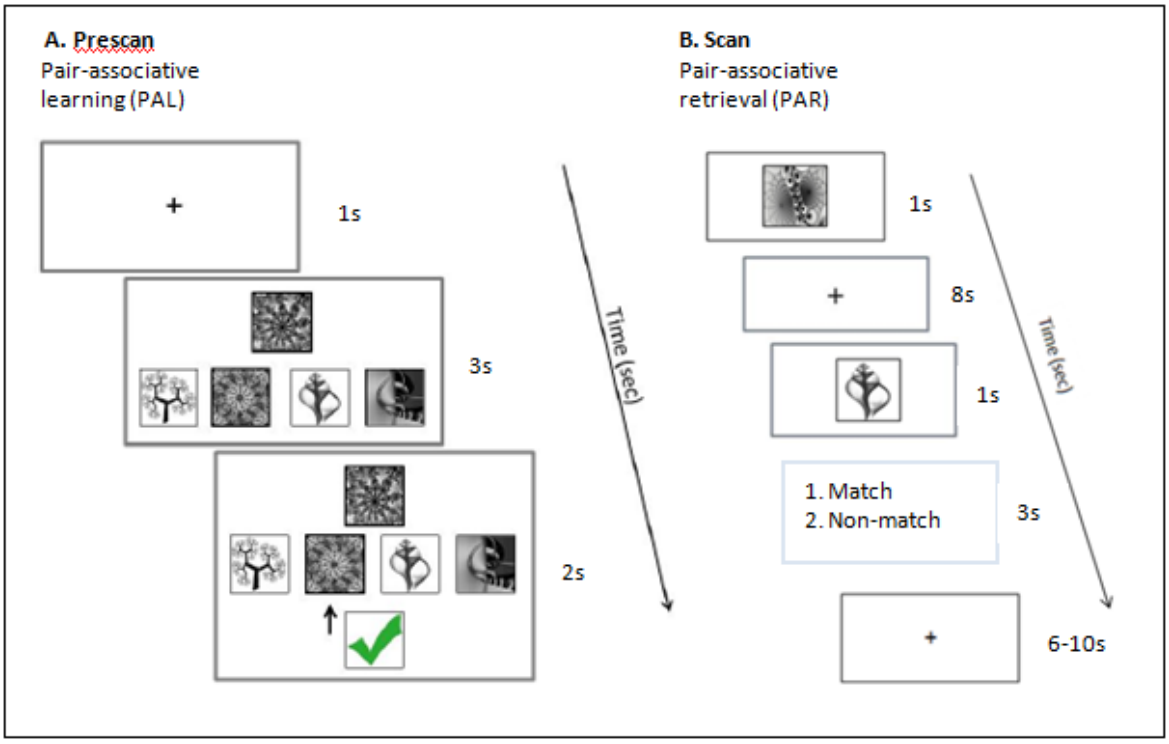


Figure 2.8. Pair-associative learning and retrieval tasks (PAL, PAR). A) Each trial of the PAL task contained a fixation cross (1s), followed by the stimulus presentation, during which participants were asked to select one of 4 possible pair-associates to match with the cue image at the top (3s), and feedback (2s). B) For the PAR phase, participants were asked to use the cue (1s) to retrieve the matching pair-associate. During the delay period (8s), participants were required to hold the retrieved picture in mind. The target presentation (1s) comprised the associative recognition stage, where participants were asked to recognise whether it was the matching or non-matching pair-associate. The response window appeared and stayed on screen for a maximum of 3 seconds. Responses were followed by a variable intertrial interval (ITI) of 6 – 10s. Adapted from Pfeifer et al., 2016.

N-back

While in the MRI scanner, the visual N-back task (Figure 2.9) was used to measure working memory and therefore training-induced near transfer effects. This involved a task script adapted from Campbell et al. (2016), whereby participants saw a series of stimuli consisting of individual upper- and lower-case consonant letters, which were presented sequentially on a computer screen. The task was to decide whether the current stimulus on the screen matched the one that was presented *N* items back in the series. We used four different conditions during the task: a control 0-back condition whereby participants press a button when the target letter appears, and increasing difficulty conditions (i.e.,

working memory load) of 1-back, 3-back, and 4-back. The instruction indicating whether the task for a particular series was 0-back, 1-back, 3-back, or 4-back was presented on the screen just before the series started. There were 4 blocks of each condition, with 20 letters per block, giving 80 total trials per level, and a total of 320 trials for the entire task. The order of blocks was pseudo-random with each level presented once during a rotation of 4 blocks. Each letter appeared on screen for 1 second, and there was 1 second between letters, giving a total of 40 seconds per block. The task lasted approximately 11 minutes. There were 28 total targets per condition of 80 letters. Participants were required to press a button indicating when the target was a match to the letter presented N items back (i.e., Hit), and to not press the button if they didn't think the target was a match (i.e., Correct Rejection). If they pressed the button when a target was not a match, this was recorded as a False Alarm. If they failed to press the button when the target was a match, this was recorded as a Miss. A score for each condition was calculated as the total combined number of Hits and Correct Rejections, with a possible range of 0-80.

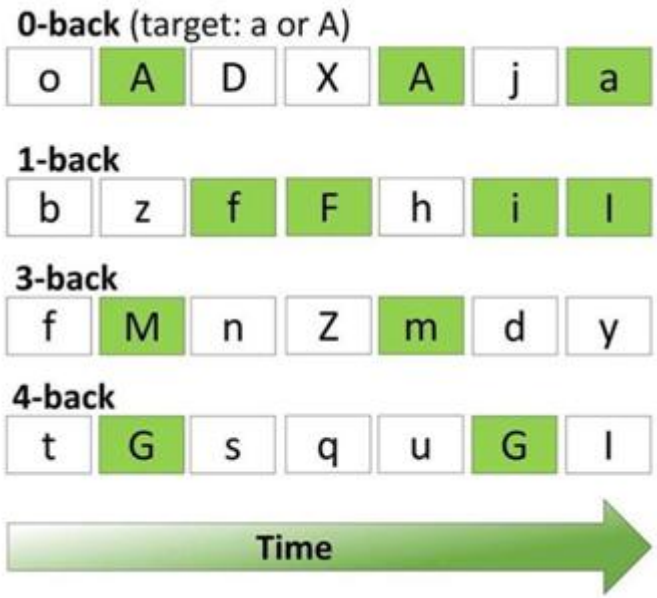


Figure 2.9. N-back task. The goal is to decide whether the current stimulus on the screen matches the one that was presented *N* items back in the series. There were four different conditions during the task: a control 0-back condition whereby participants press a button when the target letter appears, and increasing working memory loads of 1-back, 3-back, and 4-back.

2.2.3 Data analysis

Analyses were performed using SPSS IBM V. 25. Tests of assumptions were carried out to check that the chosen statistical analyses were appropriate for our data. Descriptive statistics are expressed as mean and standard deviation for continuous variables, and frequencies for categorical variables. Multiple independent samples t-tests were performed comparing the groups (adaptive vs non-adaptive) on the demographic data and baseline (pre-training) performance for each transfer task. All tests for demographic and baseline data were two-tailed; significance level was set at $p < .05$.

Performance on the CogniPlus training exercises was analysed using paired samples t-tests comparing session 1 to session 12 for all tasks in adaptive and non-adaptive groups. Performance was calculated as the last level of difficulty reached at the end of a session. Statistical significance was set at $p < .05$ (two-tailed).

Post-training performance scores on the near and far transfer tasks (RAPM, PAL, PAR, 3-back, 4-back) were entered as dependent variables in separate one-way analyses of covariance (ANCOVA), with group (adaptive, non-adaptive) as a between-subjects factor, and baseline performance entered as covariates. Statistical significance for all tests was set at $p < .05$ (two-tailed). We then ran paired samples t-tests comparing pre- and post-training performance on each of the transfer tasks for the total sample (combined adaptive and non-adaptive training groups, $N = 40$), with statistical significance set at $p < .05$ (two-tailed).

In addition, we conducted Kendall's tau-b correlations of performance on CogniPlus tasks with post-training performance on transfer tasks. This was to determine whether a specific type of training (i.e., working memory, attention, or inhibition) was associated with improved performance on particular transfer tasks. Significance for the correlations was set to $p < .05$ (two-tailed).

Effect sizes. Cohen's *d* was used as an effect size measure for paired t-tests (Cohen, 1992). Cohen's *d* can be interpreted as: $d = .20$ (small effect); $d = .50$ (medium effect); and $d = .80$ (large effect). Partial eta squared (η_p^2) was used as an effect size

measure in ANCOVAs. Partial eta squared can be interpreted as: η_p^2 = .01 (small effect); η_p^2 = .06 (medium effect); and η_p^2 = .14 (large effect).

Power analysis. Given the relatively small sample sizes in our 2 groups, we calculated the achieved power in all statistical comparisons to supplement our null hypothesis significance tests. The power calculations were performed using SPSS IBM V. 25 for ANCOVAs, and using the G*Power calculator v. 3.1.9.4 (Faul et al., 2007) for t-tests.

2.3 Working memory, attention, and executive function training in middle-aged adults: MRI experiment (Chapter 5)

The aim of this experiment was to investigate how the brain responds to cognitive training in healthy middle-aged adults (40-50 years old). We sought to characterise functional plasticity as a result of training with task-based fMRI. In particular, training-induced functional changes were assessed on the near transfer tasks (PAR, N-back). To further investigate the neural mechanisms involved in transfer of training gains, we used the NODDI technique in addition to traditional DTI. Thus, we examined the microstructural alterations that may occur in the brain following cognitive training.

2.3.1 Participants

The same participants as in the previous section were tested for the MRI part of the experiment. Details can be found in section 2.2.1. In sum, a total of 40 middle-aged adults completed the study. Of these, 20 were part of the adaptive (experimental) training group, and 20 were part of the non-adaptive (control) training group. One person (non-adaptive group) was excluded from the PAR fMRI analyses due to major artefacts found on the scan, leaving 39 data sets for analysis (adaptive: n = 20; non-adaptive: n = 19). One person (adaptive group) was excluded from the N-back fMRI analyses due to data corruption during transfer from the scanner, leaving 39 data sets for analysis (adaptive: n = 19; non-adaptive: n = 20). A single non-adaptive participant's diffusion data were corrupted during transfer from the scanner and therefore excluded, leaving 39 data sets for analysis (adaptive: n = 20; non-adaptive: n = 19).

2.3.2 Procedure

The procedure was the same as in the previous section, consisting of a PAR task and an N-back task performed in the scanner. Details are described in section 2.2.2 and will be summarised here. The study involved two scanning sessions for each participant: a pre-training session and a post-training session. These sessions aimed to image structural and functional brain changes underlying performance improvements as a result of training. In the pre-training MRI session, participants first learned a set of 8 paired associates (PAL) outside of the scanner and were then tested on them during a memory

task in the scanner (PAR). Following which they completed the N-back task, also in the scanner. Participants then completed 12 sessions of either the adaptive or non-adaptive training (CogniPlus, Shuhfried GmbH) over 4-6 weeks (2-3 sessions per week). For the post-training scan, participants again completed the PAR and N-back tasks (with different stimuli, in order to reduce practice effects) to measure possible changes in brain function and cognitive ability.

Figure 2.10 shows the MRI protocol used during both the pre- and post-training scanning sessions. Each session included PAR task fMRI (13min), followed by a structural T1 scan (6min), then N-back task fMRI (11min), then quantitative magnetisation transfer (qMT) and associated DESPOT1 and b1 maps for 20min (data not reported in this thesis), and finally a NODDI/DTI scan (9min). Total scanning time per session was about 1 hour.

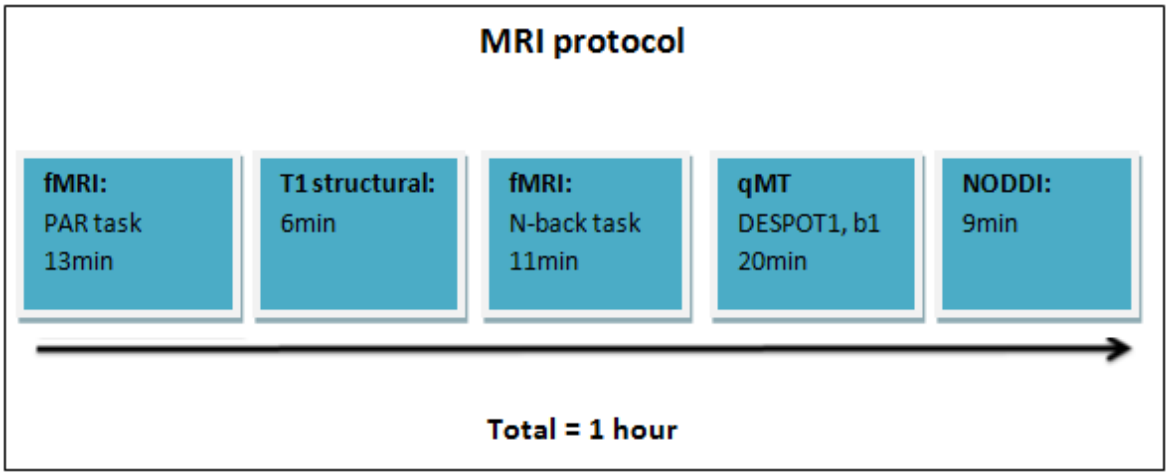


Figure 2.10. MRI protocol for the pre- and post-training sessions: each session included PAR fMRI (13min), followed by a structural T1 scan (6min), then N-back fMRI (11min), then qMT and associated DESPOT1 and b1 maps (20min), and finally a NODDI/DTI scan (9min). Total scanning time per session was 1 hour.

2.3.3 MRI data acquisition

fMRI

Imaging data for each session were collected using a Siemens Prisma scanner (Siemens, Erlangen, Germany), equipped with a 3.0-T magnet and 64-channel phased-

array receive-only head coil. The PAR and N-back tasks were presented on an LCD monitor, at a viewing distance of approximately 45 cm, subtending 5° of visual angle. Stimuli were delivered using Cogent 2000 v1.32 running under MATLAB R2015a (The MathWorks, Inc., Natick, MA). Time-course series of the two tasks were acquired using a T2*-weighted multiband echo planar imaging (EPI) sequence, with a slice acquisition acceleration factor of 8, obtaining about 960 volumes of the PAR task and 880 volumes of the N-back task. Each volume consisted of 72 axial slices oriented 30° to the AC–PC line and covering the whole brain. Slices were acquired bottom-up in the interleaved mode. The following functional imaging parameters were used: repetition time (TR) = 800 ms, echo time (TE) = 37 ms, flip angle = 52°, matrix = 104 × 104, field of view (FoV) = 208×208 mm, slice thickness = 2.0 mm with a 20% gap, resulting in 2.0 mm isotropic voxels. A single-band reference image of high quality and increased contrast was acquired for each fMRI task and was used for registration.

Structural T1

A whole-brain, high-resolution T1-weighted 3D structural image was obtained using a magnetisation-prepared gradient-echo sequence, consisting of 192 contiguous axial slices (TR = 2300 ms, TE = 2.19 ms, flip angle = 9°, matrix = 256 × 256, FoV = 256 × 256 mm, 1.0 mm isotropic voxel size). The T1-weighted image was used as an anatomical reference for each participant's functional data.

Diffusion MRI

Multi-shell diffusion-weighted data were acquired with single-shot, twice-refocused pulse gradient spin-echo EPI using multiband (MB) acceleration factor 2. Sixty axial slices oriented 30° to the AC–PC line and covering the whole brain were acquired with the following parameters: TR = 4000 ms, TE = 80 ms, matrix size = 96 x 96, FoV = 205 x 205 mm, slice thickness = 2.14 mm, 2.14 mm isotropic voxel size. Two b-value shells were acquired, b = 800 and 2800 s/mm^2, with 30 and 64 non-collinear diffusion-weighted directions, respectively. Two images with no diffusion weighting (b = 0) were acquired. Further images with b = 0 were acquired in the opposite phase encoding direction in order to estimate and correct for susceptibility induced distortions.

2.3.4 fMRI analyses

Preprocessing

We used SPM12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; www.fil.ion.ucl.ac.uk/spm) running under MATLAB R2019a for data preprocessing and statistical analyses. Preprocessing of functional images was carried out for both the pre- and post-training PAR and N-back tasks. High pass temporal filtering (128s) was applied to remove low frequency signals relating to scanner drift. Spatial realignment to the single band reference image and motion correction was applied using the Realign and Unwarp algorithms in SPM (Andersson et al., 2001; Hutton et al., 2002). All EPI data were brought into an approximate alignment across scans and sessions using an affine transformation with the FLIRT tool in FMRIB software library (FSL, version 5.0.7, Oxford, UK). Each T1-weighted structural image was segmented and used to compute a group template image using the DARTEL toolbox. EPI data were warped to MNI space with transformation parameters derived from the group template image (Ashburner, 2007). The normalised functional images were spatially smoothed using a 5mm full-width-half-maximum (FWHM) Gaussian kernel.

2.3.4.1 fMRI PAR task

We used an event-related design for the PAR task and conducted region of interest (ROI) analyses for 3 types of memory: associative retrieval, working memory, and recognition. During the cue period (1s) of the PAR task, participants were asked to use the cue to retrieve the matching target (associative retrieval). During the delay period (8s), participants were required to hold the retrieved picture in mind (working memory). The target presentation (1s) comprised the associative recognition stage, where participants were asked to recognise the target as the matching or non-matching pair-associate. Following target presentation, a response window appeared and stayed on screen for 3 seconds, during which participants were asked to press 1 of 2 buttons, providing decisions about the target (match/non-match). The button-presses were followed by a variable intertrial interval (ITI) of 6 – 10s, pseudorandomly biased towards 8 and 10s.

First-level analysis

A first-level general linear model (GLM) analysis was conducted to estimate BOLD responses to each component of the correctly remembered memory items. At the single-subject level, we specified regressors associated with the cue, delay, and target period for each session. This resulted in two regressors of interest relating to associative retrieval: pre-training_cue, post-training_cue; two regressors of interest relating to working memory: pre-training_delay, post-training_delay; and two regressors of interest relating to associative recognition: pre-training_target, and post-training_target. Associative retrieval (cue period), working memory (delay period), and associative recognition (target period) were analysed by including only correct responses (collapsing across Hit and correct rejection trials, i.e., correct match and non-match trials). Regressors of no interest included the prompt (containing a participant's button presses), and a nuisance regressor (containing all misses, false alarms, and non-responses). Additional nuisance regressors included: 6 affine motion parameters, their first-order derivatives, and regressors censoring periods of excessive motion (rotations > 1°, and translations > 1mm). For each regressor representing a cue and target period, activation was modelled using a boxcar function starting at onset and lasting for 1 second. Regressors representing a delay period were modelled to start 3 seconds after delay onset and lasted for 5 seconds until the end of the delay period. This was done to avoid capturing any residual activity pertaining to the cue period, but instead explaining a largely unique source of variance pertaining to delay period activity (Rissman et al., 2004). All regressors were convolved with a canonical hemodynamic response function available in SPM12.

Second-level analyses

Results of the single-subject analysis were taken to group-level to examine activation differences following training in regions of interest (ROI). The subject-specific contrast images of pre-training and post-training cue, delay, and target period were entered into separate 2 group (adaptive, non-adaptive) × 2 session (pre-training, post-training) x 3 period (cue, delay, target) mixed ANOVAs for each ROI using the full factorial design specification in SPM12. Group (adaptive, non-adaptive) was entered as the between-subject factor, and session (pre-training, post-training) and period (cue, delay,

target) as the within-subject factors. All main and interaction effects derived from the ANOVAs are reported using a statistical significance of $p < .05$ after False Discovery Rate (FDR) correction for multiple comparisons at the cluster level, clusters formed using $p < .001$ (Genovese et al., 2002; Chumbley & Friston, 2009). Significant clusters for all analyses were localised according to the Anatomy toolbox (v 2.2b, Eickhoff et al., 2005).

ROI analyses were carried out based on areas that were thought to overlap between our cognitive training programme and the PAR task. In particular, we expected brain regions involved in working memory to be recruited during our training programme and during the PAR task. Working memory emerges from the dynamic interaction of a large number of brain areas including dorsolateral PFC, ventrolateral PFC, frontal pole, superior parietal cortex, inferior parietal cortex, inferior temporal cortex, striatum, and cerebellum (Curtis & D'Esposito, 2003; Wager & Smith, 2003; Ranganath et al., 2004; Owen et al., 2005; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019; Pappa et al., 2020). Thus, we specified 8 anatomical ROIs bilaterally that included dorsolateral PFC, ventrolateral PFC, frontal pole, superior parietal cortex, inferior parietal cortex, inferior temporal cortex (including inferior temporal gyrus, fusiform gyrus, and parahippocampal gyrus), striatum (including caudate and putamen), and cerebellum. All ROI masks were from the WFU PickAtlas v2.4 (http://www.nitrc.org/projects/wfu_pickatlas/; Maldjian et al., 2003).

2.3.4.2 fMRI N-back task

We used a block design for the N-back task and conducted ROI analyses for the 4 conditions of the task (0-back, 1-back, 3-back, and 4-back). The 0-back was designed to act as a control condition (vigilance state) and provided the baseline activation for comparison in fMRI analyses. The 1-back, 3-back, and 4-back conditions provided increasing working memory demands. The task was to decide whether the current letter on the screen matched the one that was presented *N* items back in the series. Participants were required to press a button indicating when the target was a match to the letter presented *N* items back (i.e., Hit), and to not press the button if they didn't think the target was a match (i.e., Correct Rejection). There were 4 blocks of each condition (0-back, 1-back, 3-back, and 4-back).

First-level analysis

Imaging data from the N-back experiment were analysed within the framework of the GLM to estimate BOLD responses to each of the four levels. For the single-subject analysis, we specified regressors associated with the experimental conditions of 0-, 1-, 3-, and 4-back for each session. This resulted in two regressors of interest relating to the 0-back condition: pre-training_0-back, post-training_0-back; two regressors of interest relating to the 1-back condition: pre-training_1-back, post-training_1-back; two regressors of interest relating to the 3-back condition: pre-training_3-back, post-training_3-back, and two regressors of interest relating to the 4-back condition: pre-training_4-back, and post-training_4-back. Regressors of no interest included the on-screen instructions, and a nuisance regressor (containing all misses and false alarms). Additional nuisance regressors included: 6 affine motion parameters, their first-order derivatives, and regressors censoring periods of excessive motion (rotations > 1°, and translations > 1mm). For each regressor representing an N-back condition, activation was modelled using a boxcar function starting at the onset of a block and lasting until the end of the block (i.e., 40 seconds). All regressors were convolved with a canonical hemodynamic response function available in SPM12. A series of contrasts was then produced for each session representing mean activation during each N-back condition minus the 0-back condition, which acted as the baseline activation (pre-training: 1-back – 0-back, 3-back – 0-back, 4-back – 0-back; post-training: 1-back – 0-back, 3-back – 0-back, 4-back – 0-back).

Second-level analyses

Results of the single-subject analysis were taken to group-level to examine activation differences following training in regions of interest (ROI). The subject-specific contrasts of pre- and post-training 0-back, 1-back – 0-back, 3-back – 0-back, and 4-back – 0-back, were entered into separate 2 group (adaptive, non-adaptive) × 2 session (pre-training, post-training) x 4 condition (0-, 1-, 3-, and 4-back) mixed ANOVAs for each ROI using the full factorial design specification in SPM12. Group (adaptive, non-adaptive) was entered as the between-subject factor, and session (pre-training, post-training) and condition (0-, 1-, 3-, and 4-back) as the within-subject factors. All second level analyses

were thresholded at cluster-wise FDR-correction $p < .05$ (cluster-forming threshold $p < .001$). Significant clusters for all analyses were localised according to the Anatomy toolbox (v 2.2b, Eickhoff et al., 2005).

The N-back task was specifically developed as a test of working memory (Kirchner, 1958; Mackworth, 1959). Therefore, ROI analyses were carried out using the same working memory regions as used for the PAR task. We specified 8 anatomical ROIs bilaterally: dorsolateral PFC, ventrolateral PFC, frontal pole, superior parietal cortex, inferior parietal cortex, inferior temporal cortex (including inferior temporal gyrus, fusiform gyrus, and parahippocampal gyrus), striatum (including caudate and putamen), and cerebellum. All masks were from the WFU PickAtlas v2.4 (Maldjian et al., 2003; http://www.nitrc.org/projects/wfu_pickatlas/).

2.3.5 Diffusion MRI analyses

Preprocessing

Diffusion data were first preprocessed using tools from FSL (version 5.0.7, Oxford, UK). FSL's topup tool was used to correct for susceptibility and the Eddy command was used to correct for eddy current distortions (Andersson et al., 2003). Following this, b-vectors from the transformation matrix were rotated accordingly (Leemans & Jones, 2009).

The NODDI model was then fitted to the data using the toolbox by Zhang et al. (2012) provided for Matlab (The MathWorks, Inc., Natick, MA, USA), generating voxel-wise whole-brain maps of NDI and ODI for each participant per session. The NODDI analysis was performed using Matlab (v.2012b) on the University of Sussex high-performance computing cluster with 128 cores. The diffusion tensor model was then fitted to the same data using the FSL tool DTIfit in order to compute FA and MD whole-brain maps. The resulting NODDI and DTI parameter maps were normalised to MNI space using the Advanced Normalization Tools (ANTs, version 2.1.0) in order to permit group-

level statistical comparison. Parameter maps were then spatially smoothed with a 5 mm FWHM Gaussian kernel in FSL.

Statistical analyses

We used FSL (version 5.0.7, Oxford, UK) for all statistical analyses. Whole-brain parameter maps from session one were subtracted from whole-brain parameter maps from session two in order to obtain ODI, NDI, FA, and MD change from baseline for each participant. These difference maps (session two – session one) were entered into whole-brain voxel-wise one- and two-sample t-tests to identify effects of overall training, as well as adaptive versus non-adaptive training, on regional differences in NDI, ODI, FA, and MD parameters. A statistical significance threshold of $p < .05$ FWE-corrected at the cluster level was used, after clusters were formed with an uncorrected $p < .001$.

Chapter 3: Perceptual-cognitive-motor training in middle-aged adults: Behavioural and MRI findings

3.1 Introduction

3.1.1 Motor skill learning in middle-age

Most motor skill learning studies investigating age-related changes, like most cognitive studies investigating age-related changes, compare older adults' performances with that of younger adults, but do not include middle-aged participants (Voelcker-Rehage, 2008). This is a significant omission given that the few life-span studies that have been conducted indicate that the reduction in motor plasticity occurs not particularly in older age, but in middle-age (after a peak in youth and younger adulthood) (Gershon, 1978; Voelcker-Rehage & Wilimczik, 2006; Voelcker-Rehage, 2008; Janacsek et al., 2012). Studies looking at the acquisition of a complex motor skill showed that performance decrements start early in middle-age (30–45 years) (Gershon, 1978; Voelcker-Rehage & Wilimczik, 2006; Janacsek et al., 2012). For example, Janacsek et al. (2012) investigated motor sequence learning across the life span, between 4–85 years of age, and found that in terms of reaction time and accuracy, age groups between 9 and 44 years of age showed similar degrees of sequence learning, and this was significantly higher than the youngest (4–8) and the two oldest (45–59 and 60–85) groups. Thus, it appears that motor skill learning ability starts to decline in middle-age, therefore, this would be a good age group for the initiation of training programmes.

3.1.2 fMRI and motor skill training

Researchers have used fMRI and other methodologies to demonstrate differences in brain function and structure after practice at perceptual-motor tasks (e.g., Floyer-Lea & Matthews, 2005), or perceptual-cognitive tasks (e.g., Forstmann et al., 2008). For example, short-term training at a computer-based tracking task led to improved performance and increased activity in subcortical circuits of the brain (striatum, cerebellum), whereas longer-term training led to changes in the primary somatosensory and motor cortex that increases the implicit representation for sequences learned (Floyer-Lea & Matthews, 2005). These findings are consistent with the view of neuroplasticity where structural and functional changes occur in the brain as a result of training, practice, and experience (Jancke, 2009; Dayan & Cohen, 2011).

The brain regions involved in motor skill learning differ depending on whether it is the early or late phase of training, and on the nature of the cognitive processes required (Doyon et al., 2003; Coynel et al., 2010; King et al., 2013). Doyon and Ungerleider (2002) have proposed a model for characterising the complex pattern of brain activation underlying motor skill training. Two loop circuits, a cortico-striatal and a cortico-cerebellar system, are both recruited and operate in parallel during the fast learning stage. Early in the learning phase, the following structures are recruited: the striatum, cerebellum, motor cortical regions (e.g., premotor cortex, SMA, preSMA, anterior cingulate), as well as prefrontal and parietal areas.

Similarly, in a model proposed by Hikosaka et al. (2002), two loop circuits are recruited which specialise in learning spatial and motor features of sequences independently. Learning spatial coordinates is supported by a frontoparietal-associative striatum-cerebellar circuit, while learning motor coordinates is supported by an M1-sensorimotor striatum-cerebellar circuit. The coordinate transformation between the spatial and motor sequences depends on the SMA, pre-SMA, and premotor cortices. Importantly, it is argued that learning spatial coordinates is usually explicit and faster as it may be accompanied by increased attention or working memory, putatively involving prefrontal and parietal cortical regions (Miller & Cohen, 2001). By contrast, motor coordinates are usually processed implicitly and require minimum attention, therefore they are slowly acquired during learning.

3.1.3 Diffusion MRI and motor skill training

Studies using DTI have shown that inter-individual variation in white-matter microstructure, as measured by FA, correlates with behavioural performance (e.g., Tuch et al., 2005; Johansen-Berg et al., 2007). Moreover, studies have demonstrated microstructural differences in white matter after long-term motor skill training (Scholz et al., 2009; Takeuchi et al., 2010). For example, Scholz et al. (2009) used DTI to measure white matter changes following training of a novel complex visuomotor skill (i.e., juggling). Participants were scanned before and after a 6-week training period, or following no training (control group). The trained group revealed significant increases in FA within white matter underlying the posterior intraparietal sulcus.

In addition to the structural changes shown to occur following long-term training (days or weeks) of a new motor skill (e.g., Draganski et al., 2004; Scholz et al., 2009), these types of changes have also been demonstrated with relatively short timescales (Sagi et al., 2012; Hofstetter et al., 2013). Invasive microscopy procedures have been able to detect regional structural changes such as dendritic spine formation and oligodendrogenesis after short-term motor skill training within 1 – 2.5 hours (Xu et al., 2009; Xiao et al., 2016). Such short-term effects have been more difficult to detect so far by non-invasive techniques such as diffusion MRI. However, Sagi et al. (2012) have shown that this is indeed possible using DTI. Sagi et al. (2012) scanned participants before and after a spatial navigation task based on a computer car race game. Microstructural changes in grey matter were significant after only 2 hours of training. Specifically, the training group showed a reduction in MD in the hippocampus and parahippocampus. An increase in FA was found in the parahippocampus, supramarginal/angular cortex, superior temporal gyrus, amygdala, and pulvinar. Moreover, there was a significant negative correlation between improvement rate in the car racing task and MD reduction in the hippocampus and parahippocampus.

The interpretation of such changes in DTI indices is challenging. FA in part reflects anatomical features of white matter such as axon calibre, fibre density, and myelination (Beaulieu, 2009). Modifications in these properties might underlie training improvements by altering conduction velocity and synchronisation of nervous signals (Fields, 2008). It is possible that newly generated myelin is laid down preferentially in circuits that are engaged during training (McKenzie et al., 2014). This activity-dependent myelination, which would be expected to influence FA, is therefore a potential mechanism through which the properties of white matter are affected by experience (Scholz et al., 2009). Changes in other structural features of white matter, such as axon diameter (which could itself be regulated by myelin; Fields, 2008), or packing density, could also underlie differences in FA (Scholz et al., 2009). Changes in MD might be attributed to alterations in extracellular volume (Ransom et al., 1985; Sykova, 1997; Hofstetter et al., 2013), swelling of cells (Le Bihan, 2007; Hofstetter et al., 2013), or an increase in glia cell volume (Kleim et al., 2007; Theodosis et al., 2008; Markham et al., 2009; Hofstetter et al., 2013). Therefore, although widely used, DTI indices are average measurements across a voxel from multiple

different compartments, including both intracellular and extracellular spaces (Kodiweera et al., 2016). Hence, a change in these measurements cannot be attributed to specific changes in tissue microstructure (Pierpaoli et al., 1996; Zhang et al., 2012; Jones et al., 2013; Jelescu et al., 2016).

NODDI is a diffusion MRI model that is able to differentiate between three different (and more specific) microstructural indices: intracellular, extracellular, and cerebrospinal fluid (CSF) (Zhang et al, 2012). This means that NODDI indices are less ambiguous microstructural interpretations. Indeed, NODDI has been used with success to investigate age-associated changes to white matter (Kodiweera et al., 2016), and cortical grey matter (Nazeri et al., 2015). Nazeri et al. (2015) examined age-related effects on grey matter neuritic organisation and density in humans across the adult lifespan (21– 84 years). A detailed analysis using 48 ROIs revealed that ODI extracted from a majority of cortical regions (27 of 48) showed a significant decline with age. Importantly, the researchers demonstrated that neocortical ODI outperformed cortical thickness and white matter FA for the prediction of chronological age. NODDI can therefore provide information about underlying microstructure beyond that of traditional diffusion methods such as DTI.

3.1.4 Experiment aims and design

The aim of the current experiment was to investigate the functional and structural correlates of short-term training in healthy middle-aged adults (40-50 years old). Motor skill learning ability and grey matter volume start to decline in middle-age (Gershon, 1978; Courchesne et al., 2000; Voelcker-Rehage & Wilimczik, 2006; Janacsek et al., 2012). As such, we sought to investigate training in this age group.

Participants in this study trained on a novel and complex perceptual-cognitive-motor (PCM) task (Bennett et al., 2018). This task requires motor as well as cognitive processes (including decision making, working memory, attention, and pattern recognition). Therefore, we decided to use the PCM task as it is multidomain, and as discussed, this form of training has been shown to be particularly effective in improving

cognitive function (Green & Bavelier, 2003; Basak et al., 2008; Lustig et al., 2009; van Muijden et al., 2012).

For this experiment, we sought to characterise functional plasticity at the early stage of training, as such, we used fMRI to investigate changes in activation over 1 session (i.e., 31 minutes of training = 160 trials). In addition, we sought to link functional plasticity as a result of training, with underlying structure. Thus, we used both DTI and NODDI to analyse microstructural variation in grey and white matter in relation to training outcome.

3.1.5 Experiment hypotheses

We tested four hypotheses for this experiment. First, if training in middle-aged adults is effective at inducing cognitive plasticity, then we should see significant training gains for the PCM task. PCM training has been shown to greatly improve performance on this task in young adults when compared to age-matched controls that received no training (*M* = 22.3 years of age, Bennett et al., 2018; *M* = 21.8 years of age, Uji et al., unpublished data). Moreover, several studies have shown substantial improvements on trained tasks, and with multidomain training in particular, in both young and older adults (e.g., Green & Bavelier, 2003; Rebok et al., 2007; Basak et al., 2008; Lustig et al., 2009; Karbach & Verhaeghen, 2014). As the PCM task is multidomain (for example, it involves working memory, decision-making, and motor processes), as trained tasks have shown improvements in both young and older adults, and as training on the PCM task in particular has previously resulted in better performance in young adults, we expected significant improvements in PCM performance with training in middle-aged adults.

Second, if increased activity occurs in the brain following short-term training, whereas longer-term training results in decreases in activity (Braver et al., 2009; Lustig et al., 2009), then we should see increased activation in cognitive and motor networks for the PCM task. According to the Doyon and Ungerleider (2002) model, early in the learning phase of motor skill training (i.e., session 1), the following structures are recruited: the striatum, cerebellum, premotor cortex, SMA, preSMA, anterior cingulate, as well as prefrontal and parietal areas. The Hikosaka et al. (2002) model suggests that learning spatial coordinates is supported by a frontoparietal-associative striatum-cerebellar circuit,

while learning motor coordinates is supported by an M1-sensorimotor striatum-cerebellar circuit, and transformations between the two coordinate systems depend on the SMA, preSMA, and premotor cortices. In addition, the ability to perform complex problems is initially supported by extensive attentional and strategic resources, which engage a prefrontal, orbitofrontal, and anterior cingulate network (Minati & Sigala, 2013). The hippocampus has shown increases in activity in both the early and later stages of motor skill learning (Schendan et al., 2003; Albouy et al., 2008; Fernández-Seara et al., 2009; Gheysen et al., 2010; King et al., 2013). And finally, the parahippocampal cortex is highly engaged during visuospatial processing (van Strien et al., 2009; Aminoff et al., 2013; Hohenfeld et al., 2020), a key aspect of the PCM task. Specifically, we expected PCM learning to be supported by increased activity in the striatum, cerebellum, hippocampus, parahippocampus, SMA, preSMA, M1, premotor cortex, anterior cingulate, dPFC, orbitofrontal cortex (oPFC), and inferior parietal cortex. The precuneus and vPFC were selected to serve as control regions. We did not expect to see a change in activity in these areas as they show increased activation during later stages of motor skill learning (Doyon, 1997; Sakai et al., 1998; Doyon & Ungerleider, 2002; Ungerleider et al., 2002; Doyon et al., 2003; Lehéricy et al., 2005; King et al., 2013).

Third, if learning is supported by changes in brain function, then we would expect to see differences in activity for successful vs. unsuccessful trials on the PCM task. Some studies have shown increases in brain activity for successful vs. unsuccessful trials (Daniel & Pollmann, 2010; Swann et al., 2012). Specifically, posterior putamen activation was increased for successful *vs.* unsuccessful categorisation with either monetary reward or informative (correct/incorrect) feedback (Daniel & Pollmann, 2010). In addition, Swann et al. (2012) found significantly increased activity in preSMA and inferior frontal gyrus for successful vs. unsuccessful trials on an inhibitory motor task. Therefore, we predicted that successful trials would show increased activation compared to unsuccessful trials in the above cognitive and motor networks.

Finally, if brain structure influences motor skill learning ability, then variation in microstructure should be related to training outcome for the PCM task. Studies using DTI have shown that inter-individual differences in brain structure correlate with behavioural

performance (e.g., Tuch et al., 2005; Johansen-Berg et al., 2007). Therefore, we expected microstructural variance in grey and white matter to correlate with learning outcome. Specifically, lower MD and higher FA would be associated with greater improvement in PCM performance. With regards to NODDI indices, higher levels of NDI indicate a greater density of axons in white matter and dendrites in grey matter (Zhang et al., 2012). Therefore, we expected that higher NDI in both grey and white matter would correlate with improved performance on the task. For ODI, in voxels containing very directional white matter tracts, lower ODI indicates less axonal dispersion and high axonal coherence (Zhang et al., 2012). Whereas higher ODI in grey matter indicates areas that are rich in multi-directional dendritic structure (Dowell et al., 2019). As such, we predicted that ODI would correlate with improved performance depending on whether in the white matter (i.e., lower ODI), or grey matter (i.e., higher ODI).

3.2 Summary of methods

3.2.1 Participants

Twenty-two middle-aged adults between 40 and 50 years old were recruited for this experiment. All participants had normal or corrected-to-normal vision and were right-hand dominant. The participants had no history of psychiatric or neurological illness, or brain injury. Participants also had no history of alcohol or drug use disorders. Participants were not taking prescribed medications at the time of the experiment. All participants were carefully screened for MRI contraindications. Due to low task-engagement during the session, one participant was excluded, leaving 21 participants in the final sample (female: n = 11; age: M = 44.67 years, SD = 3.23) in a within-subjects study design. The mean number of years of education for the sample was 18.24 (SD = 2.72).

3.2.2 Procedure

All participants underwent one MRI scanning session during which they performed the perceptual-cognitive-motor (PCM) task. The task goal was for participants to move the white cursor to the red target while avoiding a number of moving green objects on the screen. They completed 80 trials (~15min) of the task in a pre-training phase while undergoing fMRI scanning. Following this, they completed 72 trials during a training

phase while undergoing T1 structural and diffusion scanning (~15min). Finally, they repeated 80 trials (~15min) of the task during a post-training phase while undergoing fMRI scanning.

3.2.3 Behavioural data analysis

Number of successful trials on the PCM task was analysed using a paired samples t-test comparing pre- and post-training performance. Statistical significance was set at $p < .05$ (two-tailed). Cohen's *d* was used as an effect size measure (Cohen, 1992).

3.2.4 fMRI data

ROI analyses

We examined activation changes in regions of interest (ROI) following PCM training. In addition, we compared activity for successful vs unsuccessful trials in the task-relevant ROIs. The subject-specific beta images of Pre-training_Successful, Pre-training_Unsuccessful, Post-training_Successful, and Post-training_Unsuccessful were entered into separate 2 × 2 repeated measures ANOVAs for each ROI using the full factorial design specification in SPM12. Testing Phase (Pre-training, Post-training) and Trial Performance (Successful, Unsuccessful) were entered as within-subject factors to look for differences in brain activation for successfully vs unsuccessfully performed trials during the pre- vs post-training phases. We calculated the main and interaction effects of Testing Phase and Trial Performance using an *F*-contrast, whilst inclusively masking the effects with each ROI. The WFU PickAtlas v2.4 toolbox (Maldjian et al., 2003; http://www.nitrc.org/projects/wfu_pickatlas/) was used to select masks and add the ROI dialog into the SPM GUI, restricting the search space before the analysis was run. All main and interaction effects derived from the ANOVAs were initially thresholded at a statistical significance of $p < .05$ after False Discovery Rate (FDR) correction for multiple comparisons at the cluster level, clusters formed using $p < .001$ (Genovese et al., 2002; Chumbley & Friston, 2009). However, none of the ROI ANOVAs survived the FDR correction for multiple comparisons. We therefore used an exploratory uncorrected threshold of $p < .005$ and k = 5 voxels to test for main and interaction effects. Significant

clusters for all analyses were localised according to the Anatomy toolbox (v 2.2b, Eickhoff et al., 2005).

To further explore differences in Testing Phase, we ran the contrasts Pre-training > Post-training and Post-training > Pre-training in each ROI using the uncorrected threshold of $p < .005$ and k = 5 voxels. We then computed normalised difference scores for the PCM task indicating training outcome, such that Difference Score = (Post-training score - Pre-training score) / (Post-training score + Pre-training score). Higher difference scores indicate a bigger training gain. Correlations were run between the training outcome and percent change in betas in the ROIs that showed a significant effect for the contrasts Pre-training > Post-training and Post-training > Pre-training with the exploratory threshold for significance. To this end, we used the MarsBaR (MARSeille Boîte À Région d'Intérêt) 0.44 toolbox for SPM (Brett et al., 2002) to extract the mean percent change in beta values for the ROIs with a significant effect, and correlated this with the normalised difference scores using an in-house script run in MATLAB R2015a.

Specification of ROI masks

All ROI masks were bilateral and chosen from the WFU PickAtlas. Selecting masks from the WFU PickAtlas resulted in masks being larger than required, and therefore, significant effects may also have been detected for neighbouring brain regions outside those of interest. ROIs were selected based on the models for motor skill learning by Hikosaka et al. (2002) and Doyon and Ungerleider (2002). These models include the striatum, cerebellum, premotor cortex, SMA, preSMA, M1, anterior cingulate, as well as prefrontal and parietal areas. In addition, we included the hippocampus as increases in activity have been demonstrated in this region for both the early and later stages of motor training (Schendan et al., 2003; Albouy et al., 2008; Fernández-Seara et al., 2009; Gheysen et al., 2010; King et al., 2013). And finally, the parahippocampal cortex was included as it is highly engaged during visuospatial processing (van Strien et al., 2009; Aminoff et al., 2013; Hohenfeld et al., 2020), a key aspect of the PCM task. As such, we specified 12 anatomical ROIs bilaterally: striatum (including caudate and putamen), cerebellum, hippocampus, parahippocampus, SMA, preSMA, M1, premotor cortex, anterior cingulate, dPFC, oPFC, and inferior parietal cortex. The precuneus and vPFC were

selected to serve as control regions. We did not expect to see a change in activity in these areas as they show increased activation during later stages of motor skill learning (Doyon, 1997; Sakai et al., 1998; Doyon & Ungerleider, 2002; Ungerleider et al., 2002; Doyon et al., 2003; Lehéricy et al., 2005; King et al., 2013).

3.2.5 Diffusion MRI data

Whole-brain analyses

We used diffusion imaging to examine microstructural variation in grey and white matter in relation to training outcome. Quantifying neurite morphology in terms of its density and orientation distribution provides a window into the structural basis of brain function (Zhang et al., 2012). ROI analyses were chosen for the fMRI data due to strong a-priori hypotheses based on extensive research on motor skill learning in young adults (e.g., Grafton et al., 1995; Nudo et al., 1996; Karni et al., 1998; Ungerleider et al., 2002; Doyon et al., 2003; Krakauer et al., 2005; Penhune & Steele, 2012; King et al., 2013). Conversely, diffusion analyses were whole-brain because very few studies have used DTI to investigate training (Scholz et al., 2009; Takeuchi et al., 2010; Sagi et al., 2012; Hofstetter et al., 2013), and none have used NODDI. Therefore, there is very little diffusion MRI research on which to base the selection of regions for investigation of the relationship between brain structure and training outcome. As such, an exploratory analysis examining the whole brain was deemed as the most appropriate way to analyse the diffusion imaging data. However, an exploratory analysis may result in "fishing" for statistically significant signals, rather than running analyses with the purpose of testing the hypotheses. On the other hand, research is done not only to test hypotheses and confirm theories, but also to expand them. Therefore, an exploratory whole-brain analysis might be useful in the first instance when using relatively new techniques such as NODDI, and could potentially give us novel information that we may otherwise miss. In terms of linking training-induced functional plasticity with underlying structure, it may have been reasonable to base our diffusion analyses on the same ROIs used in our fMRI analyses, which were based on extensive previous research on motor skill training. This limitation is somewhat mitigated if structure and training outcome relationships are demonstrated in regions with functional significance for the PCM task, and in regions within which

functional alterations occurred following training on the PCM task (discussed further in section 3.4.3.4 Diffusion MRI findings and functional significance, pg. 118).

Correlations were run between the PCM normalised difference scores and the DTI indices of FA and MD, and the NODDI indices of NDI and ODI. The whole-brain voxel-wise analyses were conducted using a simple regression (converted to t-contrast) procedure. We ran the contrasts 0 1 to check for positive correlations and 0 -1 to check for negative correlations between each index and difference scores. A statistical significance threshold of $p < .05$ FDR-corrected at the cluster level was used, after clusters were formed with an uncorrected $p < .001$.

3.3 Results

3.3.1 Behavioural results

Correlations were run to determine if there were any relationships between the demographic data (gender, age, education) and the normalised difference scores. Tests of assumptions for the point-biserial correlation of gender x difference scores indicated no outliers in the difference scores for females and no outliers for males (Appendix V, Figure V.1, pg. 285). A Shapiro-Wilk test for females showed that difference scores are normally distributed, $W(11) = .961$, $p = .785$; as did a Shapiro-Wilk test for males, $W(10) = .965$, $p = .836$. Levene's test found that the assumption of homogeneity of variance for female and male difference scores was met, $F(1,19) = .424$, $p = .523$. The point-biserial correlation demonstrated that there was no significant relationship between gender and training outcome, $r_{pb} = -.049$, $p = .834$.

Tests of assumptions for the Pearson's correlation of age x difference scores indicated no outliers for age and no outliers for difference scores (Appendix V, Figures V.2 and V.3, pg. 286). A Shapiro-Wilk test showed that age is normally distributed, $W(21) = .925$, $p = .112$; as did a Shapiro-Wilk test for difference scores, $W(21) = .976$, $p = .863$. A scatterplot indicated that the assumption of homoscedasticity was potentially violated (Appendix V, Figure V.4, pg. 287). As such, Kendall's tau-b was included as this non-parametric test statistic does not require this assumption to be met. The Pearson's

correlation demonstrated that there was no significant relationship between age and training outcome, $r = .184$, $p = .424$; as did Kendall's tau-b, $\tau_b = .080$, $p = .625$.

Tests of assumptions for the Pearson's correlation of education x difference scores indicated no outliers for education (Appendix V, Figure V.5, pg. 288). Tests of assumptions for difference scores were not violated and are reported above. A Shapiro-Wilk test showed that education is normally distributed, $W(21) = .909$, $p = .052$. Scatterplots indicated the possibility of a quadratic relationship between the variables (Appendix V, Figures V.6 and V.7, pgs. 288 and 289). As such, a quadratic regression was conducted to see if this better described a potential relationship. The Pearson's correlation demonstrated that there was no significant relationship between education and training outcome, $r = -.007$, $p = .975$. The quadratic regression demonstrated that education did not significantly predict training outcome, $F(2,18) = 1.738$, $p = .204$, $R^2 = .162$. As there were no significant relationships found between th[illegible]emographics and training outcome, these variables were not used as covariates in any further analyses.

Tests of assumptions for the paired samples t-test comparing pre- and post-training scores indicated no outliers in the difference values (Appendix V, Figure V.8, pg. 290). A Shapiro-Wilk test showed that the distribution of the differences is normal, $W(21) = .970$, $p = .743$. The paired samples t-test revealed a statistically significant difference between the pre- and post-training phases, $t(20) = 7.52$, $p < .001$. Figure 3.1 shows the mean number of successful trials significantly increased from the pre-training phase (first 80 trials: $M = 24.71$; $SD = 13.96$) to the post-training phase (last 80 trials: $M = 37.00$; $SD = 14.59$). The effect size was large and positive, Cohen's $d = 0.88$. Participants performed 72 training trials between the pre- and post-training phases, during the structural and diffusion scanning sequences.

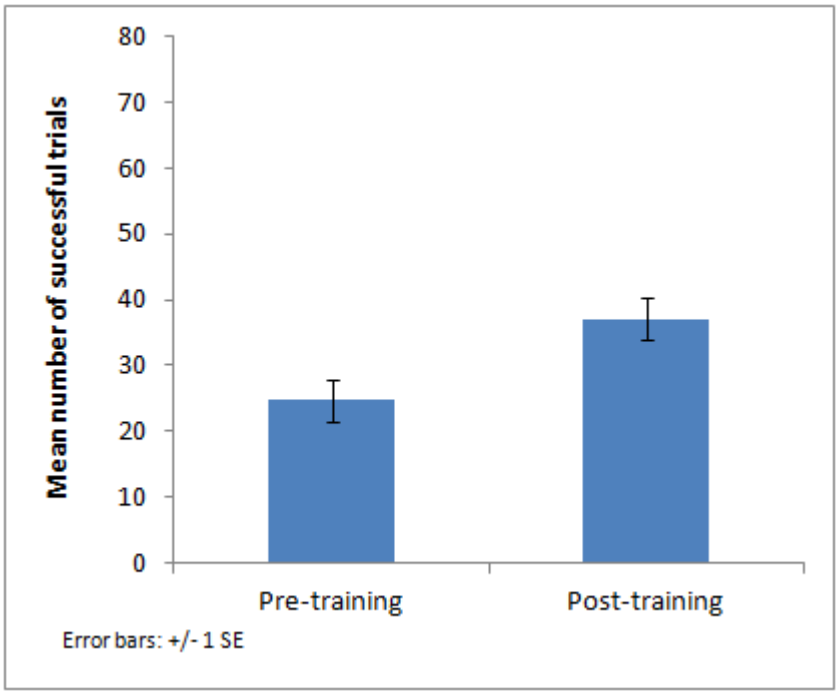


Figure 3.1. Mean number of successful trials in the pre- and post-training phases of the PCM task (out of a total of 80 trials). Error bars indicate the standard error of the mean.

3.3.2 fMRI results

ROI analyses

Separate 2 × 2 repeated measures ANOVAs were computed for each ROI with testing phase (Pre-training, Post-training) and trial performance (Successful, Unsuccessful) as within-subject factors. None of the ROI ANOVAs survived the necessary FDR correction for multiple comparisons. Using an exploratory uncorrected threshold of $p < .005$ and k = 5 voxels, we observed a main effect of testing phase bilaterally in cerebellum; in striatum (including left caudate and bilaterally in putamen); bilaterally in M1, premotor cortex, SMA, and preSMA; bilaterally in anterior cingulate cortex; left parahippocampal gyrus, left hippocampus, bilaterally in fusiform gyrus, and right lingual gyrus; bilaterally in superior parietal cortex, left inferior parietal cortex, right angular gyrus, right supramarginal gyrus, bilateral precuneus, and left postcentral gyrus; bilaterally in calcarine sulcus, and right cuneus; in right insula, right dPFC, right vPFC, and right oPFC (Table 3.1). There was no main effect of trial performance and no interaction between testing phase and trial performance in any of the ROIs.

Table 3.1. Exploratory ROI analysis: brain regions with a significant main effect of testing phase for the PCM task. Organised by ROI mask used for the analysis. A statistical significance threshold of $p < .005$ (uncorrected) with an extent threshold of 5 voxels was used.

Brain region	MNI coordinates			*F*-value	Cluster size (voxels)	*P*-value uncorrected
	x	y	z			
Cerebellum ROI mask						
Left cerebellum (Crus 2)	-6	-85	-22	39.97	79	.033
Right cerebellum (Crus 1)	21	-88	-28	24.22		
Right cerebellum (Crus 2)	6	-85	-28	14.87		
Right cerebellum (VI)	15	-82	-19	13.77		
Cerebellar vermis (10)	3	-46	-34	43.09	65	.050
Left cerebellum (Crus 2)	-21	-88	-31	12.56	11	.400
Left cerebellum (IV-V)	-6	-55	-4	12.88	7	.508
Striatum ROI mask						
Left putamen	-18	8	5	21.24	45	.096
Left caudate	-15	14	5	15.07	11	.400
Right putamen	27	-7	8	12.35	9	.449
M1 ROI mask						
Left precentral gyrus	-48	-4	44	17.25	10	.424
Right precentral gyrus	42	-13	41	11.58	10	.424
Left postcentral gyrus	-57	-16	35	13.20	9	.449
Left postcentral gyrus	-39	-25	56	11.05	5	.582
Premotor cortex ROI mask						
Right posterior-medial frontal	9	-13	53	16.87	55	.069
Right superior frontal gyrus	24	-1	59	24.08	32	.155
Left paracentral lobule	-3	-16	65	13.95	17	.294

Left posterior-medial frontal	-3	-10	65	13.00		
Left precentral gyrus	-48	-4	44	17.25	12	.379
Right posterior-medial frontal	6	2	56	11.86	10	.424
Right precentral gyrus	42	-1	41	10.82	7	.508
SMA ROI mask						
Right posterior-medial frontal	9	-13	53	16.87	103	.017
Left posterior-medial frontal	-3	-13	65	14.66		
Right posterior-medial frontal	6	5	59	12.67	31	.161
Left posterior-medial frontal	-12	8	59	15.94	20	.256
Right posterior-medial frontal	6	23	53	15.46	18	.281
preSMA ROI mask						
Right precentral gyrus	48	8	41	18.03	14	.341
Left posterior-medial frontal	3	23	53	13.02	13	.359
Right posterior-medial frontal	6	17	47	11.17		
Anterior cingulate ROI mask						
Left anterior cingulate cortex	-12	41	-1	22.92	23	.224
Right anterior cingulate cortex	9	38	-1	11.22	8	.477
Parahippocampal ROI mask						
Right lingual gyrus	27	-52	-7	20.59	19	.268
Right fusiform gyrus	30	-58	-10	11.48		
Left hippocampus	-21	-25	-13	20.39	12	.379
Left parahippocampal gyrus	-15	-34	-7	11.19		
Left fusiform gyrus	-33	-13	-31	15.67	9	.449
Hippocampus ROI mask						
Left hippocampus	-21	-22	-13	24.31	27	.189

Inferior parietal ROI mask						
Right supramarginal gyrus	63	-43	35	20.40	22	.234
Right angular gyrus	33	-55	44	20.03	21	.245
Left inferior parietal cortex	-30	-52	47	21.48	16	.309
Precuneus ROI mask						
Right precuneus	12	-70	44	20.99	68	.046
Right cuneus	15	-79	41	11.14		
Left precuneus	-12	-49	53	22.76	34	.143
Left inferior parietal cortex	-27	-52	44	17.55	24	.214
Left superior parietal cortex	-24	-61	47	9.70		
Right calcarine sulcus	3	-64	17	11.61	22	.234
Left calcarine sulcus	-3	-70	17	11.34		
Right precuneus	12	-43	53	25.97	20	.256
Right superior parietal cortex	27	-61	50	17.04	13	.359
dPFC ROI mask						
Right precentral gyrus	48	5	38	18.38	26	.195
Left posterior-medial frontal	3	23	53	13.02	13	.359
Right posterior-medial frontal	6	17	47	11.17		
vPFC ROI mask						
Right precentral gyrus	60	8	20	18.53	13	.359
Right IFG (p. Opercularis)	57	11	17	16.73		
Right IFG (p. Orbitalis)	39	20	-16	14.62	7	.508
Right insula lobe	33	26	2	10.79	5	.582
oPFC ROI mask						
Right superior frontal gyrus	24	62	2	17.40	14	.341
Right middle frontal gyrus	33	53	2	9.07		

P values are reported at the cluster level. The MNI coordinates refer to the peak *F*-value. Local maxima that are more than 8 mm apart are shown for each cluster. IFG = inferior frontal gyrus.

To further explore the differences in testing phase, we used an uncorrected threshold of $p < .005$ and k = 5 voxels with the contrasts Pre-training > Post-training and Post-training > Pre-training in each ROI. There was increased activity during pre-training bilaterally in cerebellum, left parahippocampal gyrus, and left hippocampus (Figure 3.2). There was increased activity during post-training bilaterally in cerebellum; in striatum (including left caudate and bilaterally in putamen); bilaterally in M1, premotor cortex, SMA, and preSMA; bilaterally in anterior cingulate cortex; bilaterally in superior parietal cortex, left inferior parietal cortex, right angular gyrus, right supramarginal gyrus, bilaterally in precuneus, and postcentral gyrus; bilaterally in cuneus, calcarine sulcus, right lingual gyrus, and right middle occipital gyrus; bilaterally in fusiform gyrus; in right insula; in right dPFC, right vPFC, and bilaterally in oPFC (Figure 3.3).

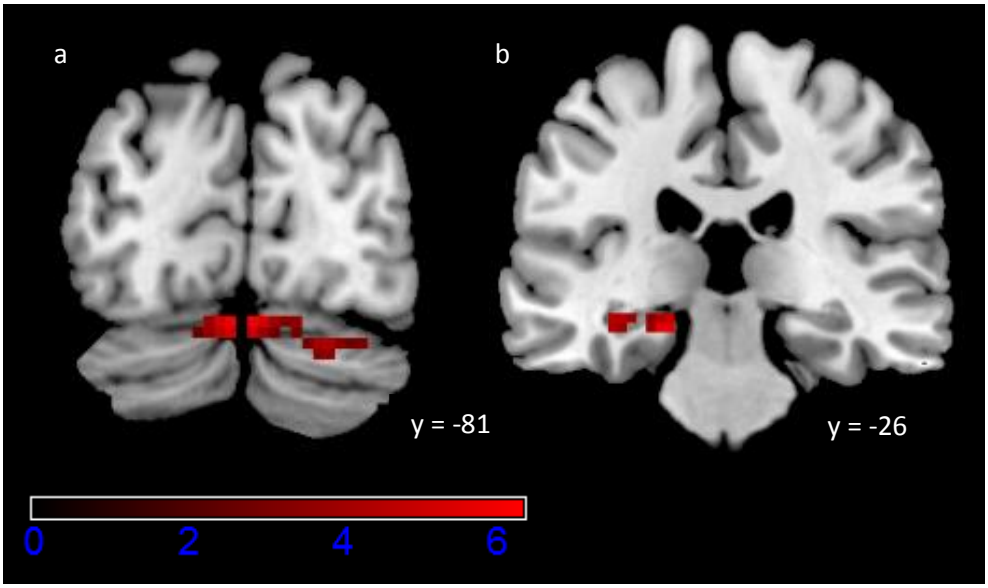


Figure 3.2. Exploratory ROI analysis for the PCM task: increased activity during pre-training a) bilaterally in cerebellum, b) left parahippocampal gyrus and hippocampus. A statistical significance of $p < .005$ (uncorrected) with an extent threshold of 5 voxels was used.

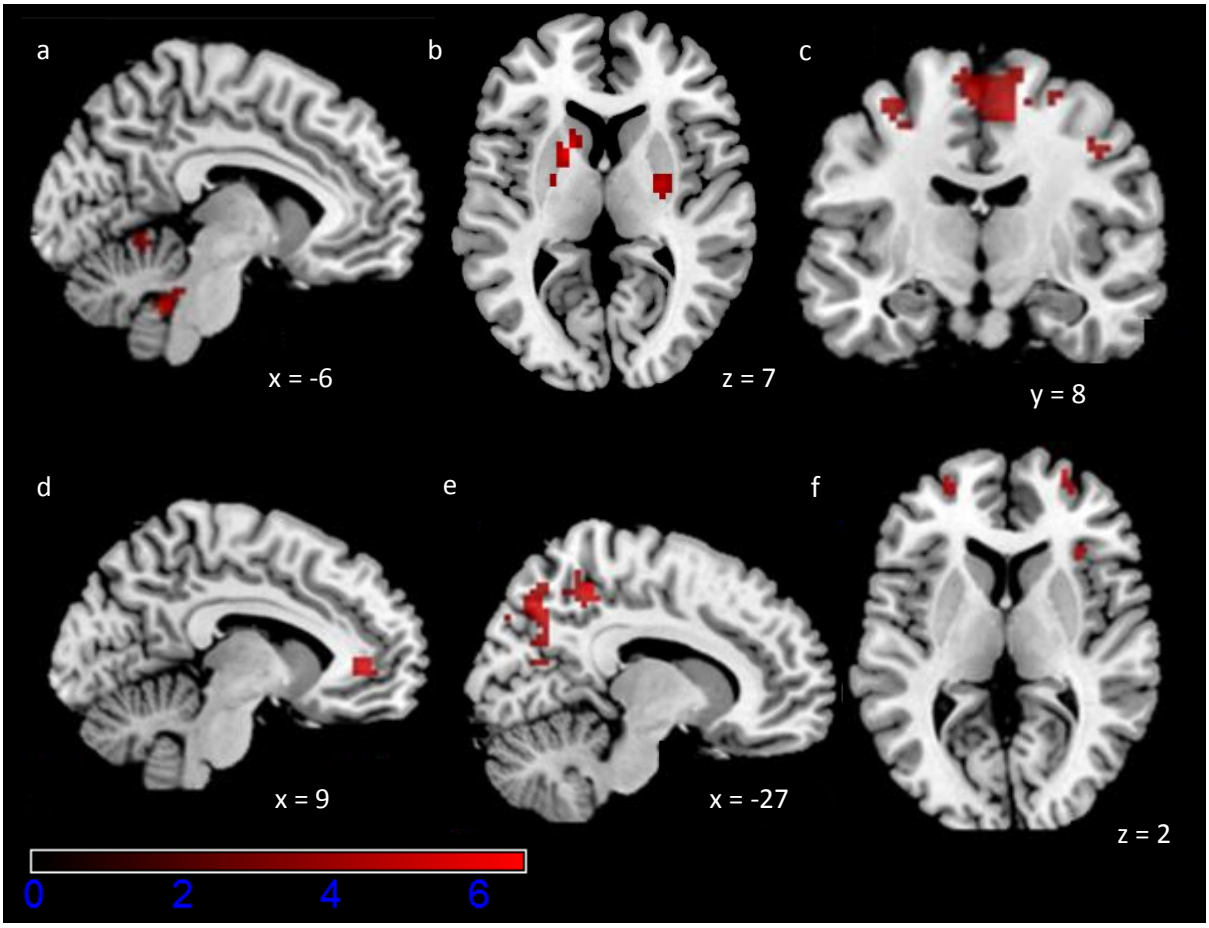


Figure 3.3. Exploratory ROI analysis for the PCM task: increased activity during post-training bilaterally in a) cerebellum; b) striatum; c) M1, premotor cortex, SMA, and preSMA; d) anterior cingulate cortex; e) superior parietal cortex, left inferior parietal cortex, right angular gyrus, right supramarginal gyrus, bilaterally in precuneus, postcentral gyrus (not shown), cuneus, calcarine sulcus (not shown), right lingual gyrus (not shown), right middle occipital gyrus, and bilaterally in fusiform gyrus (not shown); f) in right insula (not shown), right vPFC, bilateral oPFC, and right dPFC (not shown). Statistical significance was set at $p < .005$ (uncorrected), k = 5 voxels.

Correlations were run between the normalised difference scores and percent change in betas in the ROIs that showed a significant effect for the contrasts Pre-training > Post-training and Post-training > Pre-training. Percent change in betas in post-training is significantly and positively correlated with difference scores bilaterally in putamen, r = .493, p = .023; and anterior cingulate cortex, r = .524, p = .015.

3.3.3 Diffusion MRI results

Whole-brain analyses

Correlations were run between the normalised difference scores and the DTI and NODDI indices of FA, MD, NDI, and ODI. We found a significant negative correlation of the difference scores and FA in the grey and white matter of right SMA; a significant negative correlation between the difference scores and MD in the grey matter of left middle temporal gyrus (specifically in human mid-temporal area: hMT+/V5) and bilaterally in cerebellum; and a significant positive correlation of difference scores with ODI in the white matter of right SMA (Table 3.2).

Table 3.2. Whole-brain diffusion analysis: brain regions with significant correlations between DTI/NODDI indices and normalised difference scores.

Brain region	MNI coordinates			*t*-value	Cluster size (voxels)	*P*-value FDR-corrected
	x	y	z			
FA negative correlation with training outcome						
Right SMA (WM)	18	-20	58	5.28	35	.002
Right SMA (WM and GM)	12	-20	60	4.83		
MD negative correlation with training outcome						
Left cerebellum (IV-V) (GM)	-20	-48	-22	5.30	95	<.001
Left cerebellum (VI) (GM)	-22	-54	-20	5.19		
Left hMT+/V5 (GM)	-48	-54	14	5.61	33	.038
Right cerebellum (VI) (GM)	24	-72	-18	4.65	29	.049
ODI positive correlation with training outcome						
Right SMA (WM)	16	-22	58	5.25	22	.014

A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, after clusters were formed with an uncorrected $p < .001$. *P* values are reported at the cluster level. The MNI coordinates refer to the peak *t*-value. Local maxima that are more than 8 mm apart are shown for each cluster. WM = white matter, GM = grey matter, hMT+/V5 = human mid-temporal area.

3.4 Discussion

In the present experiment, we investigated the neural correlates of short-term training on a novel and complex perceptual-cognitive-motor task in healthy middle-aged adults (40-50 years old). We found a significant improvement in performance following training. There was an increased engagement of both cortical and subcortical areas in a relatively short space of time, supporting improved performance on the task. And finally, we found significant associations between brain microstructure and training outcome.

3.4.1 Behavioural findings

We found that the number of successful trials significantly increased from the pre- to the post-training phase of the PCM task, and the effect size was large and positive. Participants completed 160 trials (31 minutes of training) before the post-training test, indicating that with a relatively short training duration and a relatively low number of training trials they were able to greatly improve their performance. This is in line with several studies showing big improvements on the trained task following training (e.g., Howard & Howard, 1992; Singer et al., 2003; Rebok et al., 2007; Spencer et al., 2007; Basak et al., 2008; Rieckmann & Bäckman, 2009; Nemeth & Janacsek, 2010; Wilson et al., 2012; Karbach & Verhaeghen, 2014). This is also in line with studies looking specifically at multidomain approaches (i.e., training several cognitive functions within the same task) in younger and older adults (Green & Bavelier, 2003; Basak et al., 2008; van Muijden et al., 2012; for a review see Kueider et al., 2012). Correlations were run to determine if there were any relationships between the demographic data and the normalised difference scores. As there were no significant relationships found between the participant demographics and training outcome, it can be concluded that the training itself was effective in improving scores regardless of participant gender, age, and education.

3.4.1.1 Mechanisms underlying improvement on the PCM task

We demonstrated that even short-term training on the PCM task resulted in improved performance in middle-aged adults. This is in line with previous research in young adults showing that practice at the PCM task led to improved performance compared to controls that received no training (*M* = 22.3 years of age, Bennett et al.,

2018; *M* = 21.8 years of age, Uji et al., unpublished data). The control groups in these studies remained in their seats facing a blank computer screen for 30 min after the pre-test in order to closely replicate the time it took the practice group to perform their training trials.

Uji et al. (unpublished data) demonstrated that the practice group developed specific cognitive processes for decision making and visual search behaviours that underpinned their better performance. The practice group exhibited a significantly higher proportion of goal-directed visual saccades, more smooth pursuit eye movements, and more condition-action statements in the post-test when compared to the pre-test and control group. Saccades and smooth pursuit eye movements are two different forms of oculomotor control (Orban de Xivry & Lefevre, 2007). Saccades are primarily directed toward stationary targets such as the red target in the PCM task, whereas smooth pursuit is elicited to track moving targets such as the green objects in the PCM task (Orban de Xivry & Lefevre, 2007). Visual search behaviours of both groups were measured using an eye movement registration system. In addition, participants were required to write down all of the thought processes that they used to complete the task in separate condition-action formatted statements. Condition-action statements were collected at the end of the pre- and post-test. Condition-action pairs match task, environmental, or individual conditions to actions designed to achieve a goal (Neves & Anderson, 1981; Anderson et al*.,* 2004; Uji et al., unpublished data). In the PCM task, condition statements refer to the movements of the objects and the positioning of the cursor, and specify under what conditions to apply an action or patterns of actions (Uji et al., unpublished data). Action statements in the task are defined by motor responses that involve cursor movement, or visual responses that involve fixating or tracking certain information on the screen, and may include characteristics of the type of action (e.g., direction, placement, and speed) (Uji et al., unpublished data). The authors suggest that development of condition-action pairs in the practice group most likely contributed to successful performance by providing rule-governed processes used to match certain task conditions with the appropriate visual and/or motor actions (McPherson & Thomas, 1989). In the PCM task, these processes would include strategies to monitor current conditions (e.g., cursor position; movement/location of objects) with respect to previous successful or unsuccessful

attempts, and specify under what conditions or when to apply an action or patterns of actions to attain the desired goal (McPherson & Thomas, 1989; McPherson & Kernodle, 2003; McPherson & MacMahon, 2008; Uji et al., unpublished data). The authors propose that the significant increase in condition-action pairs for the practice group is a key finding because it indicates that in addition to the expected changes in motor performance and eye behaviour, training led to the development of cognitive decision making processes that facilitated improvement in task performance (Uji et al., unpublished data). The mechanisms involved in the acquisition of these perceptual-cognitive-motor processes may be the same for middle-aged adults. However, we can only speculate as to whether this is indeed the case as we did not explicitly examine visual search behaviours and condition-action statements in order to test this assumption.

3.4.1.2 PCM acquisition in middle-aged adults compared to young adults

It is important to note that the PCM scores for our participants were very low, and there was still much room for improvement. The mean percent of successful trials significantly increased from the pre-training phase (*M* = 30.89%) to the post-training phase (*M* = 46.25%). By comparison, in the study by Uji et al. (unpublished data), the practice group significantly increased their mean percent of successful trials from the pre-training phase (*M* = 12.5%) to the post-training phase (*M* = 62.5%). In the study by Bennett et al. (2018), performance improved significantly in the post test for the practice group (*M* = 55%) compared to the control group that received no training (M = 20%). Furthermore, young adults were able to outperform the middle-aged adults with the same amount of training, i.e., 31 minutes of practice (104 trials) (Uji et al., unpublished data; Bennett et al., 2018). One explanation for the lower training gains in our experiment could be that middle-aged participants are less able to learn the task than young adults. This would be in line with studies looking at the acquisition of a complex motor skill that showed performance decrements start in middle-age (Gershon, 1978; Voelcker-Rehage & Wilimczik, 2006; Janacsek et al., 2012).

However, direct comparisons of the middle-aged adults and young adults of these different studies is difficult because the Uji et al. (unpublished data) and Bennett et al. (2018) studies were behavioural, whereas the present study was carried out in an MRI

scanner. It can be argued that the task would be more difficult in the scanner as participants have to habituate to the scanner environment, in addition to completing the task while lying down, with a head coil mounted around the face, visualising the computer screen through a mirror system, and manipulating an unfamiliar mouse apparatus without being able to see one's hand. In the studies by Uji et al. (unpublished data) and Bennett et al. (2018), the participant sat on a chair at a desk so they were comfortable when moving a stylus on a digitising tablet to control the cursor location on the computer screen. Thus, the extent to which plasticity varies with age could not be considered with the present experiment and could only be assessed if younger and older adults were also included within the same study.

It is also possible that 31 minutes of training was simply not enough time for the middle-aged participants to achieve expertise at such a difficult and complex task. Indeed, changes in motor skill performance are known to evolve slowly, requiring many repetitions over several training sessions (Karni, 1996; Ungerleider et al., 2002; Doyon et al., 2003). Studies have demonstrated that the acquisition of motor skills follows distinct stages including an early, fast learning stage in which considerable improvement in performance can be seen within a single training session and a later, slow learning stage in which further gains can be observed across several sessions of training (Nudo et al., 1996; Karni et al., 1998; Ungerleider et al., 2002; Doyon et al., 2003). With extended practice, the skilled behaviour is thought to become resistant to both interference and the simple passage of time, and can thus be readily retrieved with reasonable performance despite long periods without practice (Penhune & Doyon 2002; Ungerleider et al., 2002; Doyon et al., 2003). While it is clear that the middle-aged participants demonstrated significant performance improvements and plasticity in the early fast learning stage, longer-term training would be needed to see if further gains could be observed, and whether the perceptual-cognitive-motor skills could be trained comparable to levels seen in young adults.

3.4.2 fMRI findings

3.4.2.1 Short-term PCM training and functional neuroplasticity

Our results indicate that there was functional plasticity in middle-aged adults following training on the PCM task. We demonstrated that experience-related functional reorganisation begins to develop within cortical and subcortical regions as training progresses. These findings are consistent with the view of neuroplasticity where functional changes occur in the brain as a result of training, practice, and experience (Jancke, 2009; Dayan & Cohen, 2011).

Successful trial completion required working memory for effective paths of navigation to the target, anticipation/prediction of obstacle trajectories, and monitoring allocentric spatial relationships between objects, in addition to motor aspects, such as fine motor control, and adaptation to kinematics of self-referent motion and to cursor movement (i.e., gain of movement). Furthermore, the present protocol used a dynamic and complex task environment in which the task goal could be attained in multiple ways by executing cursor trajectories from a range of potential options, some of which were more effective than others. Using this task, we were able to examine the cognitive and motor networks involved in the acquisition of the sensorimotor and decision making processes required for successful completion of the task.

As expected, there was increased engagement of both cognitive and motor networks with just 31 minutes of training (160 trials), supporting improved performance on the PCM task. Using an exploratory uncorrected threshold of $p < .005$ and k = 5 voxels, we observed increased activity post-training bilaterally in cerebellum; in striatum (including left caudate and bilaterally in putamen); bilaterally in M1, premotor cortex, SMA, and preSMA; bilaterally in anterior cingulate cortex; bilaterally in superior parietal cortex, left inferior parietal cortex, right angular gyrus, right supramarginal gyrus, bilaterally in precuneus, and postcentral gyrus; bilaterally in cuneus, calcarine sulcus, right lingual gyrus, and right middle occipital gyrus; bilaterally in fusiform gyrus; in right insula; in right dPFC, right vPFC, and bilaterally in oPFC. Our results are in line with studies showing increased activity occurs in short-term training before the task is well-practiced (i.e., single-session studies) (e.g., Nyberg et al., 2003; Kelly & Garavan, 2005; Soldan et al.,

2008; Braver et al., 2009; Lustig et al., 2009). Activation seen early in training involves generic attentional and cognitive control areas —prefrontal cortex, anterior cingulate cortex, and posterior parietal cortex together with changes in task-specific areas (Kelly & Garavan, 2005; Halsband & Lange, 2006; Voelcker-Rehage, 2008; Lustig et al., 2009; Hardwick et al., 2013). Indeed, we found increased activity in a frontoparietal network (i.e., SMA, pre-SMA, premotor cortex, parietal cortex, anterior cingulate, prefrontal, and orbitofrontal cortex), indicating the recruitment of these regions to support learning on the PCM task. The frontoparietal network is suggested to provide top-down control of executive resources to support learning in motor and non-motor domains (Hikosaka et al., 2002; Zanto & Gazzaley, 2013).

3.4.2.2 PCM training and models of motor skill learning

As we were examining the fast early stage of motor skill learning, we expected increased activity in the striatum, cerebellum, SMA, preSMA, M1, premotor cortex, anterior cingulate, dPFC, and inferior parietal cortex. Indeed, we found activation in these regions in middle-aged adults. Activity in this network has been interpreted as representing the enhanced need for error correction (cerebellar cortex) and planning (premotor cortex) during early learning (Steele & Penhune, 2010). Our results are in line with extensive research in young adults showing that the early fast learning phase of motor skill acquisition (i.e., session 1) elicits widespread activation in subcortical areas (basal ganglia, cerebellum, hippocampus), as well as relevant cortical areas (SMA, preSMA, M1, premotor cortex, anterior cingulate, inferior parietal regions, and dPFC) (e.g., Grafton et al., 1995; Sakai et al., 1998; Ungerleider et al., 2002; Doyon et al., 2003; Floyer-Lea & Matthews, 2005; Albouy et al., 2008; Steele & Penhune, 2010; Albouy et al., 2012; King et al., 2013).

The Doyon and Ungerleider (2002) model proposes that there are two loop circuits, a cortico-striatal and a cortico-cerebellar system, which are both recruited during the early learning stage of motor skill training regardless of the type of motor task. However, in the later stage, after several sessions of training, the cortico-striatal and cortico-cerebellar systems contribute differentially to different types of motor tasks. For example, for motor sequence training (learning a new sequence of movements) the

cerebellum becomes no longer essential, and the long-lasting retention of the skill will now involve representational changes (as reflected through increased activity) in the striatum and its associated motor cortical regions, including the parietal and motor-related structures (Doyon et al., 2003). By contrast, a reverse pattern of plasticity is proposed to occur for motor adaptation (learning to adapt to environmental perturbations), the striatum is no longer necessary for the execution and retention of the acquired skill; increased activity in regions representing this skill will now be present in the cerebellum, parietal cortex and motor-related cortical regions (Doyon et al., 2003). Thus, both the cortico-striatal and cortico-cerebellar loops are thought to be recruited in the early stage of motor skill training, while the later stage of motor sequence learning is thought to recruit the cortico-striatal system, whereas motor adaptation skills recruit the cortico-cerebellar system. Both the cortico-striatal and cortico-cerebellar systems were recruited in middle-aged adults. Indeed, our findings corroborate the regions suggested to be recruited in the early learning phase of the model – we found increased activity in the striatum, cerebellum, motor cortical regions (e.g., premotor cortex, SMA, pre-SMA, anterior cingulate), as well as prefrontal and parietal areas. However, in the present experiment we did not assess motor skill acquisition over the entire course of learning, and thus cannot assess the late training stage in order to fully examine this model.

In a similar model proposed by Hikosaka et al. (2002), learning spatial coordinates during motor skill training is supported by a frontoparietal-associative striatum-cerebellar circuit, while learning motor coordinates is supported by an M1-sensorimotor striatum-cerebellar circuit. The Hikosaka et al. model postulates that the regions engaged in the early stage of motor skill training are associative and involved in the fast learning of spatial coordinates, whereas in the late stage of training it is sensorimotor areas that are involved in the slower learning of motor coordinates. In line with this model, we found increased activity in frontoparietal-associative striatum-cerebellar regions (i.e., dPFC, inferior parietal cortex, anterior cingulate, caudate, rostrodorsal regions of the putamen, and regions in the cerebellum) indicating that this circuit was recruited to learn spatial coordinates in the PCM task. We also found increased activation in M1-sensorimotor striatum-cerebellar regions (i.e., M1, caudoventral areas of the putamen, and cerebellar regions) suggesting this circuit was being recruited to learn motor coordinates in the PCM

task, although further increases in activity would be expected in this circuit with additional training as more expertise is achieved in the task (i.e., during the late phase of learning). In addition, we found increased activity in premotor cortex, SMA, and preSMA, supporting the suggestion that transformation from spatial to motor coordinates involves these areas. As with the Doyon and Ungerleider model, we did not examine the late learning stage of training with the PCM task, as such, we provide partial support for the model but cannot fully assess it.

In addition to the regions discussed above, we also found increased activation in the vPFC and precuneus during post-training. This is contrary to several studies where the vPFC and precuneus show increased activation during the late stage of motor skill learning (e.g., Doyon, 1997; Sakai et al., 1998; Doyon & Ungerleider, 2002; Ungerleider et al., 2002; Doyon et al., 2003; Lehéricy et al., 2005). Early activation in these regions may be related to the specific demands of the PCM task, with precuneus contributing to the need for visual–sensorimotor integration, and visuospatial attention and processing (Bushnell et al., 1981; Posner & Rothbart, 1991; Petrides, 1996; Clower et al., 2001; Doyon et al., 2002; Cavanna &Trimble, 2006), and vPFC contributing to response inhibition, goal-appropriate response selection, and abstract decision and action planning processes (Aron et al., 2004; Schendan, 2012; Aron et al., 2014). The studies that found activation during the late phase of training in these areas (e.g., Jenkins et al., 1994; Sakai et al., 1998; Ungerleider et al., 2002; Doyon et al., 2003; Lehéricy et al., 2005) employed motor sequence learning tasks which may have engaged these regions later in training owing to different task processes being involved than those required in the PCM task. For example, Jenkins et al. (1994) required participants to learn sequences of key presses by trial and error while having their eyes closed and using auditory feedback. Furthermore, the vPFC and precuneus are association areas of the cerebral cortex and early activation in these regions would be in line with the Hikosaka et al. model, which suggests that associative regions are engaged early in the learning process to acquire spatial coordinates. In addition, it is possible that the observed increase in activation in the precuneus and vPFC early during training would increase further with practice on the PCM task (i.e., during the late stage of training). However, the present experiment cannot assess this and longer-term training would be needed to answer this question.

3.4.2.3 PCM training and cerebellar, hippocampal, and parahippocampal function

We found decreased activity post-training in cerebellum, hippocampus, and parahippocampal gyrus. This is contrary to what was expected; we expected PCM learning to be supported by increased activity in these regions as this was short-term training during the early learning stage of motor skill acquisition. The cerebellum is especially critical for early motor skill learning and its activity is not thought to decrease until the later phase of motor skill acquisition after longer-term training (e.g., Jenkins et al., 1994; Grafton et al., 1995; Doyon et al., 1996; Penhune & Doyon, 2002; Tamás Kincses et al., 2008; Doyon et al., 2009; Orban et al., 2010; Steele & Penhune, 2010). While we did indeed find increased activity in the cerebellum in Crus I, lobule IV-V, and cerebellar vermis X which is in line with the above studies, we also found decreased activity in cerebellum Crus I, Crus II, and lobule VI despite it being the early stage of training. This result seems inconsistent but may reflect anatomical and functional differentiation in the cerebellum between sensorimotor and cognitive regions (Schmahmann, 2019).

The sensorimotor cerebellum is mostly in the anterior lobe (lobules I through V), parts of lobule VI, lobule VIII, and the cerebellar vermis is interconnected with the vestibular and other brainstem nuclei which are engaged in midline body control, gait, and equilibrium (Schmahmann, 2001; Kelly & Strick, 2003; Schmahmann et al., 2004; Habas et al., 2009; Krienen & Buckner, 2009; O'Reilly et al., 2010; Buckner et al., 2011; Guell et al., 2018a; Guell et al., 2018b; Stoodley & Schmahmann, 2009; Schmahmann, 2019); whereas the cognitive cerebellum is in the posterior lobe (Buckner et al., 2011; Guell et al., 2018a; Guell et al., 2018b; Schmahmann, 1991; Schmahmann, 2019). Task-based fMRI using cognitive paradigms has demonstrated that there are functionally distinct regions within the cerebellar posterior lobe with lobule VI engaged in visuospatial tasks; and lobules VI, Crus I, Crus II, and VIIB are activated by executive functions such as working memory, planning, organising, and strategy formation (Stoodley & Schmahmann, 2009; Stoodley & Schmahmann, 2010; Stoodley et al., 2012; Stoodley et al., 2016; Schmahmann, 2019). Interestingly, we found increased activity mostly in sensorimotor areas of the cerebellum, i.e., lobule IV-V and cerebellar vermis X; while decreased activation was found in the cognitive regions, i.e., Crus I, Crus II, and lobule VI which are involved in visuospatial processing and executive functions such as working memory –

important processes for the PCM task. Decreases in these regions may indicate more efficient processing, however, such efficient processing would be rather unexpected with only 31 minutes of training.

Alternatively, our findings may be consistent with a role for the cerebellum in correcting motor errors (Flament et al., 1996; van Mier et al., 1998; Imamizu et al., 2000; van Mier & Petersen, 2001; van Mier et al., 2004; Orban et al., 2010). A decrease in cerebellar activity being associated with a reduction in error rate and improved performance (Flament et al., 1996; van Mier et al., 1998; Imamizu et al., 2000; van Mier & Petersen, 2001; Doyon et al., 2002; van Mier et al., 2004; Orban et al., 2010). Thus, the decrease in cerebellar activity seen in the present experiment may be related to the significant improvement in the PCM task. However, it should be noted that although there was significant improvement in the task, the error rate was still quite high (*M* = 53.75%) and there was further room for improvement.

Climbing fibres in the cerebellum are thought to not only encode sensorimotor error signals, but also a timing error (Kitazawa et al., 1998; Doya, 2000; Medina et al., 2000; Sakai et al., 2000; Hikosaka et al., 2002). Indeed, the cerebellum, and in particular lobule VI, is thought to be a key structure for the timing of movement (Medina et al., 2000; Sakai et al., 2000; Schubotz & von Cramon, 2001; Sakai et al., 2004). In the study by Sakai et al. (2000), the authors examined how the brain decides 'what to do' (response selection) and 'when to do it' (timing adjustment). The preSMA was selectively involved in response selection, whereas the cerebellar posterior lobe was selectively involved in timing adjustment. An essential element for successful completion of the PCM task is the timing of movement, for example, when to move the white cursor in order to avoid the green objects. Thus, the decreased activity that was found in lobule VI may reflect improved timing of movement in the PCM task.

The decreases in activity in the hippocampus and parahippocampus were also contrary to what we predicted. The hippocampus has shown increases in activity in both the early and later stages of motor skill learning (Schendan et al., 2003; Albouy et al., 2008; Fernández-Seara et al., 2009; Gheysen et al., 2010; King et al., 2013). However, studies have also found decreases in activity in the hippocampus during the early learning

stage, or increased activity only in the later phase of motor skill training (Jenkins et al., 1994; Schendan et al., 2003; Albouy et al., 2008; Steele & Penhune, 2010; Rieckmann et al., 2010). For example, Jenkins et al. (1994) found an extensive decrease in the activity of the hippocampus in both new learning during the initial stage of motor skill training, and during the overlearned sequence in the later stage of training. The authors suggest that this is evidence that motor learning need not engage the hippocampal system. In the study by Steele and Penhune (2010), hippocampal regions increased in activity on day 2 of training, but were not part of the early learning network identified on day 1. The relatively few studies investigating the role of the hippocampus in motor skill training have yielded heterogeneous findings that are likely to be the result of different types of tasks tapping into different cognitive processes. Thus, the research on hippocampal activation in motor skill learning remains contradictory and inconclusive.

The parahippocampal cortex is involved in many cognitive processes, including visuospatial processing (van Strien et al., 2009; Aminoff et al., 2013; Hohenfeld et al., 2020). This region is highly engaged by tasks involving scene perception, spatial representation, and navigation (e.g., Aguirre et al., 1996; Epstein & Kanwisher, 1998; Maguire et al., 1998; Mellet et al., 2000; Ekstrom et al., 2003*;* Janzen et al., 2007; Kravitz et al., 2011; Mullally & Maguire, 2011; Park et al., 2011; Stevens et al., 2012; Aminoff et al., 2013). Visuospatial processing is a key aspect of the PCM task. For example, monitoring the location of the green objects with respect to the cursor and to each other is a necessary component of the task. Thus, we predicted increased activation in this region. The observed decreased activation after half an hour may be an indication of early increased efficiency in this region for this particular task.

3.4.2.4 PCM training outcome and activity in the putamen and anterior cingulate cortex

We found that increased activity post-training was significantly and positively correlated with training outcome in the putamen and anterior cingulate cortex. This suggests that increased activity in these areas might underlie the improvements seen in performance on the task. This is in line with studies showing that the rostrodorsal (associative) regions of the putamen are involved early in the learning process and are critical for acquiring a new motor skill (Jueptner et al., 1997; Lehericy et al., 2005; King et

al., 2013). By contrast, activity in the caudoventral (sensorimotor) areas of the putamen increases as a function of practice, suggesting that this region is involved in the execution of well-learned motor skills (Jueptner et al., 1997; Lehericy et al., 2005; King et al., 2013). Lehericy et al. (2005) demonstrated that performance (movement accuracy) was positively correlated with signal changes in areas activated during early learning, including the associative putamen, whereas reaction time (movement speed) was negatively correlated with signal changes in areas activated during late learning stages, including the sensorimotor putamen. In addition, Jueptner et al. (1997) showed that the shift of activation from the associative to the sensorimotor territories of the putamen was already completed after 50 min of training. These results indicate that motor representations shift from the associative to the sensorimotor territories of the putamen during early learning, and do so relatively rapidly (Jueptner et al., 1997; Hikosaka et al., 2002; Lehericy et al., 2005). Notably, we found increased activation in both rostrodorsal and caudoventral areas of the putamen, providing support for the notion that motor representations shift from the associative to the sensorimotor territories of the putamen during learning. However, longer-term training with more sessions would better demonstrate that this shift is indeed taking place.

The pivotal role of the putamen in motor skill learning is thought to be the processing of reward error signals originating from midbrain neurons that provide the basal ganglia with dopaminergic inputs (Aosaki et al., 1994; Jog et al., 1999; Doya, 2000; Hikosaka et al., 2002; Schultz et al., 2003; Orban et al., 2010). Reward error signals attach a positive value to movements and decisions accurately produced during the early stage of learning, which can then be stored long term (Doya, 2000; Hikosaka et al., 2002; Orban et al., 2010). In the PCM task, increased putamen activation may reflect the intrinsic positive reward associated with successfully reaching the target and an error signal for when a trial is unsuccessful.

Furthermore, it is likely that putamen activation in our experiment reflects not only the sensorimotor aspects of the PCM task, but also the cognitive aspects. This would be in line with reports of striatal activations in the early phase of motor skill learning when participants have to rely more strongly on the use of cognitive strategies and

working memory (Jenkins et al., 1994; Jueptner et al., 1997; Toni et al., 1998; Dagher et al., 1999; Lehericy et al., 2005). Improved performance on the PCM task requires working memory for successful trajectories to the target.

Moreover, activation in the putamen has been shown to increase in non-motor tasks involving a reward prediction error (Daniel & Pollmann, 2012; Sommer & Pollmann, 2016). Sommer & Pollmann (2016) investigated if the occurrence of a target in a visual search display would elicit an increase of activation if the target's location is predicted by a previously learnt spatial context. They compared target appearance at locations predicted with 50% probability, at locations predicted with 100% probability, and at unpredicted locations. If putamen activation reflects an internal reward prediction error, it should be increased if the target appears at the learnt (*versus* the changed) location in the 50% probability displays. No prediction error signal would be expected for the displays that predict the target location with 100% certainty. They observed increased putamen activation when visual search targets were presented at the location predicted by the spatial context and when the prediction was uncertain (50% probability = prediction error) rather than certain (100% probability = no prediction error). Thus, they demonstrated an intrinsic prediction error signal in the putamen in memory-driven visual search (i.e., visual search in repeated displays). Similarly, in the PCM task, participants performed a visual search of the spatial context to monitor cursor position in relation to the movement/location of green objects and to the target. There were a total of eight repeating movement patterns of the green objects. A successful trial would result in a positive intrinsic reward for a particular pattern and for the trajectory taken to the target, whereas an unsuccessful trial would generate a prediction error signal because at the early stage of learning, the possibility of reward is still very uncertain. Thus, it is possible that the increased activity in the putamen reflected a reward prediction error signal for the PCM task. As the activity in the putamen increases, indicating processing of reward prediction error signals, so the training outcome improves.

As with the putamen activation, the positive correlation of activity in the anterior cingulate cortex and training outcome in the PCM task might also reflect a reward prediction error signal. The anterior cingulate is thought to be involved in error detection

and performance monitoring (Carter et al., 1998; Gehring & Knight, 2000; Luu et al., 2000; Procyk et al., 2000; Daniel & Pollmann, 2010). Anterior cingulate cortex activation in response to negative feedback has been shown in a large body of research (Carter et al., 1998; Gehring & Knight, 2000; Luu et al., 2000; Procyk et al., 2000; Daniel & Pollmann, 2010; for an overview, see Ridderinkhof et al., 2004a). This activation is often interpreted as reflecting the transmission of a reward prediction error signal that conveys the increased need for control and to induce behavioural adjustments thereby maximising performance (Carter et al., 1998; Gehring & Knight, 2000; Luu et al., 2000; Procyk et al., 2000; Ridderinkhof et al., 2004b; Daniel & Pollmann, 2010; for an overview, see Ridderinkhof et al., 2004a). In addition, in the study by Daniel and Pollmann (2010), the observed activations within the anterior cingulate cortex were not modulated by the types of reward presented, i.e., whether monetary reward or cognitive feedback/intrinsic reward. The PCM task required evaluation of the trial outcomes based on whether a trajectory to the target was successful or not, i.e., cognitive feedback/intrinsic reward. Interestingly, in the current experiment, increased activity in both the putamen and anterior cingulate was associated with a better training outcome — both regions are thought to process reward prediction error signals, indicating this might be a critical learning mechanism in the early stage of PCM training as a way for behaviour to be modified and maximise performance.

It is also possible that activity in the anterior cingulate cortex may reflect the decision-making component of the PCM task, in line with other published work (e.g., Shima & Tanji, 1998; Bush et al., 2000; Bush et al., 2002). In the PCM task, the goal could be attained in multiple ways by executing cursor trajectories from a range of potential options. Thus, deciding which option to take may be mediated by activity in anterior cingulate cortex.

Alternatively, it has been suggested that the anterior cingulate cortex contributes to the attentional brain network, composed of the prefrontal, anterior cingulate, and posterior parietal cortices, which has previously been proposed to have a “scaffolding” role that allows coping with unskilled performance (Petersen et al., 1998; Kelly & Garavan, 2005; Orban et al., 2010). Jenkins et al. (1994) showed that the anterior

cingulate was activated during new learning but not during automatic performance. The authors suggest that the anterior cingulate cortex plays a role in directed attention as the participants had to attend to the task during new learning, but not when the task had become automatic. In addition, the ability to solve complex problems has been shown to be initially supported by extensive attentional and strategic resources, which engage a prefrontal, orbitofrontal, and anterior cingulate network (Minati & Sigala, 2013). With practice, these resources are gradually replaced by access to long term working memory for familiar material, which engages predominantly occipital and medial temporal areas (Minati & Sigala, 2013). Indeed, we found increased activity in prefrontal, orbitofrontal, and anterior cingulate cortex. Thus, in the PCM task, the anterior cingulate may be part of a network including the prefrontal and orbitofrontal cortex which is engaged during unskilled performance in the early learning stage, while significant attentional resources are required for new learning.

3.4.2.5 Patterns of activity in middle-aged adults compared to young and older adults

In contrast to the increased activity in the putamen seen in middle-aged adults in the PCM task, motor skill learning in older adults is associated with decreased activation in the putamen (Aizenstein et al., 2006; Van Impe et al., 2009; Goble et al., 2012; King et al., 2013). This decreased activation in the putamen is especially surprising given that widespread age-related and task-dependent *increases* in activation are frequently reported (Mattay et al., 2002; Ward & Frackowiak, 2003; King et al., 2013). Dennis and Cabeza (2011) showed increased activity in the medial temporal lobe for motor skill learning in older adults, while striatal activity decreased compared with young adults. Still other studies have found increases in striatal activity in older adults (Schendan et al., 2003; Albouy et al., 2008; Rieckmann et al., 2010; King et al., 2013). Specifically, in young adults, hippocampal activity was shown to decrease and striatal activity increased as a function of motor sequence learning, whereas in the older adults, activity in both the medial temporal lobe, including the hippocampus, and the striatum *increased* (Schendan et al., 2003; Albouy et al., 2008; Rieckmann et al., 2010; King et al., 2013). The increased hippocampal activity during motor sequence learning in older adults may serve a compensatory function in order to maintain similar levels of performance despite age-

related decreases in the structure and function of the striatum (Rieckmann & Bäckman, 2009; Rieckmann et al., 2010; King et al., 2013). However, in task conditions with an increased cognitive load (i.e., greater task complexity), the performance of older adults during the initial learning is *not* maintained, potentially due to an inability of the medial temporal lobe and other neural substrates to compensate for age-related degradations in the striatum (Rieckmann & Bäckman, 2009; King et al., 2013). Findings in the middle-aged participants in the present experiment mostly corroborate what is found in the young adults. However, it is difficult to make direct comparisons between the age groups as different tasks are used in the experiments. In order to assess possible similarities and differences in brain function, young, middle-aged, and older adults would need to be included within the same PCM study.

3.4.2.6 PCM trial performance and brain activity

We did not observe a main effect of trial performance, nor an interaction between testing phase and trial performance in any of the ROIs. This is possibly due to the same skills and same processes being used to solve the task. Therefore, the regions involved in those processes will be activated regardless of whether the trial is successful or unsuccessful. It may be that because it is the very early stage of learning, an exploratory stage, the patterns for successful and unsuccessful trials are not yet differentiated at the fMRI resolution level – i.e., the patterns are yet indistinguishable, at least with this method.

Some studies have shown increases in brain activity for successful *vs.* unsuccessful trials (Daniel & Pollmann, 2010; Swann et al., 2012). Specifically, posterior putamen activation was increased for successful *vs.* unsuccessful categorisation with either monetary reward or informative (correct/incorrect) feedback (Daniel & Pollmann, 2010). In addition, Swann et al. (2012) found significantly increased activity in preSMA and inferior frontal gyrus for successful *vs.* unsuccessful trials on an inhibitory motor task (preparing to stop finger presses and stopping action outright in response to a particular cue). However, direct comparison of these studies is difficult as the tasks used were very different and examining processes which were not investigated by the PCM task. For example, the study by Daniel and Pollmann (2010) was examining classification learning

with complex visual stimuli (selecting the category membership of a particular stimulus during stimulus presentation).

Another possibility is that we may have been under-powered due to low trial numbers when comparing activation in successful and unsuccessful trials, especially if it is a subtle effect as might be expected given that training was only for 31 minutes. The mean number of pre-training successful trials was about 24, pre-training unsuccessful trials was 56, post-training successful trials was 37, and post-training unsuccessful was 43. Whereas comparing all 80 pre-training trials with all 80 post-training trials allowed us to detect activation differences between pre- and post-training phases.

3.4.2.7 Multiple comparisons

It is important to note that these results were observed without a correction for multiple comparisons and therefore should be interpreted with caution. It is possible that such a relatively short time frame, i.e., 31 minutes of training, would only result in small functional brain changes that would be difficult to detect with a stringent correction for multiple comparisons. Indeed, in motor skill learning studies, training is relatively longer and ranges from 60 – 120 minutes for the early learning stage (e.g., Jenkins et al., 1994; Jueptner et al., 1997; Doyon et al., 2002; Orban et al., 2010; Steele & Penhune, 2010). Furthermore, despite the longer length of training in the above mentioned studies, some of them did not correct for multiple comparisons in order to reveal the full extent of performance related responses (Jueptner et al., 1997; Doyon et al., 2002; Orban et al., 2010; Steele & Penhune, 2010). In addition, in the study by Orban et al. (2010), inferences were drawn at an uncorrected threshold because strong a priori hypotheses on brain regions were driven by the large existing literature on motor skill learning.

In sum, this is the first study to examine training on a perceptual-cognitive-motor task in middle-aged adults. Our results corroborate a wealth of findings in motor skill learning and add a more complex cognitive component. There were changes in activity in both cognitive and motor networks with a relatively short training period, indicating training-induced functional neuroplasticity in this age group. Furthermore, some of the functional changes were associated with better training outcome (i.e., increased activity

post-training in the putamen and anterior cingulate), suggesting that changes specifically in these areas might play a key role in learning the task.

3.4.3 Diffusion MRI findings

3.4.3.1 Microstructure and training outcome in middle-aged adults

Diffusion indices can be used to indirectly localise microstructural variation that might be indicative of learning outcome. Indeed, we found significant relationships between MD, FA, ODI, and PCM training outcome in middle-aged adults. These results indicate that inter-individual variation in brain structure was associated with extent of learning. This is in line with studies using diffusion MRI in young adults to demonstrate relationships between tissue microstructure and performance on cognitive and motor tasks (Klingberg et al., 2000; Moseley et al., 2002; Madden et al., 2004; Tuch et al., 2005; Johansen-Berg et al., 2007; Sasson et al., 2010; Sagi et al., 2012; Hofstetter et al., 2013). For example, Johansen-Berg et al. (2007) used DTI to show that variation in white matter integrity (as reflected by FA) in the corpus callosum is significantly associated with variation in performance of a bimanual coordination task, supporting the idea that variation in brain structure reflects inter-individual differences in skilled performance. Our results are also in line with diffusion imaging studies in older adults investigating associations between brain microstructure and performance in cognitive and motor domains (Bennett et al., 2011; Nazeri et al., 2015). For example, Bennett et al. (2011) found that caudate–dPFC and hippocampus-dPFC tract integrity were significantly related to motor skill learning in healthy older adults (aged 63–72 years). Specifically, for both tracts, higher integrity as indexed by FA was related to greater motor sequence learning. Thus, our results are in line with those found in both young and older adults, and provide strong evidence of a relationship between brain microstructure and learning outcome, such that pre-existing inter-individual differences in brain structure could determine variations in skill learning.

3.4.3.2 DTI findings

We used diffusion imaging to analyse potential mechanisms underlying learning on the PCM task. Correlation of the diffusion indices with PCM training outcome was explored with the anticipation that parameters indicating grey matter complexity and white matter integrity would be associated with better learning. With regards to the DTI indices, we found a significant negative correlation between the training outcome and MD in the grey matter of left middle temporal gyrus (specifically in human mid-temporal area: hMT+/V5) and bilaterally in cerebellum; and a significant negative correlation of the training outcome and FA in the grey and white matter of right SMA.

MD maps represent the overall water diffusion in a voxel whereby high intensities indicate higher diffusion rates, and are similar for both white and grey matter. Lower levels of MD indicate lower diffusion rates which would be the result of being restricted by tissue boundaries. MD is generally believed to depict tissue density (Basser, 1995; Pierpaoli & Basser, 1996; Assaf & Pasternak, 2008; Sagi et al., 2012; Hofstetter et al., 2013). Greater tissue density would restrict the overall rate of diffusion. Therefore, lower MD would indicate greater tissue density, i.e., a greater density of axons or dendrites, which in turn could indicate greater dendritic complexity and axonal integrity. Thus, we expected lower MD to be associated with greater improvement in PCM performance and indeed, this was the case in the grey matter of left hMT+/V5 and bilaterally in cerebellum. This is in line with studies using DTI that demonstrated an association between reduced MD in grey and white matter and greater task improvement (Sagi et al., 2012; Hofstetter et al., 2013). For example, Sagi et al. (2012) used DTI to examine grey matter microstructure in individuals that performed a spatial navigation task. Analysis revealed significant negative correlations between improvement rates on the task and MD reduction in the left hippocampus and right parahippocampus. Using the same spatial learning and memory task, Hofstetter et al. (2013) used DTI to investigate white matter microstructure and found that more improvement on the task correlated with reductions in MD in the fornix. However, although diffusion metrics are sensitive markers for subtle microstructural tissue organisation, they are not specific and are difficult to attribute to particular biological processes (Dowell et al., 2019). For example, lower MD might be

attributed to extracellular volume, swelling of cells, or glia cell volume (Ransom et al., 1985; Sykova, 1997; Kleim et al., 2007; Le Bihan, 2007; Theodosis et al., 2008; Markham et al., 2009; Hofstetter et al., 2013). Therefore, lower MD might reflect increased tissue density due to neuronal or glial processes, or due to strengthened axonal or dendritic backbones (Assaf & Pasternak, 2008; Sagi et al., 2012), and these processes might result in strengthened communication between the cortical areas involved in motor skill training. Thus, although we have established a clear relationship between lower MD and better training outcome on the PCM task, we can only speculate as to the cellular mechanisms underlying the variation in structure that supports better learning on this task.

FA is a commonly used measure of fibre organisation and "integrity" that refers to the orientation of water diffusion, independent of rate, and is calculated as the fraction of total diffusion that is anisotropic (Basser, 1995; Basser & Pierpaoli, 1996; Pierpaoli & Basser, 1996; Assaf & Pasternak, 2008; Bennett et al., 2011; Sagi et al., 2012). Higher FA values indicate that the diffusion of water molecules is restricted in the direction along axons, whereas lower values would indicate that the water molecules are going in the perpendicular direction. Thus, higher values would indicate that fibres are more coherent and aligned which is thought to reflect more tissue integrity. Tissue features such as axon diameter and myelination are thought to underlie behavioural improvements by altering conduction velocity and synchronisation of nervous signals (Jack et al., 1983; Tuch et al., 2005; Fields, 2008; Scholz et al., 2009). Fine tuning the timing and integration of sensorimotor signals is an important step in skill learning (Serrien & Brown, 2003; Fields, 2008; Sampaio-Baptista et al., 2013). For example, increased FA could reflect increased myelin thickness and faster nerve conduction velocity, which would result in better communication between the functional networks involved in PCM training. As such, we expected higher FA to be associated with greater improvement in PCM performance. Contrary to this prediction, we found that lower FA was associated with better training outcome in the grey and white matter of right SMA. This result is surprising, as stated, it is increased FA that would be expected to be associated with better training outcome. Indeed, previous studies have shown that higher FA is associated with improved behavioural performance on visuospatial and cognitive tasks (e.g., Klingberg et al., 2000;

Madden et al., 2004; Wolbers et al., 2006; Johansen-Berg et al., 2007; Sampaio-Baptista et al., 2013). For example, higher FA in white matter underlying the inferior parietal cortex is associated with more efficiency in mental rotation (Wolbers et al., 2006). Madden and colleagues (2004) reported that increased FA correlated with better performance on a visual target detection oddball task in the corpus callosum in young adults. In the study by Sampaio-Baptista and colleagues (2013), rate of motor skill learning in rats was positively correlated with FA in white matter of the external capsule, cingulum, corpus callosum, and internal capsule. However, there are also studies that have reported counterintuitive results with regards to correlations between FA and performance (Tuch et al., 2005; Hofstetter et al., 2013). For example, Hofstetter and colleagues (2013) showed that reductions in FA in the fornix were correlated with improvement on a spatial learning and memory task. Tuch et al. (2005) demonstrated that reaction time performance on a visuospatial task was significantly correlated with FA in white matter of the right optic radiation, right posterior thalamus, right medial precuneus, and left superior temporal sulcus. Specifically, increasing (i.e., slower) reaction times correlated with higher FA. As with our results, these relationships are less intuitive as higher FA should indicate more 'integrity', for example reflecting increased packing density or myelination, which should correlate with better performance on the PCM task, or with faster response times in the Tuch et al. (2005) study, and with improvement in the Hofstetter et al. (2013) study.

However, FA is a complex measure that is influenced not only by myelination, axon diameter, and axon density (Beaulieu, 2002; Beaulieu, 2009), but also by path geometry and the presence of crossing fibre pathways (Johansen-Berg et al., 2007; Jones et al., 2013; Jeurissen et al., 2013). In anatomical regions containing intravoxel fibre crossings, higher FA of an individual fibre population can result in a lower overall FA (Wiegell et al., 2000; Pierpaoli et al., 2001; Tuch et al., 2003; Tuch et al., 2005). For example, in the junction between the optic radiation and the posterior forceps a selective increase in the FA of the optic radiation could result in less overall FA (Tuch et al., 2005). The fibre crossing effect might also be a factor when rapidly bending fibres produce intravoxel orientation dispersion (Tuch, 2004; Tuch et al., 2005). Thus, the interpretation of DTI indices in microstructural environments containing crossing fibres or fanning as

found in areas of complex axonal or dendritic architecture is not straightforward (Vos et al., 2012; Jeurissen et al., 2013; Jones et al., 2013; Broad et al., 2019). Furthermore, the relationship between axon diameter and FA is not fully understood, although increased axon diameter could result in lower FA due to an increase in the mobility of water in the intraaxonal compartment (Takahashi et al., 2002; Tuch et al., 2005). In addition, FA is very small in grey matter and more sensitive to noise, making it more difficult to interpret (Beaulieu, 2009; Zhang et al., 2012). Therefore, although we have demonstrated a strong relationship between lower FA in both grey and white matter of the SMA and better training outcome on the PCM task, the exact nature of this association remains unknown.

3.4.3.3 NODDI findings

Using NODDI, we found a significant positive correlation of training outcome with ODI in white matter of the right SMA, indicating higher ODI in white matter was associated with better learning outcome. This was contrary to what we predicted as lower ODI values in white matter would indicate less dispersion of water molecules and thus less fanning of the axons, i.e., the tracts are more compact, parallel, very directional and aligned (Zhang et al., 2012), which is thought to result in faster signal transmission (Jack et al., 1983; Tuch et al., 2005). Thus, lower ODI values would be expected to correlate with improved performance, as low values indicate high axonal coherence and faster signal transmission. Therefore, our result of higher white matter ODI being associated with better training outcome is not in line with this expectation. With regards to grey matter ODI, higher values indicate more dispersion and thus more fanning, therefore areas that are rich in multi-directional dendritic structure would have higher values of ODI (Dowell et al., 2019). A rich and complex dendritic structure would result in better signal transmission. As such, we predicted that higher grey matter ODI would correlate with better training outcome on the PCM task. Previous research has demonstrated a significant relationship between grey matter ODI and cognition in the context of normal ageing (Nazeri et al., 2015). Higher levels of frontal pole and hippocampal ODI contributed positively to working memory/processing speed performance (Nazeri et al., 2015). However, we did not find an association between grey matter ODI and training outcome on the PCM task.

Higher levels of NDI indicate a greater density of axons in white matter and dendrites in grey matter, i.e., NDI values are high in neurite rich areas (Zhang et al., 2012). The branching complexity of dendritic trees can be measured in terms of dendritic density, such that a greater density indicates greater complexity (Zhang et al., 2012). A higher density of axons and dendrites might be indicative of faster or better signal transmission. Therefore, we expected that higher NDI in both grey and white matter would correlate with improved performance on the PCM task. Previous studies have found associations between grey matter NDI and cognitive performance (Nazeri et al., 2017; Parker et al., 2018). For example, throughout the frontotemporal cortical areas, higher NDI was associated with better performance in spatial working memory (Nazeri et al., 2017). Specifically, performance in spatial span was significantly associated with higher grey matter NDI in areas such as the dPFC; orbitofrontal, medial prefrontal, superior temporal, and cingulate cortices; and temporal pole, insula, hippocampus, and striatum (Nazeri et al., 2017). However, no associations were found between grey and white matter NDI and training outcome in the present study. Therefore, NDI may not play a significant role in PCM training outcome and it is possible other processes such as myelination of axons would play a bigger role. As both DTI and NODDI indices cannot tell us specifically about the myelination of axons, diffusion methods that give us more information about myelin content would be beneficial in a study investigating the relationship of PCM training outcome and underlying structure.

3.4.3.4 Diffusion MRI findings and functional significance

Quantifying neurite morphology in terms of its density and orientation distribution provides a window into the structural basis of brain function (Zhang et al., 2012). We demonstrated that functional neuroplasticity occurred as a result of training on the PCM task in middle-aged adults. We sought to link this functional plasticity as a result of training, with underlying structure. These functional changes may be supported by underlying brain structure such that diffusion indices indicating more structural integrity were associated with better learning outcome. Better structural integrity could result in faster or better signal transmission resulting in increased functional activity in PCM task related regions. We demonstrated significant relationships between training outcome

and MD in human mid-temporal area (hMT+/V5) and cerebellum; between training outcome and FA in SMA; and between training outcome and ODI in SMA, suggesting that structural variation has functional consequences. These structure and training outcome relationships are colocalised to regions within which functional alterations occurred following training on the PCM task. For example, we observed increased activity post-training on the PCM task in cerebellum and SMA. Thus, functional plasticity occurred within the same cortical regions as the structure-behaviour correlations, and this provides evidence that morphological variation contributes to the training outcome of a skilled motor behaviour. Indeed, functional MRI studies in healthy individuals have shown that these regions (i.e., cerebellum, SMA, and hMT+/V5) become consistently activated during visuomotor tasks (e.g., Jenkins et al., 1994; Sakai et al., 1999; Doyon et al., 2003; Oreja-Guevara et al., 2004; Floyer-Lea & Matthews, 2005; Steele & Penhune, 2010; van Kemenade et al., 2014).

Task-based fMRI has demonstrated that the cerebellum is engaged by visuospatial processing, and also activated by executive functions such as working memory (e.g., Stoodley & Schmahmann, 2009; Stoodley & Schmahmann, 2010; Stoodley et al., 2012; Stoodley et al., 2016). In addition, the cerebellum has a role in detecting and correcting motor errors, and in the timing of movement (Doya, 2000; Imamizu et al., 2000; Medina et al., 2000; Schubotz & von Cramon, 2001; Sakai et al., 2004; van Mier et al., 2004).

The SMA is also a key structure for motor skill learning (Jenkins et al., 1994; Hikosaka et al., 1995; Hikosaka et al., 1996; Nakamura et al., 1998; van Mier et al., 1998; Sakai et al., 1999; Brass & von Cramon, 2002; Garavan et al., 2003). Activation in SMA is associated with planning of self-initiated or externally generated movements (Cunnington et al., 2002; Grèzes & Decety, 2002; Vollmann et al., 2013). The SMA is thought to play a crucial role in motor memory formation (Tanaka et al., 2010). The SMA is also thought to play an important role in short-term visuomotor learning (Vollmann et al., 2013). In addition, it has been suggested that the SMA represents learned sequences of hand–eye movements (Hikosaka et al., 2002). In line with these studies, successful completion of the PCM task requires these functions and indeed, we demonstrated increased activity post-training in cerebellum and SMA.

Learning a new visuomotor skill has been shown to induce grey matter structural change in the human mid-temporal area (hMT+/V5) (Draganski et al., 2004). Specifically, Draganski et al. (2004) used voxel-based morphometry to show expansion in grey matter of hMT+/V5 following juggling training and found a close relationship between the structural grey matter changes in hMT+/V5 and visuomotor performance. The hMT+/V5 is thought to play a crucial role in motion processing (e.g., Oreja-Guevara et al., 2004; Kamitani & Tong, 2006; Castelo-Branco et al., 2009; Seymour et al., 2009; van Kemenade et al., 2014). Furthermore, Oreja-Guevara and colleagues (2004) demonstrated that hMT+/V5 contributes to the control of visually guided hand movements, comparable to its contribution to the cortical network that controls visually guided eye movements. Participants performed visually guided right hand movements, either continuously tracking a horizontally moving target, or moving the cursor to a stationary target (ballistic tracking). There was greater activation of hMT+/V5 during continuous tracking than during ballistic tracking. To separate the influence of arm movements, replay conditions were used where only visual motion of the identical target and cursor trajectories on the screen were watched. Activation was increased significantly during continuous tracking movements in comparison to the replay of the identical visual scene. Ballistic tracking vs. replay also showed activation in hMT+/V5, but less than during continuous tracking. Thus, Oreja-Guevara and colleagues (2004) demonstrated a role for hMT+/V5 not only in visual motion perception, but also in the control of action during visually guided hand movements. This study highlights the importance of hMT+/V5 in visuomotor integration and not only in visual motion analysis, i.e., hMT+/V5 has an important role in transforming visual information into motor behaviour.

Furthermore, hMT+/V5 is activated not only by visual motion, but also by tactile (Beauchamp et al., 2007; Blake et al., 2004; Hagen et al., 2002; Ricciardi et al., 2007; Sani et al., 2010; Wacker et al., 2011; van Kemenade et al., 2014) and auditory motion (Poirier et al., 2005, 2006; Wolbers et al., 2011), suggesting that hMT+/V5 may be a multimodal motion processing area. The PCM task involves visual tracking of the moving green balls, as well as tactile information processing from moving the computer mouse to move the cursor, and motor output in the form of avoiding the green balls and moving the cursor to the target. Therefore, a correlation between PCM training outcome and MD in hMT+/V5

is in line with the functional role of this area. We have shown that the cerebellum, SMA, and hMT+/V5 are involved in functions that are important for successful completion of the PCM task. Thus, the structure and training outcome relationships were demonstrated in regions with functional significance for the PCM task.

The learning of a novel skill relies upon changes in brain function. Differences in functional plasticity could reflect variation in underlying structure as reflected by diffusion indices. We determined the functional correlates of variations in grey and white matter structure by relating this microstructural variation to the behavioural data. However, it is important to note that diffusion indices were not correlated with the functional changes seen within these regions. To further strengthen the evidence for a structure–function relationship with the PCM task, it would be beneficial not only to demonstrate associations between structure and behavioural outcome, but also between structure and functional changes in the brain.

3.4.4 Limitations

3.4.4.1 Behavioural study limitations

The primary limitations we identified for this study include issues common to within-subjects study designs. Results observed after PCM training could be attributed to test-retest effects (typically performing better the second time, regardless of training), or the fact that participants would have higher expectations of themselves due to the training (Collie et al., 2003; McCarney et al., 2007; Green & Bavelier, 2012). For example, the practice effect might mean that performance improved not because of the training, but simply because the general experience of participating in an experiment made participants more confident and accomplished at taking tests. This may have skewed the results and made it more difficult to determine if the effect is due solely to the training. However, the very short training duration in the current experiment mitigates that possibility. To further resolve these issues, a between-subjects design could be implemented, such that a training condition could be compared to an active control treatment to ensure that any group differences that are observed are not attributed to test-retest effects, or to participants' higher expectations of themselves.

A further limitation of our study is that we did not assess the cognitive function of our sample with standardised tests, such as the Mini Mental State Exam (MMSE; Folstein et al., 1975). However, we investigated a group of healthy middle-aged adults, which should have minimised the influence of relevant age-related changes, such as atrophy or amyloid plaques (Emch et al., 2019). Furthermore, individuals had no self-reported history of neurological and psychiatric disorders, or brain injuries. Nonetheless, we cannot be certain that participants with cognitive impairments were excluded from the study.

An important issue that has been overlooked in this experiment is whether benefits of training with the PCM task can transfer to untrained tasks testing the same cognitive processes (near transfer), or even to tasks measuring different abilities (far transfer) leading to a general improvement in the level of cognitive functioning or motor control. Interventions targeting age-associated cognitive decline should be trying to maximise the transfer of skills as much as possible. Indeed, identifying tasks that can lead to improvement in other tasks is crucial and recommends investigation of transfer effects.

3.4.4.2 fMRI study limitations

With a complex task such as the PCM task, it is inherently difficult to draw from alternative explanations the exact role of the brain regions that were activated, due to the lack of manipulations to isolate the processes involved in the task. It is one thing to say that particular regions were involved in PCM training, but another to identify the specific roles these regions played. Putative functional roles of these regions in the PCM task could only be inferred from previous neuroimaging research. Future research could attempt to disentangle the relative contributions of these regions to PCM learning using tasks that isolate the various functions involved.

In addition, the present experiment does not provide data on how the activated regions interact with one another and how information is transferred from one circuit to another during the course of motor training (for example, from the associative circuit to the sensorimotor circuit, i.e., transformation from spatial to motor coordinates; Hikosaka et al., 2002). Functional and effective connectivity approaches could be used to assess

connections between regions of a network, as well as between networks. Functional connectivity is classically defined as the temporal correlation between regions' time courses of the BOLD signal (Friston, 1994). This method is aimed at assessing functional interactions between several regions and is a way to measure correlations within and between large-scale networks. Effective connectivity, on the other hand, describes the causal influences that neural units exert over one another (Friston, 1994; Stephan & Friston, 2010). Effective connectivity can be understood as the experiment- and time-dependent, simplest possible circuit diagram that would replicate the observed timing relationships between the recorded neurons, and requires a causal model of the interactions between the elements of the neural system of interest (Aertsen & Preißl, 1999; Stephan & Friston, 2010). Applying these approaches to examine PCM training would allow us to characterise the interactions within each network, as well as information exchanges between them, during learning**.**

3.4.4.3 Diffusion MRI study limitations

Biological interpretation of diffusion measures is challenging and it is important to emphasise that diffusion indices provide only an indirect marker of microstructural properties. Diffusion imaging works by sensitising MRI measurements to the displacement pattern of water molecules undergoing diffusion (Zhang et al., 2012). As the water displacement pattern is influenced by tissue microstructure, by measuring this displacement pattern, diffusion MRI is able to distinguish different structural properties (Zhang et al., 2012). The question regarding the detailed underlying biological mechanisms of the observed relationships between the diffusion indices and training outcome in the PCM task cannot be addressed in this study. Histology offers the possibility to validate diffusion indices and to shed light on the cellular events that underlie the measures obtained in human neuroimaging studies of motor skill training (Sampaio-Baptista et al., 2013). An animal study with a similar PCM protocol that correlates diffusion indices with histological measures such as the number of synaptic vesicles, number of dendritic spines, number of astrocytic processes, myelin staining, etc. would provide further information on the mechanisms underlying better training outcomes. Indeed, evidence suggests that in both grey and white matter, there is a strong

link between neurite morphology determined from diffusion MRI and independent measures derived from histology (Sagi et al., 2012; Zhang et al., 2012; Hofstetter et al., 2013; Sampaio-Baptista et al., 2013).

We have demonstrated specific associations between diffusion indices and training outcome in healthy middle-aged adults, suggesting that inter-individual variation in brain structure influences variation in skill learning. However, as this is a correlation study, we cannot confirm a causal role of brain structure on differences in skill learning behaviour. It is possible that common genetic factors influence both brain structure and the propensity to train (Scholz et al., 2009). In addition, genotype has been shown to not only influence brain structure (Bueller et al., 2006; Johansen-Berg et al., 2007), but also the degree of functional plasticity in the motor system (Kleim et al., 2006; Johansen-Berg et al., 2007). Therefore, it is not clear whether inter-individual differences in brain structure are responsible for inter-individual differences in PCM training outcome, i.e., the results reported here reflect associative, as opposed to causal relationships, and we acknowledge the limited interpretability of these single-session correlation data.

Moreover, we did not examine structural neuroplasticity with regards to the PCM task. Certainly, our current experiment would not be expected to induce changes in diffusion metrics with such a short timescale, and in order to examine structural neuroplasticity it is likely that longer-term training would be necessary. Further research should use a longitudinal design to investigate whether training with the PCM task can indeed result in structural changes and whether these changes can be related with better training outcome. There is emerging evidence that changes in diffusion indices can also occur in response to short-term training (Sagi et al., 2012; Hofstetter et al., 2013; Marins et al., 2019). For example, Marins and colleagues (2019) trained healthy individuals to reinforce brain patterns related to motor execution while performing a motor imagery task. After just 1 h of training, participants showed increased FA in the sensorimotor segment of corpus callosum. Therefore, it may also be possible to design a pre- and post-training study of structural brain changes with short-term training.

3.4.5 Conclusions

Despite these limitations, our findings suggest that even with short-term practice, middle-aged adults show significant plasticity in cognitive and motor abilities as evidenced by the training gains made on the task. As there were no significant relationships found between the demographics and training outcome, it can be concluded that it is very likely the training itself was effective in improving performance regardless of gender, age, and education. The effect size was large and indicates that PCM training had a substantial outcome. Thus, this particular form of training may be useful as an intervention for preventing cognitive decline.

In addition, we provide novel evidence for training-induced functional neuroplasticity in middle-aged adults. There was increased engagement of both cognitive and motor networks in a relatively short space of time, supporting improved performance on the task. We demonstrated that experience-related functional reorganisation begins to develop within cortical and subcortical regions as training progresses. Some of the functional changes were associated with better training outcome (i.e., increased activity post-training in putamen and anterior cingulate), suggesting that changes specifically in these areas might underlie learning of the task. Thus, targeting these areas in training could be particularly beneficial in improving cognitive function.

We found significant relationships between brain microstructure and training outcome, indicating that inter-individual variation in brain structure was associated with extent of learning. Thus, the diffusion findings suggest that individual differences in brain structure had behavioural relevance, such that pre-existing structural differences could determine variations in skill learning. Therefore, inducing changes in these indices with training, i.e., inducing changes in brain structure, may be a way to mitigate cognitive decline in later life.

In the next experiment, we aimed to address some of the limitations discussed above and included an active control treatment as well as an assessment of transfer effects. We investigated if functional and structural neuroplasticity could be induced with longer-term cognitive training in middle-aged adults. Changes in structural properties

might underlie cognitive improvements by altering conduction velocity and synchronisation of neural signals (Fields, 2008), supporting functional brain changes. If cognitive training can induce structural changes in addition to functional changes, then this may be a way to prevent cognitive decline in later life.

Chapter 4: Working memory, attention, and executive function training in middle-aged adults: Behavioural findings

4.1 Introduction

4.1.1 Cognitive training and transfer

The goal of improving cognitive abilities through training has been pursued in numerous intervention studies, particularly with older adults (e.g., Verhaeghen et al., 1992; Kramer & Willis, 2002; Rebok et al., 2007; Hertzog et al., 2009; Lustig et al., 2009; Noack et al., 2009; Schmiedek et al., 2010). However, cognitive training research faces criticisms that effects are often limited to the trained tasks, whereas transfer to untrained tasks is inconsistent (Dougherty et al., 2016; Melby-Lervag & Hulme, 2013; Melby-Lervag et al., 2016; Soveri et al., 2017; Flegal et al., 2019; Pappa et al., 2020). Thus, an important issue to consider is whether benefits transfer to untrained tasks testing the same cognitive function as the trained tasks (near transfer), or transfer to untrained tasks measuring different abilities (far transfer).

Far transfer has been demonstrated in young adults from working memory training to fluid intelligence measures such as the Raven Progressive Matrices (Klingberg et al., 2002, 2005; Jaeggi et al., 2008, 2010; Schmiedek et al., 2010; Jaeggi et al., 2011). For example, in a study conducted by Schmiedek et al. (2010), young (age: 20–31 years) and older adults (age: 65–80 years) were trained for over 100 days on perceptual speed, working memory, and episodic memory tasks. While near transfer effects were observed for working memory updating tasks in both the young and older age groups, far transfer effects to fluid intelligence measures were observed only in the younger age group.

In older adults, far transfer effects have been demonstrated from working memory training to tests of attention (Brehmer et al., 2011), and to long-term memory retrieval (Brehmer et al., 2011; Richmond et al., 2011). In contrast, far transfer effects were not found in older adults from working memory training to fluid intelligence measures (Dahlin et al., 2008; Schmiedeck et al., 2010; Brehmer et al., 2011; Richmond et al., 2011). In addition, studies that trained reasoning, speed, or memory in older adults did not obtain far transfer (Neely & Backman, 1995; Ball et al., 2002; Edwards et al., 2002; Rebok et al., 2007). On the other hand, studies that trained complex strategy use, problem solving, task-switching, and auditory perception did obtain far transfer (Basak et al., 2008; Stine-Morrow et al., 2008; Karbach & Kray, 2009; Strenziok et al., 2014). For

instance, Karbach and Kray (2009) observed far transfer effects in 62 to 76 year olds following task-switching training. Older adults improved performance on executive control tasks related to interference control, verbal and spatial working memory, and fluid intelligence.

It should be noted that the literature is not balanced, such that working memory training is the predominant type studied in young adults, but complex skills training is the predominant type studied in older adults (Strenziok et al., 2014). Therefore, a possible reason for the negative results reported in older participants could be the type of training they underwent. While previous programmes focused more on strategy-based exercises, such as in the mnemonic memory component tasks of the ACTIVE study (Rebok et al., 2014), which reliably enhanced performance on the practiced tasks but did not induce far transfer, Karbach and Kray's (2009) study focused more on process-based training. Process-based training targets broad cognitive abilities rather than explicit training of strategies to use for a particular task. Karbach and Kray (2009) achieved this by using variable task-switching exercises in order to train executive control abilities, such as inhibition of task-irrelevant information and maintenance of task-relevant goals.

Indeed, transfer is thought to occur more readily if cognitive functions that are presumed to form the basis of general cognitive abilities are trained, rather than training task-specific strategies (Schmiedek et al., 2010). Examples for such processes are working memory and other executive functions, perceptual speed, and sensory discrimination (Klingberg et al., 2005; Mahncke et al., 2006; Ball et al., 2007; Diamond et al., 2007; Dahlin et al., 2008; Jaeggi et al., 2008; Li et al., 2008; Karbach & Kray, 2009; Schmiedek et al., 2010). Training general cognitive functions should extend to other activities that engage the same processes (Westerberg & Klingberg, 2007; Klingberg, 2010; Takeuchi et al., 2010; Astle et al., 2015; Barnes et al., 2016; Caeyenberghs et al., 2016; Salmi et al., 2018; Gathercole et al., 2019).

4.1.2 Methodological considerations

As discussed, different cognitive training studies have presented contradictory findings regarding the key issue of transfer (Soveri et al., 2017; Flegal et al., 2019; Pappa

et al., 2020). One reason for the inconsistent findings may be that there are large differences in the type, intensity, and duration of the training regimes as well as different methodologies adopted in the studies (Karbach & Verhaeghen, 2014; Flegal et al., 2019; Pappa et al., 2020). For example, as stated above, strategy-based training (such as with mnemonic techniques) often results in large improvements to the trained task, but rarely in any transfer (Rebok et al., 2007; von Bastian et al., 2013; Karbach, 2014; Rebok et al., 2014). On the other hand, process-based training that targets more general processing capacities, such as reasoning or working memory, has yielded widespread near transfer and some far transfer in different age groups (Hertzog et al., 2009; Karbach & Kray, 2009; Karbach & Unger, 2014; Karbach & Verhaeghen, 2014).

With regards to the methodological heterogeneity of the studies, issues also include variation in the age of the study samples, neglecting the fact that older populations present differences not only in brain function, but also in behavioural performance compared to younger populations (Emch et al., 2019). Thus, participant age variation may contribute to contradicting results regarding transfer and the overall efficacy of cognitive training programmes. This implication is highlighted in two studies conducted by the same colleagues, using the same design on adults aged under 60 (Owen et al., 2010), and over 60 (Corbett et al., 2015). While the older age group improved cognitive performance following training and demonstrated transfer, the younger age group did not, leading to different conclusions regarding transfer and the effectiveness of cognitive training. While Owen and colleagues (2010) concluded that cognitive training does not confer any benefits beyond the trained tasks, the follow-up study in older adults (Corbett et al., 2015) concluded that training benefits do indeed transfer to general cognitive ability.

A further issue is the intensity and duration of the training programme, which can lead to weaker or stronger effects depending on whether training is of a shorter or longer duration (Jaeggi et al., 2008; von Bastian & Oberauer, 2014; Salmi et al., 2018; Emch et al., 2019; Pappa et al., 2020). For example, more training sessions and increased total duration of training raises the probability that effects carry over to cognitive processes not directly practiced during the training, i.e., transfer (Jaeggi et al., 2008; von Bastian &

Oberauer, 2014; Salmi et al., 2018; Emch et al., 2019; Pappa et al., 2020). Thus, training duration can modify the effect of training, favouring training of longer duration (more than 10 hours), while studies with shorter training durations (less than 10 hours) are less likely to result in transfer effects (Pappa et al., 2020).

Inconsistencies regarding the use of an active or passive control group have also been reported, such that the type of control condition can significantly modify the effect of training (Emch et al., 2019; Pappa et al., 2020). Passive control groups involve participants completing the pre- and post-training assessments, but not engaging in any training. Active control conditions refer to the participants completing some form of training (usually less difficult and less challenging) in addition to the pre- and post-training tests. Some authors have determined there is little to no evidence of far transfer when comparing training groups against active control groups, suggesting that transfer effects are overestimated when employing passive control conditions (Shipstead et al., 2012; Strenziok et al., 2014; Dougherty et al., 2016; Melby-Lervag et al., 2016; Pappa et al., 2020). In a meta-analysis by Pappa and colleagues (2020), there was a significant difference between the training effect sizes from the control group analyses, such that 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. It is important to note that designs employing passive control conditions 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 are mediated by non-specific factors such as practice effects or increased effort (Shipstead et al., 2012; Strenziok et al., 2014; Dougherty et al., 2016; Melby-Lervag et al., 2016; Pappa et al., 2020).

Comparisons across studies are therefore difficult to draw when training protocols differ not only in the type of training tasks employed, but also frequency and duration of training, sample age, outcome measurement, and type of control group (Karbach & Verhaeghen, 2014; Emch et al., 2019; Flegal et., 2019, Pappa et al., 2020). These methodological issues should be considered when investigating the effects of any training intervention. In response to recent critiques of the wide variability in training study methodology, there has been an emphasis on the need for greater experimental rigour

and protocol standardisation (Shipstead et al., 2012; Green et al., 2014; Noack et al., 2014; Flegal et al., 2019).

4.1.3 Mechanisms of cognitive training and transfer

An explanation for transfer is that the effects observed following training reflect plasticity in the neural system underpinning the particular function that has been trained; training might therefore lead to changes in the brain and improved neural efficiency which should extend to other activities that engage the same processes (Westerberg & Klingberg, 2007; Klingberg, 2010; Takeuchi et al., 2010; Astle et al., 2015; Barnes et al., 2016; Caeyenberghs et al., 2016; Salmi et al., 2018; Gathercole et al., 2019).

According to a recent theoretical model (Lovden et al., 2010; Flegal et al., 2019), transient cognitive challenges are only sufficient to promote task-specific gains, sustained cognitive challenges are required to elicit lasting neural changes that underlie transfer and improvement of general cognitive function. If environmental demand briefly approaches the upper limit of functional supply, then all available resources will be flexibly employed, but actually raising the level of maximum function requires a prolonged mismatch in which environmental demand exceeds functional supply (Lovden et al., 2010; Flegal et al., 2019).

Based on this framework, it is suggested that adapting the difficulty of training tasks to an individual's current level of ability would provide the necessary prolonged mismatch, thereby driving cognitive and neural plasticity leading to broader transfer. Indeed, previous studies have proposed that adaptivity may be a key to effective transfer (Holmes et al., 2009; Jaeggi et al., 2010; Brehmer et al., 2012; Rudebeck et al., 2012; Anguera et al., 2013; Heinzel et al., 2016; Flegal et al., 2019). For example, Flegal and colleagues (2019) investigated whether dynamically increasing task demands during adaptive working memory training would lead to successful transfer compared to non-adaptive training. Training task difficulty was individually adapted within sessions in response to performance in the adaptive group, or individually assigned on the basis of pre-training working memory capacity and fixed in the non-adaptive group. Adaptive training resulted in near transfer to other working memory tasks and far transfer to an

untrained episodic memory task (Object-Location Association), while non-adaptive training did not result in significant transfer. Furthermore, activation decreases were found in striatum and hippocampus on a trained working memory task, and the amount of training task improvement was associated with hippocampal activation changes on both near and far transfer tasks. Thus, the authors conclude that an optimal design should use adaptive, rather than non-adaptive training, in order to induce neuroplasticity and therefore broader transfer of training gains.

4.1.4 Experiment aims and design

The aim of the current experiment was to test the effectiveness of cognitive training in improving cognitive function in healthy middle-aged adults (40-50 years old). In terms of using cognitive training as a pre-emptive strategy to maintain cognitive function and prevent decline in later life, it seems likely that middle-age presents an ideal opportunity to train cognitive abilities before they start to significantly decline.

We compared the training condition to an active control treatment to ensure that any effects observed in the cognitive training group could not be attributed to test-retest effects, or to the Hawthorne effect (Landsberger, 1958), or to participants having higher expectations of themselves (Collie et al., 2003; McCarney et al., 2007; Green & Bavelier, 2012). Therefore, to make sure that training conditions were the same for both groups, participants in the experimental condition completed an adaptive cognitive training programme, while the active control group completed a non-adaptive version of the same training.

The cognitive training programme in this study included several tasks targeting working memory, attention, and other executive functions, such as inhibition. Cognitive decline is well documented in healthy older adults across these domains (for review see Karbach & Verhaeghen, 2014; Au et al., 2015; Soveri et al., 2017; Pergher et al., 2018). Therefore, a goal of our training programme was to induce plasticity in brain regions that would result in an improvement in these domains, translating to an overall improvement in cognitive function.

Furthermore, process-based training that targets more general capacities, such as working memory and other executive functions, has yielded widespread transfer in different age groups (e.g., Hertzog et al., 2009; Karbach & Kray, 2009; Schmiedek et al., 2010; Karbach & Verhaeghen, 2014; Pappa et al., 2020). Indeed, transfer is thought to occur more readily if cognitive functions that are presumed to form the basis of general cognitive ability are trained, rather than training task-specific strategies (Klingberg, 2010; Schmiedek et al., 2010; Astle et al., 2015; Barnes et al., 2016; Salmi et al., 2018; Gathercole et al., 2019). Therefore, we aimed to target these particular processes in our training programme with a view to improving broad cognitive abilities, thus increasing the probability of transfer to untrained tasks.

A varied selection of tasks was a key feature of our programme not only to train more processes and increase the likelihood of transfer, but also to keep it interesting and motivating for participants. This issue is of particular importance because recent work has identified motivation as a key condition for transfer to occur (Green & Bavelier, 2008; Jaeggi et al., 2014).

In addition, previous studies have proposed that adaptive training in particular may be important for effective transfer (Holmes et al., 2009; Jaeggi et al., 2010; Brehmer et al., 2012; Rudebeck et al., 2012; Anguera et al., 2013; Heinzel et al., 2016; Flegal et al., 2019). Adapting the difficulty of tasks to an individual's current level of ability, is thought to provide the sustained cognitive challenges required to elicit lasting neural changes that underlie transfer and improvement of general cognitive function (Lovden et al., 2010; Flegal et al., 2019). As such, for participants assigned to the adaptive group, training dynamically changed relative to performance, keeping task demands challenging and at a high level of difficulty. For participants in the non-adaptive group, task difficulty remained within a constant limited range over the entirety of training, regardless of the participant's performance. Non-adaptive training remained less challenging and at a low level of difficulty. Therefore, participants in the adaptive group were expected to be operating at a more plasticity-inducing difficulty level than the non-adaptive group.

CogniPlus software (SCHUHFRIED GmbH, Austria) was chosen for the training programme as it provided us with a selection of process-based tasks designed to train

working memory, attention, and other executive functions, such as inhibition. This software allowed us to select a variety of different tasks which kept the programme interesting and motivating for participants. Furthermore, this software allowed us to manipulate whether tasks were adaptive or non-adaptive – a feature that was not available with other software packages, and which was deemed necessary in order for us to test adaptive training against a rigorous active control group.

As discussed, in a systematic review and meta-analysis of working memory training studies, Pappa and colleagues (2020) concluded that training programmes of longer duration (more than 10 hours) are more likely to result in transfer effects. In addition, Cheng et al. (2012) have suggested that programmes exceeding ten sessions produce more reliable transfer. Thus, in the current experiment, participants in both the adaptive and non-adaptive groups completed 12 sessions of cognitive training. To measure transfer of training-related cognitive improvements, we used the Raven Advanced Progressive Matrices (RAPM: Raven & Court, 1998), an associative learning task (PAL), an associative memory task (PAR), and a working memory task (N-back).

In sum, the present cognitive training study was carefully designed to overcome some of the methodological limitations faced by previous research. As such, we included an active control group, process-based training of general cognitive abilities (i.e., working memory, attention, and inhibition), an adaptive training design, a varied selection of training tasks to keep the programme interesting, a total of 12 sessions and training duration of 10 hours, and participants within a limited age range of 40–50 years old.

4.1.5 Experiment hypotheses

We tested two hypotheses for this experiment. First, if cognitive training results in improved cognitive function in middle-aged adults, then significant gains in performance should be observed for the training tasks. Several studies have shown substantial improvements on trained tasks in both young and older adults (e.g., Green & Bavelier, 2003; Singer et al., 2003; Rebok et al., 2007; Basak et al., 2008; Owen et al., 2010; Schmiedek et al., 2010; Rebok et al., 2014). Therefore, we also expected significant improvements in training-task performance in middle-aged adults.

Second, if cognitive training results in an improvement in the general cognitive functioning of middle-aged adults, then significant gains in performance should be demonstrated for the transfer tasks. Near transfer effects following cognitive training have been widely reported for both young and older adults (e.g., Klingberg et al., 2005; Willis et al., 2006; Jaeggi et al., 2008; Mozolic et al., 2009; Schmiedek et al., 2010; Dunning et al., 2013; Karbach & Verhaeghen, 2014; Caeyenberghs et al., 2016; Emch et al., 2019). Near transfer is thought to occur when training and transfer tasks engage the same processes (Westerberg & Klingberg, 2007; Klingberg, 2010; Takeuchi et al., 2010; Astle et al., 2015; Barnes et al., 2016; Salmi et al., 2018; Gathercole et al., 2019). We therefore predicted that cognitive training in middle-aged adults would lead to significantly improved performance on the near transfer tasks (PAR, N-back). The PAR task involves working memory, in addition to retrieval and recognition processes, and therefore we expected near transfer to this task due to its working memory component that is shared with our training programme. The N-back task involves executive functions besides working memory, including inhibitory control and selective attention, thus, we expected near transfer to this task as it includes the working memory, attention, and inhibition components of the training programme used in this study.

Evidence of far transfer following cognitive training is reported much less frequently (Dahlin et al., 2008; Moody, 2009; Owen et al., 2010; Shipstead et al., 2012; Melby-Lervag & Hulme, 2013; Melby-Lervag et al., 2016; Soveri et al., 2017; Flegal et al., 2019). Indeed, transfer should only be expected if training and transfer tasks both place demands on the same underlying processes (Dahlin et al., 2008; Dahlin et al., 2009; Holmes et al., 2009; Shipstead et al., 2012; Sprenger et al., 2013; von Bastian et al., 2013; Dunning & Holmes, 2014; Minear et al., 2016; Soveri et al., 2017; Gathercole et al., 2019; Pappa et al., 2020). We therefore predicted that cognitive training in middle-aged adults would not lead to significantly improved performance on the far transfer tasks (RAPM, PAL). The RAPM is designed to test abstract reasoning and fluid intelligence, and therefore we did not expect far transfer to this task because these abilities were not directly trained by our programme. The PAL task involved the participant learning to form new associations between pairs of different black-and-white fractal pictures**.** Again, we

did not expect far transfer to this task as few cognitive processes and perceptual features were shared with the training tasks.

4.2 Summary of methods

4.2.1 Participants

A total of 40 participants between 40 and 50 years of age took part in this study. Of these, 20 were part of the adaptive (experimental) training group (14 females, 6 males; *M* age = 44.15 years, *SD* = 2.94), and 20 were part of the non-adaptive (control) training group (14 females, 6 males; *M* age = 45.80 years, *SD* = 3.04). The mean number of years of education for the adaptive group was 17.30 (*SD* = 3.80). The mean number of years of education for the non-adaptive group was 17.15 (*SD* = 3.10). There were 18 right handed participants in the adaptive group, and 19 in the non-adaptive group. Participants had normal or corrected-to-normal vision. They were carefully screened for MRI contraindications. The participants had no history of psychiatric or neurological illness, or brain injury. Participants also had no history of alcohol or drug use disorders. Participants were not taking prescribed medications at the time of the experiment.

4.2.2 Procedure

To investigate whether regular cognitive training leads to overall improvement in cognitive function in middle-aged adults, we used a mixed design with group (cognitive training, active control) as a between-subjects factor, transfer task as a within-subjects factor (RAPM, PAL, PAR, N-back), and session (pre-training, post-training) as a within-subjects factor. To make sure that training conditions were the same for both groups, participants in the experimental condition completed an adaptive cognitive training programme, while the active control group completed a non-adaptive version of the same training. Cognitive function and transfer effects were assessed using a fluid intelligence test: RAPM (far transfer), a paired associative learning task: PAL (far transfer), a paired associative memory task: PAR (near transfer), and a working memory task: N-back (near transfer).

Participants first completed a pre-training session of the transfer tasks including the RAPM, PAL, PAR, and N-back. Participants then completed 12 sessions of either the adaptive or non-adaptive training over 4-6 weeks (2-3 sessions per week). The training programme consisted of 5 computer-based exercises that aimed to train working memory, attention, and executive function. Each task was 10min long and total training time per session was 50min. Post-training, participants again completed the RAPM, PAL, PAR, and N-back tasks to measure possible changes in cognitive ability and transfer.

4.2.3 Data analysis

Multiple independent samples t-tests were performed comparing the groups (adaptive vs non-adaptive) on the demographic data and baseline (pre-training) performance for each transfer task. All tests for demographic and baseline data were two-tailed; significance level was set at $p < .05$.

Performance on the CogniPlus training exercises was analysed using paired samples t-tests comparing session 1 to session 12 for all tasks in adaptive and non-adaptive groups. Statistical significance was set at $p < .05$ (two-tailed).

Post-training performance scores on the near and far transfer tasks (RAPM, PAL, PAR, 3-back, 4-back) were entered as dependent variables in separate one-way analyses of covariance (ANCOVA), with group (adaptive, non-adaptive) as a between-subjects factor, and baseline performance entered as covariates. Statistical significance for all tests was set at $p < .05$ (two-tailed). We then ran paired samples t-tests comparing pre- and post-training performance on each of the transfer tasks for the total sample (combined adaptive and non-adaptive training groups, $N = 40$), with statistical significance set at $p < .05$ (two-tailed).

In addition, we conducted Kendall's tau-b correlations of performance on CogniPlus tasks with post-training performance on transfer tasks. This was to determine whether a specific type of training (i.e., working memory, attention, or inhibition) was associated with improved performance on particular transfer tasks. Significance for the correlations was set to $p < .05$ (two-tailed).

4.3 Results

Independent samples t-tests were performed on both the demographic data (Table 4.1) and baseline transfer task performance (Table 4.2) to ensure there were no significant differences between experimental and control groups prior to training. Indeed, there were equal numbers of males and females in each group, and all *p* values exceeded .05. Thus, the two groups did not differ significantly on age, gender, handedness, and years of education, nor did they differ significantly on baseline performance of RAPM, PAL, PAR, and N-back tasks. Therefore, any differences that were observed can be attributed to the cognitive training and type of programme (adaptive or non-adaptive), rather than to previous underlying differences between the groups.

Table 4.1. Summary of demographic data for adaptive and non-adaptive groups. Results of independent t-tests.

	Adaptive		Non-adaptive			
	Mean	± SD	Mean	± SD	t	p
Age (years)	44.15	2.94	45.80	3.04	1.75	.089
Education (years)	17.30	3.80	17.15	3.10	-0.14	.892
Right-handed	n = 18		n= 19		0.36[a]	.548
Female	n = 14		n= 14			
Male	n = 6		n=6			

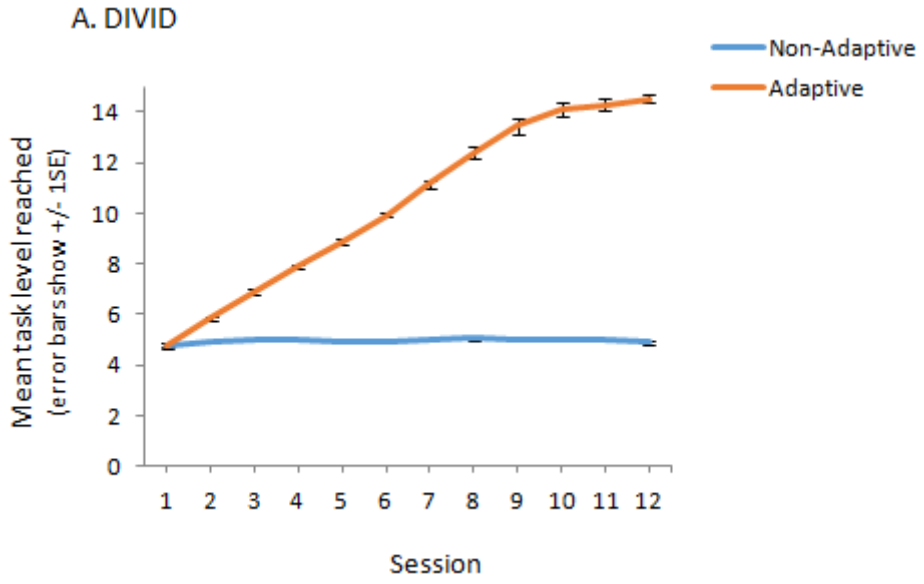
a. Results of Chi-Square test, χ^2 value shown.

Table 4.2. Baseline transfer task performance for adaptive and non-adaptive groups. Results of independent t-tests.

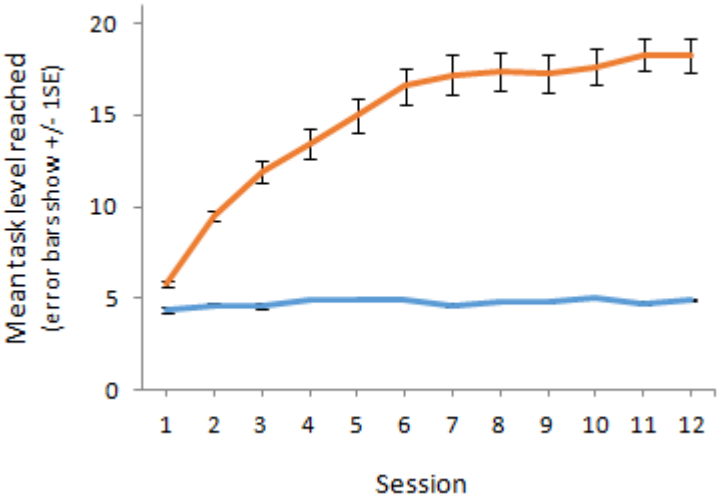
	Adaptive		Non-adaptive			
	Mean	± SD	Mean	± SD	t	p
RAPM	8.20	3.30	8.20	2.93	0.00	1.000
PAL	71.70	17.98	76.55	18.95	0.83	.412

PAR	32.10	7.28	32.55	6.50	0.21	.838
0-back	79.80	0.52	78.35	5.33	-1.21	.234
1-back	79.10	1.55	78.25	2.49	-1.30	.203
3-back	66.30	4.07	67.50	3.86	0.96	.345
4-back	63.10	3.21	62.05	4.14	-0.90	.375

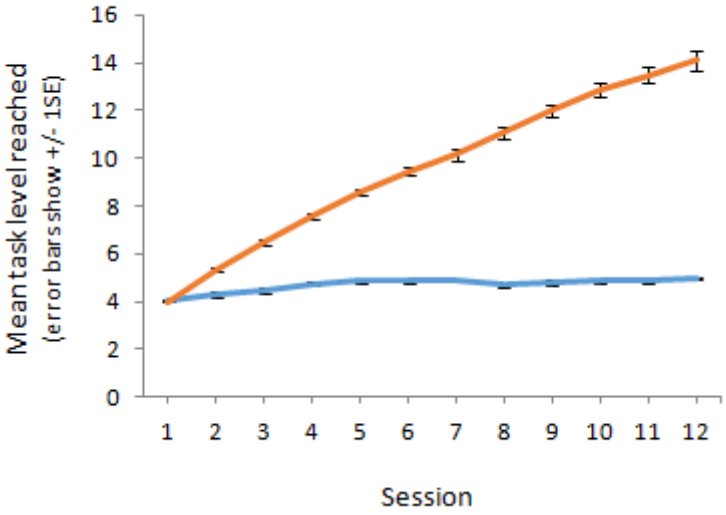
Figure 4.1 shows the performance on each of the 5 CogniPlus exercises that made up the training programmes for both the adaptive experimental and non-adaptive control groups. This illustrates how the control group was restricted to lower difficulty levels, whereas for the experimental group, task difficulty progressively increased in line with performance for the duration of the 12 sessions over 4-6 weeks. However, paired t-tests comparing session 1 and session 12 showed significant increases in performance for all tasks for the adaptive training group (Table 4.3), but also for the non-adaptive group in all tasks except DIVID (Table 4.4). Effect sizes for both the adaptive and non-adaptive groups were positive and very large for most of the training tasks (Table 4.3 and Table 4.4).



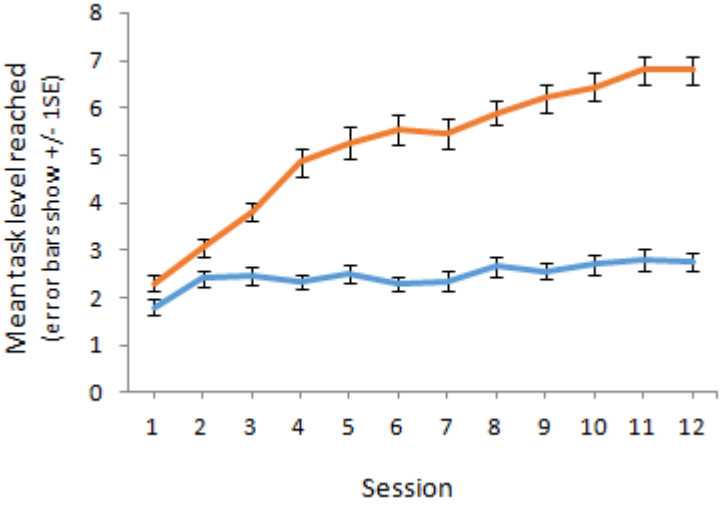
B. CODING



C. DATEUP



D. HIBITR



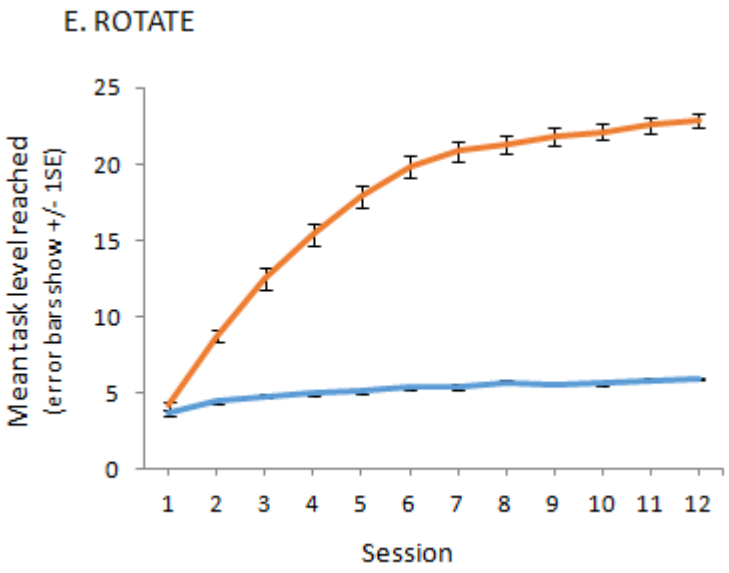


Figure 4.1. Mean level reached per session for the training tasks in non-adaptive and adaptive groups. A) Divided Attention. B) Spatial Coding. C) Spatial Updating. D) Response Inhibition. E) Mental Rotation and Spatial Processing. Error bars indicate the standard error of the mean.

Table 4.3. Adaptive group: cognitive training performance comparing session 1 and session 12 of the CogniPlus tasks. Results of paired t-tests.

	Session 1		Session 12					
	Mean	± SD	Mean	± SD	t	p	Cohen's d	Power
DIVID	4.75	0.55	14.55	0.83	49.00	<.001	14.28	1.000
CODING	5.80	0.89	18.25	4.03	14.80	<.001	4.38	1.000
DATEUP	4.00	0.00	14.10	1.71	26.36	<.001	8.57	1.000
HIBITR	2.30	0.73	6.75	1.37	13.90	<.001	4.16	1.000
ROTATE	4.20	1.20	22.85	1.95	52.18	<.001	11.82	1.000

Table 4.4. Non-adaptive group: cognitive training performance comparing session 1 and session 12 of the CogniPlus tasks. Results of paired t-tests.

	Session 1		Session 12					
	Mean	± SD	Mean	± SD	t	p	Cohen's d	Power
DIVID	4.80	0.41	4.90	0.45	0.70	.494	0.11	0.075
CODING	4.40	0.68	4.85	0.37	2.93	.009	0.84	0.945
DATEUP	4.05	0.22	4.95	0.22	13.08	<.001	4.20	1.000
HIBITR	1.80	0.70	2.75	0.91	5.15	<.001	1.20	0.999
ROTATE	3.70	0.87	5.90	0.31	11.80	<.001	3.46	1.000

Correlations were run to determine if there were any relationships between the demographic data (gender, age, education) and transfer task post-training scores. Both the non-adaptive and adaptive groups were combined for these correlations (N = 40). Tests of assumptions for the point-biserial correlation of gender x post-training RAPM scores indicated no significant outliers in the scores for females and males (Appendix VI, Figure VI.1, pg. 291). A Shapiro-Wilk test for females showed that RAPM post-training scores are normally distributed, $W(28) = .974$, $p = .697$; as did a Shapiro-Wilk test for males, $W(12) = .924$, $p = .316$. Levene's test found that the assumption of homogeneity of variance for female and male RAPM post-training scores was met, $F(1,38) = .003$, $p = .955$. The point-biserial correlation demonstrated there was no significant relationship between gender and post-training RAPM scores, $r_{pb} = -.047$, $p = .774$.

Tests of assumptions for the point-biserial correlation of gender x post-training PAL scores indicated no outliers in the scores for females and males (Appendix VI, Figure VI.2, pg. 292). A Shapiro-Wilk test for females showed that PAL post-training scores are normally distributed, $W(28) = .955$, $p = .271$; as did a Shapiro-Wilk test for males, $W(12) = .987$, $p = .999$. Levene's test found that the assumption of homogeneity of variance for female and male PAL post-training scores was met, $F(1,38) = .420$, $p = .521$. The point-biserial correlation demonstrated there was no significant relationship between gender and post-training PAL scores, $r_{pb} = .029$, $p = .858$.

Tests of assumptions for the point-biserial correlation of gender x post-training PAR scores indicated no significant outliers in the scores for females and males (Appendix VI, Figure VI.3, pg. 292). A Shapiro-Wilk test for females showed that the distribution of PAR post-training scores is significantly different from normal, $W(28) = .882$, $p = .004$; as did a Shapiro-Wilk test for males, $W(12) = .830$, $p = .021$. Levene's test found that the assumption of homogeneity of variance for female and male PAR post-training scores was met, $F(1,38) = .002$, $p = .969$. As the Shapiro-Wilk test for the distribution of female post-training PAR scores is highly significant ($p = .004$), a Mann-Whitney U test was employed as this non-parametric test does not require this assumption to be met. The Mann-Whitney U test for post-training PAR scores demonstrated there were no significant differences in performance between females and males, $U = 165.50$, $p = .941$.

As both the 0- and 1-back scores were at ceiling in the pre-training session (Non-adaptive 0-back: $M = 78.35$, $SD = 5.33$; Adaptive 0-back: $M = 79.80$, $SD = 0.52$; Non-adaptive 1-back: $M = 78.25$, $SD = 2.49$; Adaptive 1-back: $M = 79.10$, $SD = 1.55$; out of a total of 80 trials), we did not include these conditions in any further analyses. Indeed, we did not expect to see differences between the groups nor between the pre- and post-training sessions for the 0-back as this was a control condition that did not test working memory. Nor did we expect to see differences for the low working memory load of 1-back (McElree, 2001; Jaeggi et al., 2010; Heinzel et al, 2014; Beatty et al., 2015; Flegal et al., 2019). We expected near perfect scores for both these conditions and this was what was found (Non-adaptive post-training 0-back: $M = 78.80$, $SD = 2.73$; Adaptive post-training 0-back: $M = 79.90$, $SD = 0.31$; Non-adaptive post-training 1-back: $M = 77.75$, $SD = 2.59$; Adaptive post-training 1-back: $M = 78.25$, $SD = 1.77$; out of a total of 80 trials). Therefore, we restricted all N-back analyses to the 3- and 4-back conditions.

Tests of assumptions for the point-biserial correlation of gender x post-training 3-back scores indicated no outliers in the scores for females and males (Appendix VI, Figure VI.4, pg. 293). A Shapiro-Wilk test for females showed that 3-back post-training scores are normally distributed, $W(28) = .975$, $p = .717$; as did a Shapiro-Wilk test for males, $W(12) = .979$, $p = .980$. Levene's test found that the assumption of homogeneity of variance for female and male 3-back post-training scores was met, $F(1,38) = 1.064$, $p = .309$. The point-

biserial correlation demonstrated there was no significant relationship between gender and post-training 3-back scores, r_{pb} = .103, p = .526.

Tests of assumptions for the point-biserial correlation of gender x post-training 4-back scores indicated no significant outliers in the scores for females and males (Appendix VI, Figure VI.5, pg. 294). A Shapiro-Wilk test for females showed that 4-back post-training scores are normally distributed, $W(28)$ = .954, p = .246; as did a Shapiro-Wilk test for males, $W(12)$ = .908, p = .203. Levene's test found that the assumption of homogeneity of variance for female and male 4-back post-training scores was met, $F(1,38)$ = .125, p = .726. The point-biserial correlation demonstrated there was no significant relationship between gender and post-training 4-back scores, r_{pb} = .115, p = .479.

Tests of assumptions for the Pearson's correlation of age x post-training RAPM scores indicated no significant outliers for age and scores (Appendix VI, Figures VI.6 and VI.7, pgs. 294 and 295). A Shapiro-Wilk test showed that age is not normally distributed, $W(40)$ = .938, p = .030. However, as the Shapiro-Wilk test for the distribution of age is not highly significant (p = .030) and the assumption requires the data to be only approximately normally distributed (see Appendix VI, Figure VI.8, pg. 296), Pearson's correlations were run with this variable unless otherwise specified. A Shapiro-Wilk test for post-training RAPM scores indicated that scores are normally distributed, $W(40)$ = .970, p = .364. A scatterplot of age x post-training RAPM scores indicated that the assumption of homoscedasticity was met (Appendix VI, Figure VI.9, pg. 296). The Pearson's correlation demonstrated there was no significant relationship between age and post-training RAPM scores, r = -.129, p = .427.

Tests of assumptions for the Pearson's correlation of age x post-training PAL scores indicated no outliers for scores (Appendix VI, Figure VI.10, pg. 297). Tests of assumptions for age were not violated with the exception of normality (as discussed) and are reported above. A Shapiro-Wilk test showed that post-training PAL scores are normally distributed, $W(40)$ = .980, p = .695. A scatterplot of age x post-training PAL scores indicated that the assumption of homoscedasticity was met (Appendix VI, Figure

VI.11, pg. 298). The Pearson's correlation demonstrated there was no significant relationship between age and post-training PAL scores, $r = .064$, $p = .694$.

Tests of assumptions for the Pearson's correlation of age x post-training PAR scores indicated no outliers for scores (Appendix VI, Figure VI.12, pg. 298). Tests of assumptions for age were not violated with the exception of normality and are reported above. A Shapiro-Wilk test showed that post-training PAR scores are not normally distributed, $W(40) = .873$, $p < .001$. A scatterplot of age x post-training PAR scores indicated that the assumption of homoscedasticity was met (Appendix VI, Figure VI.13, pg. 299). However, as the Shapiro-Wilk test for the distribution of post-training PAR scores is highly significant ($p < .001$), Kendall's tau-b was used because this non-parametric test statistic does not require this assumption to be met. Kendall's tau-b demonstrated there was a significant relationship between age and post-training PAR scores, $\tau_b = .250$, $p = .033$.

Tests of assumptions for the Pearson's correlation of age x post-training 3-back scores indicated no outliers for scores (Appendix VI, Figure VI.14, pg. 300). Tests of assumptions for age were not violated with the exception of normality and are reported above. A Shapiro-Wilk test showed that post-training 3-back scores are normally distributed, $W(40) = .988$, $p = .931$. A scatterplot of age x post-training 3-back scores indicated that the assumption of homoscedasticity was met (Appendix VI, Figure VI.15, pg. 301). The Pearson's correlation demonstrated there was no significant relationship between age and post-training 3-back scores, $r = .124$, $p = .446$.

Tests of assumptions for the Pearson's correlation of age x post-training 4-back scores indicated no significant outliers for scores (Appendix VI, Figure VI.16, pg. 301). Tests of assumptions for age were not violated with the exception of normality and are reported above. A Shapiro-Wilk test showed that post-training 4-back scores are normally distributed, $W(40) = .965$, $p = .248$. A scatterplot of age x post-training 4-back scores indicated that the assumption of homoscedasticity was met (Appendix VI, Figure VI.17, pg. 302). The Pearson's correlation demonstrated there was no significant relationship between age and post-training 4-back scores, $r = .072$, $p = .661$.

Tests of assumptions for the Pearson's correlation of education x post-training RAPM scores indicated no outliers for education (Appendix VI, Figure VI.18, pg. 303). Tests of assumptions for post-training RAPM scores were not violated and are reported above. A Shapiro-Wilk test showed that education is normally distributed, $W(40) = .956$, $p = .125$. A scatterplot of education x post-training RAPM scores indicated that the assumption of homoscedasticity was not met (Appendix VI, Figure VI.19, pg. 303). As such, Kendall's tau-b was employed as this test statistic does not require this assumption to be met. Kendall's tau-b demonstrated there was no significant relationship between education and post-training RAPM scores, $\tau_b = .033$, $p = .777$.

Tests of assumptions for the Pearson's correlation of education x post-training PAL scores were not violated and are reported above. However, a scatterplot of education x post-training PAL scores indicated that the assumption of homoscedasticity was potentially violated (Appendix VI, Figure VI.20, pg. 304). As such, Kendall's tau-b was included as this non-parametric test statistic does not require this assumption to be met. The Pearson's correlation demonstrated there was no significant relationship between education and post-training PAL scores, $r = -.011$, $p = .945$; as did Kendall's tau-b, $\tau_b = -.007$, $p = .953$.

Tests of assumptions for the Pearson's correlation of education x post-training PAR scores indicated that some assumptions were not met. A scatterplot of education x post-training PAR scores showed that the assumption of homoscedasticity was violated (Appendix VI, Figure VI.21, pg. 305). In addition, the Shapiro-Wilk test for the distribution of post-training PAR scores is highly significant ($p < .001$). Thus, Kendall's tau-b was employed as this test statistic does not require these assumptions to be met. Kendall's tau-b demonstrated there was no significant relationship between education and post-training PAR scores, $\tau_b = .048$, $p = .680$.

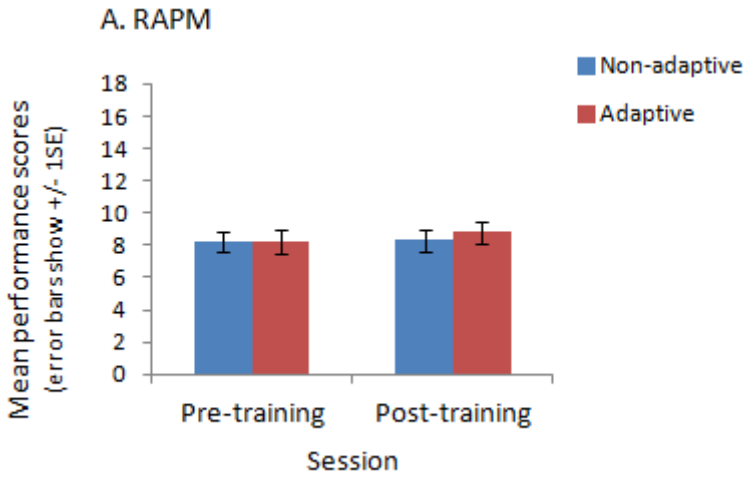
Tests of assumptions for the Pearson's correlation of education x post-training 3-back scores were not violated and are reported above. A scatterplot of education x post-training 3-back scores indicated that the assumption of homoscedasticity was met (Appendix VI, Figure VI.22, pg. 305). The Pearson's correlation demonstrated there was

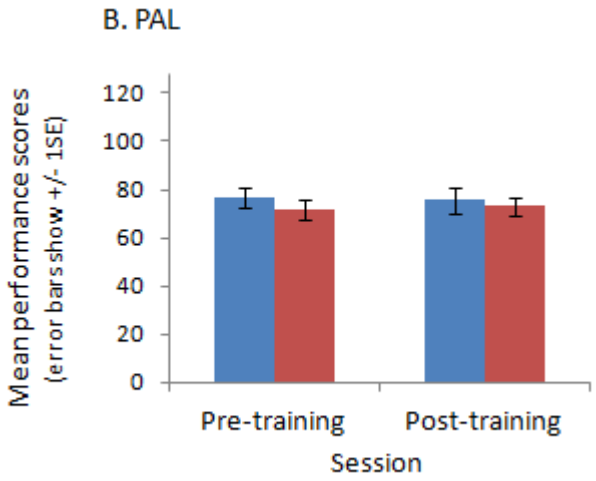
no significant relationship between education and post-training 3-back scores, r = .082, p = .616.

Tests of assumptions for the Pearson's correlation of education x post-training 4-back scores were not violated and are reported above. A scatterplot of education x post-training 4-back scores indicated that the assumption of homoscedasticity was met (Appendix VI, Figure VI.23, pg. 306). The Pearson's correlation demonstrated there was no significant relationship between education and post-training 4-back scores, r = -.053, p = .745. As there were no significant relationships found between the demographics and post-training scores, these variables were not used as covariates in any further analyses, with the exception of age which was positively correlated with post-training PAR scores (τ_b = .250, p = .033). Thus, age was included as a covariate in the ANCOVA examining post-training PAR scores.

Figure 4.2 shows the changes in performance following training for the RAPM, PAL, PAR, 3-back, and 4-back tasks. Figure 4.2A shows that for the non-adaptive group there was a small increase in RAPM performance from pre- to post-training (Pre-training: M = 8.20, SD = 2.93; Post-training: M = 8.30, SD = 2.98). The increase was slightly greater for the adaptive group (Pre-training: M = 8.20, SD = 3.30; Post-training: M = 8.80, SD = 3.22). Figure 4.2B shows that for the non-adaptive group there was a slight decrease in PAL performance from pre- to post-training (Pre-training: M = 76.55, SD = 18.95; Post-training: M = 75.55, SD = 23.44). For the adaptive group there was a small increase in performance (Pre-training: M = 71.70, SD = 17.98; Post-training: M = 73.05, SD = 15.66). Figure 4.2C demonstrates that for the non-adaptive group there was a small increase in PAR performance from pre- to post-training (Pre-training: M = 32.55, SD = 6.50; Post-training: M = 33.90, SD = 6.63). The adaptive group exhibited a similar increase in performance (Pre-training: M = 32.10, SD = 7.28; Post-training: M = 33.95, SD = 5.17). Figure 4.2D shows that for the non-adaptive group there was a decrease in 3-back performance from pre- to post-training (Pre-training: M = 67.50, SD = 3.86; Post-training: M = 66.55, SD = 3.90). For the adaptive group there was also a decrease in performance (Pre-training: M = 66.30, SD = 4.07; Post-training: M = 64.80, SD = 5.45). Figure 4.2E demonstrates that for the non-adaptive group there was an increase in 4-back

performance from pre- to post-training (Pre-training: *M* = 62.05, *SD* = 4.14; Post-training: *M* = 64.70, *SD* = 4.07). For the adaptive group there was also an increase in performance (Pre-training: *M* = 63.10, *SD* = 3.21; Post-training: *M* = 64.15, *SD* = 3.57).





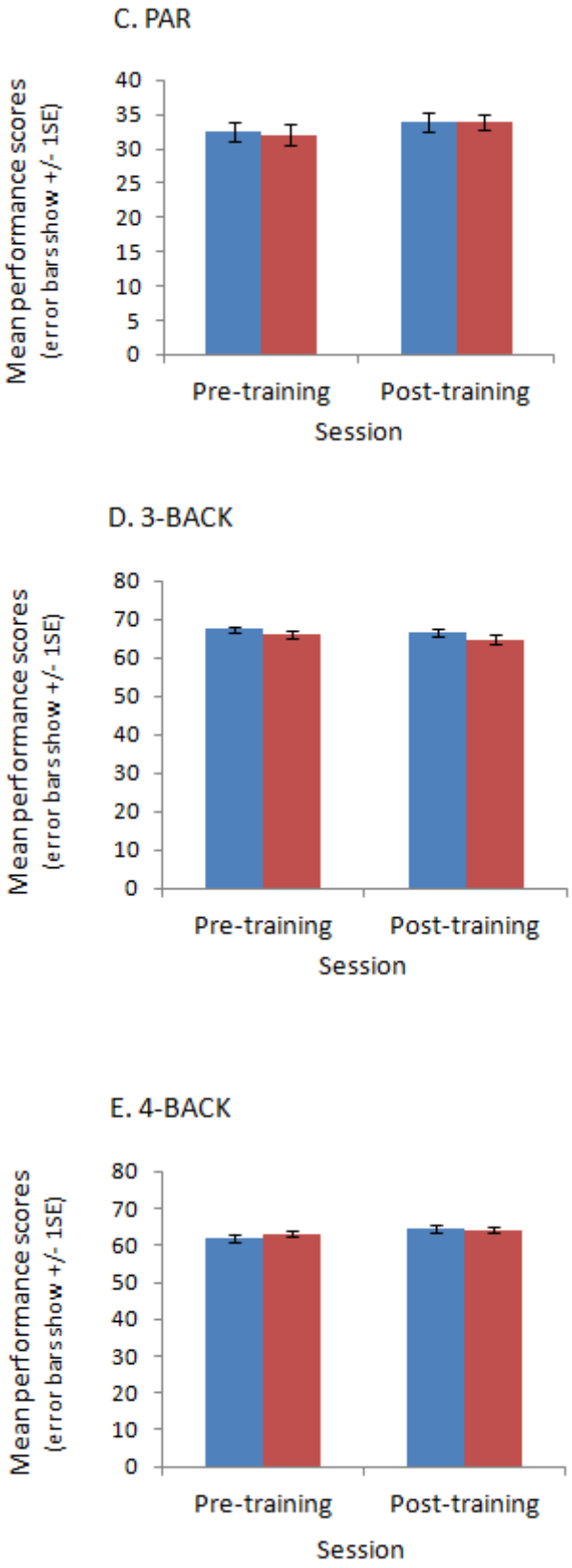


Figure 4.2. Mean performance for non-adaptive and adaptive groups in the pre- and post-training sessions of the A) RAPM, B) PAL, C) PAR, D) 3-back, and E) 4-back tasks. Error bars indicate the standard error of the mean.

To determine whether there were significant differences between training programmes on transfer task performance, separate one-way ANCOVAs were conducted with group (adaptive, non-adaptive) as the independent variable, and post-training scores (RAPM, PAL, PAR, 3-back, 4-back) as the dependent variables, while controlling for baseline performance.

The first assumption to consider for the following ANCOVAs is that the covariate is independent of the treatment effect (i.e., the covariate and independent variable are independent of each other), therefore, the covariate should not be different across the groups. Independent samples t-tests at baseline show that pre-training scores were not significantly different between the adaptive and non-adaptive groups for RAPM, PAL, PAR, 3-back, and 4-back (see Table 4.2). In addition, the post-training PAL scores used as a covariate in the PAR ANCOVA showed no significant differences between the groups [$t(38) = .40$, $p = .694$], nor did the covariate of age (see Table 4.1). Thus, this assumption has been met for all the following ANCOVAs.

Tests of assumptions for the ANCOVA examining post-training RAPM scores with pre-training RAPM scores as a covariate indicated no outliers for non-adaptive and adaptive training (Appendix VI, Figure VI.24, pg. 306). A Shapiro-Wilk test for the non-adaptive group showed that RAPM post-training scores are normally distributed, $W(20) = .950$, $p = .367$; as did a Shapiro-Wilk test for the adaptive group, $W(20) = .971$, $p = .785$. Levene's test found that the assumption of homogeneity of variances across groups was met, $F(1,38) = .096$, $p = .759$. A scatterplot indicated that the relationship between the covariate (pre-training RAPM scores) and the dependent variable (post-training RAPM scores) for the non-adaptive group was linear (Appendix VI, Figure VI.25, pg. 307); as did a scatterplot for the adaptive group (Appendix VI, Figure VI.26, pg. 308). The ANCOVA demonstrated no significant differences between the groups in post-training RAPM scores while controlling for baseline RAPM performance, $F(1, 37) = .63$, $p = .432$, power = .121.

Tests of assumptions for the ANCOVA examining post-training PAL scores with pre-training PAL scores as a covariate indicated no outliers for non-adaptive and adaptive training (Appendix VI, Figure VI.27, pg. 308). A Shapiro-Wilk test for the non-adaptive

group showed that PAL post-training scores are normally distributed, $W(20) = .962$, $p = .590$; as did a Shapiro-Wilk test for the adaptive group, $W(20) = .967$, $p = .694$. Levene's test found that the assumption of homogeneity of variances across groups was met, $F(1,38) = 3.30$, $p = .077$. A scatterplot indicated that the relationship between the covariate (pre-training PAL scores) and the dependent variable (post-training PAL scores) for the non-adaptive group was linear (Appendix VI, Figure VI.28, pg. 309); as did a scatterplot for the adaptive group (Appendix VI, Figure VI.29, pg. 310). The ANCOVA demonstrated no significant differences between the groups in post-training PAL scores while controlling for baseline PAL performance, $F(1, 37) = .03$, $p = .874$, power = .053.

Tests of assumptions for the ANCOVA examining post-training PAR scores with pre-training PAR, post-training PAL, and age as covariates indicated no outliers for non-adaptive and adaptive training (Appendix VI, Figure VI.30, pg. 310). Pearson's correlations demonstrated that the covariates were not highly correlated, i.e., $r > .80$ (Hinkle et al., 2003; Leech et al., 2005; Doncaster & Davey, 2007; Huitema, 2011; Field, 2018): pre-training PAR x post-training PAL ($r = .538$), pre-training PAR x age ($r = -.014$), post-training PAL x age ($r = .064$). A Shapiro-Wilk test for the non-adaptive group showed that PAR post-training scores are not normally distributed, $W(20) = .828$, $p = .002$; as did a Shapiro-Wilk test for the adaptive group, $W(20) = .897$, $p = .036$. ANCOVAs are robust to violations of normality (Hinkle et al., 2003; Leech et al., 2005; Doncaster & Davey, 2007; Huitema, 2011; Field, 2018), therefore, we proceeded with this analysis. Levene's test found that the assumption of homogeneity of variances across groups was met, $F(1,38) = .960$, $p = .333$. Scatterplots indicated that the relationship between each covariate (pre-training PAR, post-training PAL, age) and the dependent variable (post-training PAR scores) for the non-adaptive group was linear (Appendix VI, Figures VI.31, VI.32, VI.33, pgs. 311 and 312); as did scatterplots for the adaptive group (Appendix VI, Figures VI.34, VI.35, VI.36, pgs. 313, 314, and 315). The ANCOVA demonstrated no significant differences between the groups in post-training PAR scores while controlling for baseline PAR performance, post-training PAL performance, and age, $F(1, 37) = 1.02$, $p = .319$, power = .166.

Tests of assumptions for the ANCOVA examining post-training 3-back scores with pre-training 3-back scores as a covariate indicated no outliers for non-adaptive and

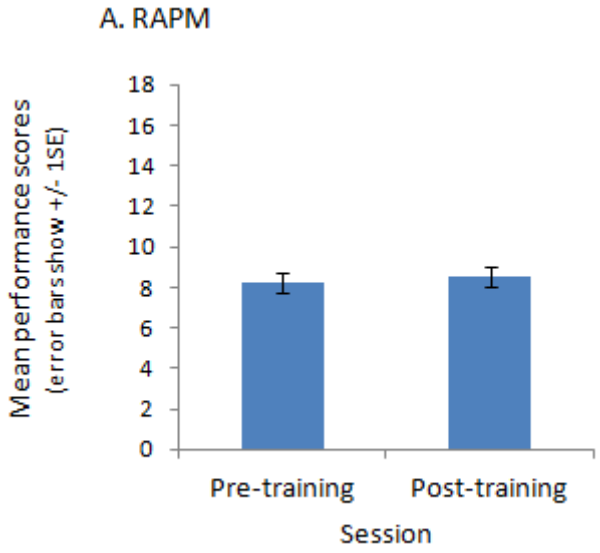
adaptive training (Appendix VI, Figure VI.37, pg. 315). A Shapiro-Wilk test for the non-adaptive group showed that 3-back post-training scores are normally distributed, $W(20) = .937$, $p = .209$; as did a Shapiro-Wilk test for the adaptive group, $W(20) = .994$, $p = 1.00$. Levene's test found that the assumption of homogeneity of variances across groups was met, $F(1,38) = 1.23$, $p = .275$. A scatterplot indicated that the relationship between the covariate (pre-training 3-back scores) and the dependent variable (post-training 3-back scores) for the non-adaptive group was linear (Appendix VI, Figure VI.38, pg. 316); as did a scatterplot for the adaptive group (Appendix VI, Figure VI.39, pg. 317). The ANCOVA demonstrated no significant differences between the groups in post-training 3-back scores while controlling for baseline 3-back performance, $F(1, 37) = .84$, $p = .366$, power = .145.

Tests of assumptions for the ANCOVA examining post-training 4-back scores with pre-training 4-back scores as a covariate indicated no significant outliers for non-adaptive and adaptive training (Appendix VI, Figure VI.40, pg. 317). A Shapiro-Wilk test for the non-adaptive group showed that 4-back post-training scores are normally distributed, $W(20) = .962$, $p = .592$; as did a Shapiro-Wilk test for the adaptive group, $W(20) = .941$, $p = .247$. Levene's test found that the assumption of homogeneity of variances across groups was met, $F(1,38) = .153$, $p = .698$. A scatterplot indicated that the relationship between the covariate (pre-training 4-back scores) and the dependent variable (post-training 4-back scores) for the non-adaptive group was linear (Appendix VI, Figure VI.41, pg. 318); as did a scatterplot for the adaptive group (Appendix VI, Figure VI.42, pg. 319). The ANCOVA demonstrated no significant differences between the groups in post-training 4-back scores while controlling for baseline 4-back performance, $F(1, 37) = 1.32$, $p = .258$, power = .201.

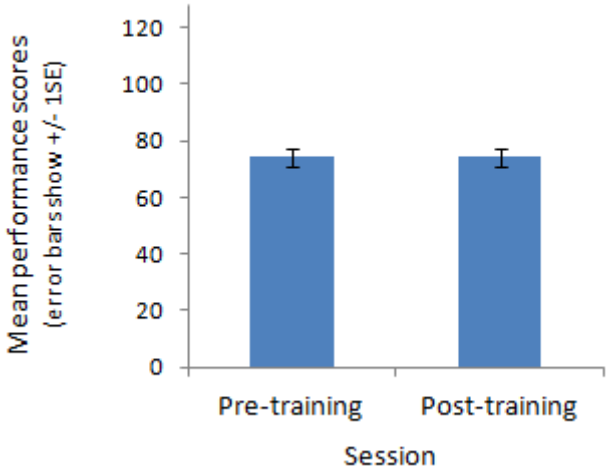
Given that the ANCOVAs for RAPM, PAL, PAR, 3-back, and 4-back were underpowered, and given that there were no significant group effects found, we decided to run paired samples t-tests comparing pre- and post-training for these tasks with both the non-adaptive and adaptive groups combined ($N = 40$). Moreover, we found a significant increase in performance from session 1 to session 12 in the CogniPlus tasks (except for the DIVID task) for the non-adaptive group, indicating that participants in this

group also benefitted from the cognitive training despite being the control group. As there is evidence to indicate that both groups received significant training, this was a further reason to combine the groups in addition to increasing the power of the t-tests.

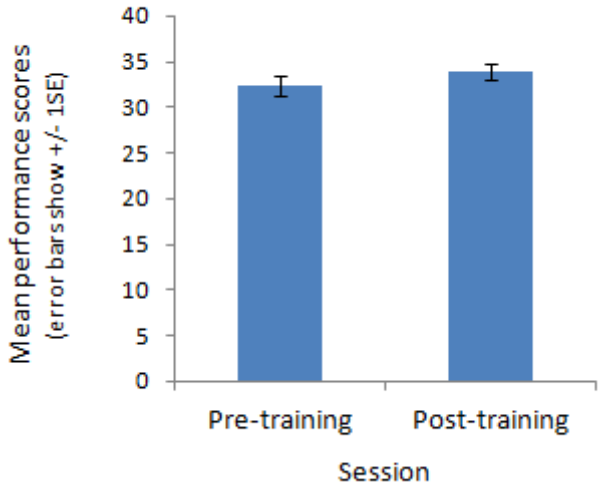
Figure 4.3 shows mean performance in the pre- and post-training sessions for each of the transfer tasks (*N* = 40). For the RAPM there was a small increase in performance from pre- to post-training (Pre-training: *M* = 8.20, *SD* = 3.08; Post-training: *M* = 8.55, *SD* = 3.07). For the PAL there was a small increase in performance from pre- to post-training (Pre-training: *M* = 74.13, *SD* = 18.40; Post-training: *M* = 74.30, *SD* = 19.71). For the PAR there was an increase in performance from pre- to post-training (Pre-training: *M* = 32.33, *SD* = 6.82; Post-training: *M* = 33.93, *SD* = 5.87). For the 3-back working memory load there was a small decrease in performance from pre- to post-training (Pre-training: *M* = 66.90, *SD* = 3.96; Post-training: *M* = 65.68, *SD* = 4.76). And finally, for the 4-back working memory load there was an increase in performance from pre- to post-training (Pre-training: *M* = 62.58, *SD* = 3.69; Post-training: *M* = 64.43, *SD* = 3.79).



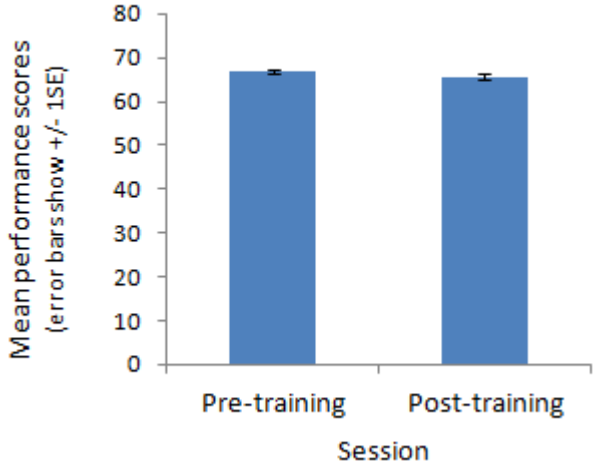
B. PAL



C. PAR



D. 3-BACK



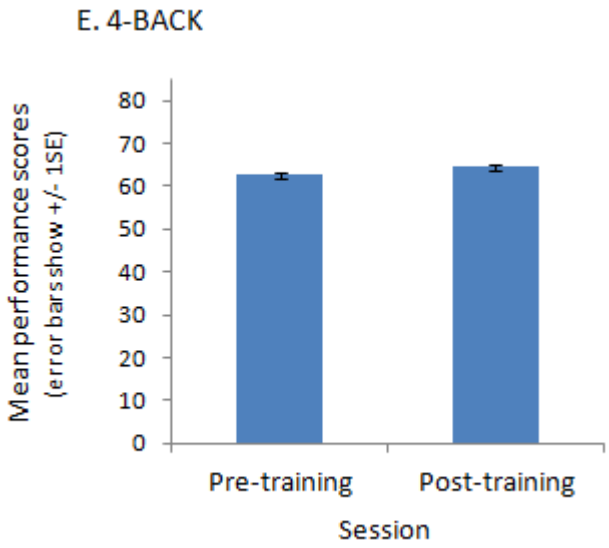


Figure 4.3. Mean performance for both the non-adaptive and adaptive groups combined (*N* = 40) in the pre- and post-training sessions for each of the transfer tasks: A) RAPM, B) PAL, C) PAR, D) 3-back, and E) 4-back. Error bars indicate the standard error of the mean.

Tests of assumptions for the paired samples t-test comparing pre- and post-training RAPM scores indicated no outliers in the difference values (Appendix VI, Figure VI.43, pg. 319). A Shapiro-Wilk test showed that the distribution of the differences is normal, $W(40) = .916$, $p = .060$. The paired samples t-test revealed no significant difference between the pre- and post-training RAPM scores, $t(39) = 1.06$, $p = .294$, power = .115.

Tests of assumptions for the paired samples t-test comparing pre- and post-training PAL scores indicated no significant outliers in the difference values (Appendix VI, Figure VI.44, pg. 320). A Shapiro-Wilk test showed that the distribution of the differences is normal, $W(40) = .949$, $p = .072$. The paired samples t-test revealed no significant difference between the pre- and post-training PAL scores, $t(39) = .068$, $p = .946$, power = .050.

Tests of assumptions for the paired samples t-test comparing pre- and post-training PAR scores indicated no significant outliers in the difference values (Appendix VI, Figure VI.45, pg. 321). A Shapiro-Wilk test showed that the distribution of the differences

is normal, $W(40) = .971$, $p = .374$. The paired samples t-test revealed no significant difference between the pre- and post-training PAR scores, $t(39) = 1.69$, $p = .099$, power = .338.

Tests of assumptions for the paired samples t-test comparing pre- and post-training 3-back scores indicated no significant outliers in the difference values (Appendix VI, Figure VI.46, pg. 322). A Shapiro-Wilk test showed that the distribution of the differences is normal, $W(40) = .967$, $p = .289$. The paired samples t-test revealed no significant difference between the pre- and post-training sessions for the 3-back condition, $t(39) = -1.49$, $p = .145$, power = .408.

Tests of assumptions for the paired t-test comparing pre- and post-training 4-back scores indicated no significant outliers in the difference values (Appendix VI, Figure VI.47, pg. 323). A Shapiro-Wilk test showed that the distribution of the differences is normal, $W(40) = .978$, $p = .633$. The paired samples t-test between pre- and post-training performance revealed that improvement in the 4-back task was significant and the effect size was moderate, $t(39) = 3.30$, $p = .002$, $d = .50$, power = .869.

We correlated performance on each of the CogniPlus training tasks (DIVID, CODING, DATEUP, HIBITR, ROTATE) with transfer task post-training scores (RAPM, PAL, PAR, 3-back, 4-back). As the non-adaptive data have little to no variability due to the training tasks being restricted to a lower level, these correlations only included data from the adaptive group ($N = 20$), which showed some variability in performance due to the training adjusting to an individual's ability. We used Kendall's tau-b for ranked data for these analyses as CogniPlus performance was measured as last level reached in session 12. Furthermore, tests of assumptions indicated that data for the CogniPlus tasks were not normally distributed, i.e., a Shapiro-Wilk test for the distribution of DIVID data is highly significant, $W(20) = .618$, $p < .001$; as is a Shapiro-Wilk test for CODING, $W(20) = .700$, $p < .001$; for DATEUP, $W(20) = .714$, $p < .001$; for HIBITR, $W(20) = .815$, $p = .001$; and for ROTATE, $W(20) = .652$, $p < .001$. In addition, the Kendall's tau-b does not require the assumption of no outliers to be met, nor the assumption of homoscedasticity. As such, this was deemed the most appropriate test to use for these data.

We predicted there would be a positive relationship between performance on the working memory training tasks (DATEUP and CODING) and post-training performance on the near transfer tasks (PAR and N-back). There was no significant correlation between DATEUP and post-training PAR, $\tau_b = .184$, $p = .313$; no significant correlation between DATEUP and post-training 3-back, $\tau_b = .199$, $p = .268$; and no significant correlation between DATEUP and post-training 4-back, $\tau_b = .313$, $p = .088$. CODING and post-training PAR did not show a significant association, $\tau_b = .213$, $p = .232$; CODING and post-training 3-back also did not show a significant association, $\tau_b = .316$, $p = .072$. However, CODING did show a positive relationship with post-training 4-back, $\tau_b = .386$, $p = .031$; and also with post-training RAPM, $\tau_b = .421$, $p = .018$. There were no significant associations between the remaining 3 cognitive training tasks (DIVID, HIBITR, ROTATE) and post-training performance on any of the transfer tasks (RAPM, PAL, PAR, 3-back, 4-back), $p > .05$ for all correlations.

4.4 Discussion

4.4.1 Summary of main findings

We tested the effectiveness of cognitive training in improving overall cognitive function in healthy middle-aged adults (40-50 years old). Participants completed 12 sessions of either adaptive or non-adaptive (active control) training. Exercises in the training programme targeted working memory, attention, and other executive functions such as inhibition. To test for transfer of training-related cognitive improvements, we used a fluid intelligence task (RAPM), an associative learning task (PAL), an associative memory task (PAR), and a working memory task (N-back). These tasks were completed before and after training.

We did not find any significant differences between adaptive and non-adaptive training on transfer task performance. However, the ANCOVAs comparing adaptive and non-adaptive training for RAPM, PAL, PAR, 3-back, and 4-back were underpowered. Furthermore, we found significant increases in performance on the training tasks not only for the adaptive group, but also for the non-adaptive group, indicating that control group participants also benefitted from the cognitive training. Therefore, we decided to

compare pre- and post-training scores on transfer tasks with both the non-adaptive and adaptive groups combined (*N* = 40). As expected, there were no significant differences comparing pre- and post-training scores for the far transfer tasks of RAPM and PAL. We also did not find differences between pre- and post-training scores for the near transfer task of PAR. As predicted, we found a significant difference between pre- and post-training scores for the near transfer task of N-back, specifically for the 4-back condition, indicating that the cognitive training was successful and resulted in transfer in middle-aged adults. As there were no significant relationships found between the demographics and post-training 4-back scores, it can be concluded that the training itself was effective in improving scores regardless of participant gender, age, and education. Moreover, there was a significant positive relationship between working memory training outcome and post-training 4-back scores, providing support for the conclusion that improvements in working memory in particular transferred to an untrained task requiring the same ability.

4.4.2 Adaptive vs. non-adaptive training

We found no significant differences between adaptive and non-adaptive training on any of the transfer tasks (RAPM, PAL, PAR, 3-back, and 4-back). This is contrary to multiple studies that have shown that adaptive training leads to larger and more consistent improvements in performance on untrained tasks, as compared to non-adaptive training (e.g., Holmes et al., 2009; Smith et al., 2009; Jaeggi et al., 2010; Brehmer et al., 2012; Rudebeck et al., 2012; Anguera et al., 2013; Heinzel et al., 2016; Flegal et al., 2019). Methodological variations may partly account for why our adaptive training protocol was not associated with transfer while others were (e.g., Rudebeck et al., 2012; Flegal et al., 2019). Continuously adaptive training task difficulty with no upper limit was a feature which both the Flegal et al. (2019) and Rudebeck et al. (2012) studies shared, and these studies showed transfer to episodic memory from adaptive working memory training. This is different from our training study where many participants achieved the highest available level of training task difficulty and remained at this ceiling level for the final sessions of training. Therefore, it is possible that our adaptive training programme potentially led to less than optimal performance demands, such that participants were not operating at a more plasticity-inducing difficulty level than the non-adaptive group. A

recent theoretical framework proposes that cognitive challenges must be sustained (e.g., continuously increasing environmental demands) rather than transient in order to increase functional supply (Lovden et al., 2010; Flegal et al., 2019), therefore, our adaptive training protocol in which the level of difficulty was capped may have been insufficient to induce plasticity that is associated with transfer.

On the other hand, it is likely that our active control was too stringent and non-adaptive participants benefitted significantly from training. This is supported by the finding that significant increases in performance for the training tasks were found not only for the adaptive group, but also for the non-adaptive group. While the evidence from previous studies is skewed in favour of adaptive over non-adaptive training, our findings suggest that adaptively increasing training task difficulty is neither necessary nor sufficient to promote transfer (Flegal et al., 2019). Indeed, there are some reviews that have concluded there is a lack of consistency in the evidence favouring training protocols with adaptive task difficulty (von Bastian & Oberauer, 2014; Pappa et al., 2020). As discussed by Morrison and Chein (2011), small effect sizes with regards to training may represent either little adaptive training-induced benefit, or unexpected cognitive enhancements related to the non-adaptive control training. With this in mind, future studies would benefit from developing training and active control programmes that differ more extensively on difficulty levels, and include control training with different tasks that are strategy-specific instead of process based. However, it is important to note that the cognitive demand of an active control treatment while being less challenging and fixed at a relatively low level of difficulty, cannot be deliberately set so low as to induce boredom and disengagement (which has been a complaint rightly levied against less-active non-adaptive control conditions in previous training studies; as discussed in Morrison & Chein, 2011; and Flegal et al., 2019). Therefore, finding the right balance of low difficulty while remaining engaging, is a very challenging task. A possible solution may be for active control training to be done with a different set of demanding tasks that do not engage the same processes as the experimental group, as well as the inclusion of a passive control group to assess test-retest effects and psychological factors.

4.4.3 Near transfer

As expected, adaptive participants showed substantial improvements over the course of training, as indicated by significant increases in performance for all training tasks. The non-adaptive group also showed significant increases in performance for all training tasks except for divided attention. Indeed, effect sizes were very large for both groups. While such gains in training task performance are notable, transfer effects are of greater interest. Indeed, if cognitive training effects are restricted to the trained tasks, such benefits would have little practical significance (Schmiedek et al., 2010).

Evidence indicated that both adaptive and non-adaptive groups received considerable training, therefore we combined the groups to test for transfer. As expected, there was near transfer of training gains to an untrained 4-back task. The improvement in the 4-back task was significant and the effect size was moderate. Furthermore, there were no significant relationships found between the demographics and post-training 4-back scores, strengthening the conclusion that this effect was due to the training and was not related to gender, age, and education. This finding is in line with several studies showing near transfer when training and untrained tasks share the same cognitive processes (e.g., Klingberg et al., 2005; Willis et al., 2006; Jaeggi et al., 2008; Mozolic et al., 2009; Schmiedek et al., 2010; Dunning et al., 2013; Karbach & Verhaeghen, 2014; Caeyenberghs et al., 2016; Emch et al., 2019). Moreover, our finding is consistent with meta-analyses of working memory training in reporting moderate-sized near transfer effects (Melby-Lervag et al., 2016; Soveri et al., 2017; Pappa et al., 2020).

The N-back task involved various working memory functions including the encoding of incoming stimuli, monitoring, maintenance, and updating of the sequence to store the last N elements, and stimulus matching (matching the current stimulus to the one presented N positions back in the sequence) (Jaeggi et al., 2010; Schmiedek et al., 2014; Pergher et al., 2018; Pappa et al., 2020). Similar working memory processes were specifically targeted by two of our cognitive training tasks: CODING and DATEUP. CODING trained visuospatial working memory. This task involved comparing a new arrangement of a set of vehicles with the previously stored layout of their original arrangement and identifying any differences. The DATEUP task in particular trained the updating function of

spatial working memory. Throughout the task, one butterfly lands and another starts its flight until eventually, at irregular intervals, the participant is asked to highlight the butterflies in a specific order, for example, the last three butterflies to land. Both of the training tasks involve the encoding of incoming stimuli, maintenance and storage, and in the case of the DATEUP task, updating the stimuli. Thus, although the stimuli were different for the N-back, CODING, and DATEUP tasks (letters, cars, and butterflies, respectively), and the task goals were different, all three tasks engaged overlapping processing components, and as such, training resulted in transfer. While changes in cognitive strategies and plasticity-based acquisition of knowledge are probably responsible for the lion's share of improvements in the trained tasks, the observed transfer effect is unlikely to be a mere result of such task-specific changes (Schmiedek et al., 2010). As discussed, the tasks were based on different content material and had different goals, thus, the near transfer observed in the middle-aged adults suggests that aspects of working memory processing efficiency have been improved (Lovden et al., 2010; Schmiedek et al., 2010).

The N-back task also involved a number of executive functions besides working memory, such as inhibitory control and cognitive flexibility, problem solving, decision making, and selective attention (Kane & Engle, 2002; Pergher et al., 2018). Therefore, near transfer to this task could also have been the result of these processes being targeted by our training programme rather than, or in addition to, the working memory component. For example, the DIVID task in our programme trained attention processes. Participants simultaneously observed a range of scenes on several control monitors, and their task was to deal with problems as they occurred in different monitors by pressing a response key as quickly as possible. The HIBIT-R task trained the executive ability to suppress unwanted reactions (response inhibition). Participants were asked to pay attention to specific cues that indicated when they needed to react and when they did not. Therefore, the variability in our training programme which included tasks that train working memory, attention, and inhibition, has made it difficult to say which aspect resulted in near transfer to the 4-back task. However, it is notable that performance on the CODING task in particular was significantly correlated with post-training 4-back scores, such that better working memory training outcome was associated with greater

post-training performance on the 4-back; while no significant relationships were found between the attention and inhibition training tasks and post-training 4-back scores. This suggests that it is likely the working memory training that contributed significantly to transfer in the 4-back task, although we cannot rule out that improved attention and inhibition might also have played a role. Moreover, no significant relationships were found between any of the other transfer and training tasks, indicating that training may have been less effective at resulting in transfer for these tasks. Indeed, no significant transfer effects were found to the near transfer task of PAR, nor to the far transfer tasks of RAPM and PAL. There is one exception to this, in that CODING performance did show a significant positive association with post-training RAPM. This is discussed further in the next section (4.4.4 Far transfer).

It is also interesting to note that performance gains on the N-back task were only observed for the 4-back working memory load, and no transfer was found for the 3-back condition. This is consistent with studies showing transfer effects only at higher working memory loads (Jaeggi et al., 2010; Heinzel et al, 2014; Beatty et al., 2015; Flegal et al., 2019). For example, in the study by Flegal and colleagues (2019), transfer effects were revealed by high difficulty N-Back trials and transfer was not found for their 3-back condition. This is consistent with the theory that raising the level of maximum function through sustained neurocognitive challenge and plasticity would enable previously unattainable high levels of task difficulty to be met (Lovden et al., 2010; Flegal et al., 2019). It is therefore possible that near transfer was not found for the 3-back working memory load in our study because this trial type was not sufficiently difficult for healthy middle-aged adults, and improvement was only captured by the 4-back condition because participants' level of maximum function had been increased through training. This interpretation is further supported by the relatively high scores achieved by participants on the pre-training 3-back condition (*M* = 84% correct, *SD* = 4.95), while there was more room for improvement on the pre-training 4-back level (*M* = 78% correct, *SD* = 4.62).

Near transfer was also not found for the PAR task. As with the 3-back task, pre-training scores for PAR were at near-ceiling levels (*M* = 81% correct, *SD* = 17.04), and as such, it may be difficult to reveal significant post-training improvements. On the other

hand, there was still some room for improvement, and it is possible that the PAR task was simply too different from the training tasks for transfer to occur. In particular, the specific features of the exercises used for training and the tasks used for assessing transfer must be taken into account. Previous research has shown that working memory transfer varies with training task features, whereby transfer is strongest when both trained and untrained tasks involve similar or overlapping properties and paradigms (Gathercole et al., 2019). Task features may include stimulus modality (auditory, visual), stimulus domain (verbal, visuo-spatial), stimulus category (words, letters, digits for verbal stimuli; objects and spatial locations for visuo-spatial stimuli), and paradigm (e.g., serial recall, complex span, backward span) (Gathercole et al., 2019). While the PAR task is similar to the training exercises of DATEUP and CODING in that they all involve working memory, they differ in a number of ways. For example, the paradigms themselves vary from a spatial updating exercise (DATEUP) and a spatial coding task (CODING), to a paired-associates retrieval paradigm (PAR). On each PAR trial, participants actively used the cue to retrieve an associated abstract picture from memory and maintained this associated image across a delay, following which, a decision was made as to whether the maintained picture matched the currently presented target image or not. Thus, although all three paradigms require working memory, what makes them vary could include the use of different strategies, the different degree to which familiarity information might be employed, the different degrees to which shifting the focus of attention is required, and the involvement of different retrieval processes from long-term memory (Oberauer, 2003; Oberauer, 2005; Unsworth & Engle, 2007; Shing et al., 2012; Schmiedek et al., 2014).

Furthermore, no task or paradigm, as valid as it might be, is process-pure; rather, in addition to the processes of interest, a host of task- and paradigm-specific processes contribute to performance (Schmiedek et al., 2014). Indeed, successful associative retrieval reaches beyond successful binding, drawing on multiple cognitive mechanisms that include bottom-up perception and top-down imagery, as well as attention, in addition to working memory (Curtis & D'Esposito, 2003; Ranganath, 2006; Ciaramelli et al., 2008; Albright, 2012; Pfeifer et al., 2014; 2016). As such, the PAR and training tasks may have differed on several features and processes, and it may not have been sufficient

for working memory gains to result in significant improvements on a paired-associates retrieval task.

It's important to note that contrary to our result, there are previous reports of transfer to associative memory from cognitive training (Schmiedek et al., 2010; Rudebeck et al., 2012; Toril et al., 2016; Flegal et al., 2019). However, the tasks used for training in these studies shared more features and processes with the transfer tasks than in our study. For example, Flegal and colleagues (2019) used a visuospatial working memory training programme and found transfer to an untrained Object-Location Association task. The Object-Location Association task was based on a paired-associates learning paradigm – the task consisted of blocks of trials arranged into an encoding phase followed by a retrieval phase. Stimuli were kaleidoscope images that were presented sequentially at random locations within a 4×4 matrix during the encoding phase, and participants were instructed to remember which object appeared in which cell for the subsequent retrieval phase. On each retrieval trial, one of the cells in which an object had appeared was highlighted, and the task was to select the object associated with that location from among three options displayed at the bottom of the screen. Therefore, the Object-Location Association task used to assess transfer in this study shared features with the visuospatial working memory training tasks such as the binding of items and spatial context, in addition to demands on executive function and working memory updating processes (Flegal et al., 2019). Whereas the working memory training tasks in our programme were visuospatial, yet our paired-associates retrieval task was not.

4.4.4 Far transfer

As predicted, we did not find any evidence of far transfer. Our results are in line with the consensus that there are data to support near transfer to other similar tasks, but mostly no indication of far transfer (e.g., Shipstead et al., 2012; Melby-Lervag & Hulme, 2013; Rapport et al., 2013; Sonuga-Barke et al., 2013; Karbach & Verhaeghen, 2014; Cortese et al., 2015; Redick et al., 2015; Schwaighofer et al., 2015; Melby-Lervag et al., 2016; Simons et al., 2016; Weicker et al., 2016; Soveri et al., 2017; Gathercole et al., 2019; Pappa et al., 2020). For the PAL task, there were no significant differences between the

pre- and post-training scores. This finding is not surprising given that process-based training would only be expected to transfer if the same processes were engaged by the transfer tasks. The PAL is a test of visual associative learning (Pfeifer et al, 2014; 2016). The task involved the participant learning to form new associations between pairs of different black-and-white fractal pictures, and learn the correct pairing of the pictures through trial and error**.** Thus, the PAL task shares few cognitive processes and perceptual features with the training tasks, i.e., associative learning abilities were not a target for training in our programme which focused on working memory, attention, and executive function processes such as inhibition. Consequently, it can be concluded that far transfer to visual associative learning abilities did not occur because the PAL was too dissimilar to the training tasks and did not share the same underlying processes. This is consistent with the notion that overlapping cognitive processes are necessary for transfer to occur as previously suggested (e.g., Dahlin et al., 2009; Holmes et al., 2009; Shipstead et al., 2012; Sprenger et al., 2013; von Bastian et al., 2013; Dunning & Holmes, 2014; Minear et al., 2016; Soveri et al., 2017; Pappa et al., 2020).

However, process-based accounts of transfer suggest that when broad cognitive abilities are trained, gains in general mechanisms and capacities should lead to improved performance across a wide range of tasks and everyday functions (Schmiedek et al., 2010). Indeed, if training successfully improves processing efficiency, then training gains should generalise beyond superficially similar tasks to untrained tasks that rely on the same processing elements, resulting in far transfer (Jonides, 2004; Dahlin et al., 2008; 2009; Flegal et al., 2019). Certainly, one would not expect far transfer to tasks that do not engage *any* of the same cognitive processes as the training tasks. One could make the case that training working memory, attention, and executive functions should have resulted in far transfer if process-based theories are to be convincing, as these processes underlie most tasks to some degree. In fact, we have shown that even when training and transfer tasks share some of the same processes, such as working memory for the PAR and training tasks, it may still not be enough for near transfer to occur, let alone far transfer. Why is it that shared underlying processes are not sufficient for transfer to occur? This was discussed with regards to task features and process overlap in the

previous section (4.4.3 Near transfer), and can be elaborated further using process-based theories of transfer.

Process-based explanations suggest that rather than expanding the fundamental capacity of a cognitive system in an undifferentiated manner, training enhances the specific processes within the system that are engaged by particular tasks (Dahlin et al., 2008; Holmes et al., 2009; Shipstead et al., 2012; Sprenger et al., 2013; Dunning & Holmes, 2014; von Bastian & Oberauer, 2014; Minear et al., 2016; Soveri et al., 2017; Gathercole et al., 2019). This accounts for the absence of transfer across working memory paradigms by assuming that training results in increases in the efficiency of individual processes within the working memory system, such as updating, inhibitory function, and short-term memory storage that are engaged by some, but not all working memory tasks (Dahlin et al., 2008; Minear et al., 2016; Gathercole et al., 2019). Thus, the magnitude of transfer is related to the extent of task overlap, with the highest levels of transfer for tasks with the greatest numbers of shared processes (Soveri et al., 2017; Gathercole et al., 2019). Our findings are consistent with this interpretation, in that we found near transfer to the N-back task which shared several working memory processes including the encoding of incoming stimuli, monitoring, maintenance, and updating, as well as a number of other executive functions such as inhibitory control, and selective attention with the training tasks, while transfer was not found for PAR which is an associative retrieval task that involved the binding of stimuli, bottom-up perception and top-down imagery, in addition to working memory, and thus shared fewer processes with the training tasks, and finally, no transfer was found for the PAL task which trained visual associative learning and shared still fewer processes with the training tasks. Therefore, it might be more useful to conceptualise breadth of transfer along a continuum (Barnett & Ceci, 2002; Flegal et al., 2019), as opposed to categorising it as either “near” or “far”, such that the fewer the shared features and processes, the further the transfer, and indeed, the less likely the transfer.

It is also important to point out that there are discrepancies in what authors identify as “near” and “far” transfer across studies (Pappa et al., 2020). For example, while we considered the PAR as a near transfer task given the substantial working

memory component that was shared with the training tasks, the study by Flegal et al. (2019) considered a similar task as far transfer owing to it being in the cognitive domain of associative memory, while their training tasks were in the cognitive domain of working memory. Certainly, the use of these terms is not consistent in the cognitive training literature, contributing to the difficulty of defining the concept of transfer adequately and ultimately reaching a consensus (Pappa et al., 2020). We acknowledge the complexity of this issue and suggest it may be best to drop these terms altogether, focusing instead on designing training programmes whereby tasks share several features and processes. Indeed, training various processes with a variety of tasks should lead to more transfer. This was evident in our N-back result where processes involved in this task were trained by two working memory tasks (CODING, DATEUP), and also by the attention (DIVID) and inhibition (HIBITR) tasks; whereas our training programme may not have been extensive enough to result in transfer to the PAR and PAL tasks as fewer processes were shared in those cases. Therefore, whether the transfer is "near" or "far" becomes irrelevant when designing programmes with a view to preventing cognitive decline. What is important is that many processes are trained with a wide variety of tasks so that it is more likely there is transfer to everyday functioning.

With regards to the RAPM, there were no significant differences between the pre- and post-training scores. Again, this was as predicted because this task shared few features and processes with the training tasks. Specifically, the RAPM is designed to test abstract reasoning and fluid intelligence, and therefore we did not expect transfer to this task as these abilities were not trained by our programme. Indeed, a measure of fluid intelligence such as the RAPM may be considered to represent transfer "farther" from the training tasks in the present study, than a measure of working memory such as the N-back task (Flegal et al., 2019).

However, the literature is inconsistent with respect to the RAPM in that some positive transfer effects have been found to this test from cognitive training (e.g., Basak et al., 2008; Karbach & Kray, 2009; Strenziok et al., 2014), and also from working memory training in particular (Klingberg et al., 2002, 2005; Jaeggi et al., 2008, 2010; Schmiedek et al., 2010). The differences in findings may reflect the methodological variation of the

studies. For example, in the studies by Klingberg and colleagues (2002; 2005), working memory training was undertaken by children with ADHD, making these results less generalisable – it is possible that there was more room for improvement of working memory processes in the children with ADHD than in healthy middle-aged adults, and this resulted in positive transfer to fluid abilities. The studies by Schmiedek et al. (2010) and Jaeggi et al. (2008, 2010) employed a no-training control group, the study by Basak et al. (2008) employed a no-training/no-contact control group, and the study by Karbach & Kray (2009) employed no control group – this raises the question to what degree non-specific factors such as practice effects, increased motivation, and increased effort contributed to their results, and indeed there's the possibility of placebo effects.

Interestingly, there was a significant positive relationship found between working memory training outcome (CODING task) and post-training RAPM. Notably, studies have established close links between working memory and fluid intelligence (Kyllonen & Christal, 1990; Engle et al., 1999; Wiley et al., 2011; Chooi, 2012; Emch et al., 2019; Gathercole et al., 2019). Indeed, fluid intelligence is thought to share anatomical substrates with working memory mechanisms (Barbey et al., 2014), and predominantly those that are engaged by executive control processes (Ramnani & Owen, 2004). However, this positive relationship did not translate to a transfer effect for the RAPM task in our study. Although working memory may play a role in fluid intelligence, there are several other processes required for successful RAPM performance, such as the application of rules to transform the spatial form of one stimulus for another (Cattell, 1963; Raven, 2003). As these processes didn't overlap with our training protocol, working memory gains may not have been sufficient to result in a significant improvement on the RAPM. Alternatively, it is possible that the RAPM task was simply too difficult for middle-aged adults. Indeed, participants were performing at below chance on both the pre-training (M = 8.20 out of a total of 18, SD = 3.08) and post-training (M = 8.55 out of a total of 18, SD = 3.07) sessions. This task was timed and participants only had 10 minutes to complete as many problems as possible, conceivably restricting the opportunity for middle-aged adults to display improvements in fluid intelligence. Indeed, in a study by Schmiedek et al. (2010), transfer to fluid intelligence was not reliable in older adults, such that improvements were not found on tests of transfer that were paced, however,

positive effects were found for tests of fluid intelligence that were carried out under less time pressure. Therefore, it is possible that middle-aged adults would also show transfer to the RAPM if given more time to perform this task.

4.4.5 Limitations

There were no significant differences between the training (adaptive) and active control (non-adaptive) groups on the transfer assessments, however, this study was underpowered due to the limited sample size obtained (*N* = 20 per group). Indeed, post-hoc power calculations demonstrated that achieved power for the RAPM, PAL, PAR, 3-back, and 4-back ANCOVAs was very low (range from .053 to .201). Subtle changes in the efficiency of cognitive processes may generate relatively small degrees of transfer that cannot be reliably detected in the low- to moderately-powered studies that dominate training research (Gathercole et al., 2019). As such, future research in this area should focus on investigating the effects of training on large-scale samples. It is possible that with increased sample sizes we might have observed a significant training advantage for adaptive relative to non-adaptive participants. However, the high p-values (range from *p* = .258 to .874) coupled with small effect sizes (range from η_p^2 = .001 to .034) suggest that adaptive and non-adaptive training were not different in our study, and as discussed, our active control group received a significant amount of training making it difficult to discern differences between our groups.

Our total sample size included 28 females and 12 males, and therefore, the gender imbalance has to some degree affected the generalisability of the data. However, independent samples t-tests indicated that there were no significant differences in performance between females and males on any of the pre-training transfer assessments, nor on the post-training transfer assessments (see Appendix VII for results of t-tests, pg. 324). Thus, it is reasonable to assume that the findings from this study would generalise across other populations of middle-aged adults, although further data with larger sample sizes are required to confirm this.

A potential explanation for the absence of significant transfer on the RAPM, PAL, PAR, and 3-back, and a possible limitation of our study, is the length of the training programme. A total of 12 sessions and training duration of 10 hours (50min per session) was used in our study. This total duration was chosen as previous work has demonstrated dose-dependent transfer effects such that the longer the training, the more likely there is transfer (Jaeggi et al., 2008; von Bastian & Oberauer, 2014; Salmi et al., 2018; Emch et al., 2019; Pappa et al., 2020). In addition, Cheng et al. (2012) have suggested that programmes exceeding 10 sessions produce more reliable and transferrable results, as demonstrated by the increased effect size between their 24-session study compared with the ACTIVE (Ball et al., 2002) 10-session study. However, the 12 sessions of training used in the current study is at the lower end of what may be required to produce transfer effects. Indeed, the 12 sessions equated to a total of 10 hours of training, and a recent systematic review and meta-analysis of working memory training studies concluded that programmes of more than 10 hours are more likely to result in transfer effects (Pappa et al., 2020). Furthermore, it should be noted that only 10 minutes per day was spent on attention training, 10 minutes on inhibition, 10 minutes on spatial rotation, and 20min on working memory. This equates to a total of just 2 hours of training on each cognitive domain, and 4 hours for working memory; far less than the more than 10 hours of training on one cognitive domain (i.e., working memory) that was shown to be more likely to produce transfer effects (Pappa et al., 2020). Interestingly, we found an association between the working memory training (CODING) and a working memory transfer task (4-back), and a significant transfer effect to this task; as there was more time spent on the working memory domain than the others (i.e., 4 hours), this suggests that more hours of training on the other domains might have resulted in more transfer effects. Therefore, a higher number of sessions and total hours of training may be required to show effects that translate to a behavioural change for these tasks.

It must be noted that transfer may only occur once a threshold for training performance level has been reached, in addition to a magnitude of improvement. For example, Dahlin et al. (2008) found that younger participants achieved a superior level of performance on the training tasks compared to older adults, despite both groups displaying improvement over the course of training. The authors suggested that the lack

of transfer observed for the older adults was due to this group failing to reach a certain level of task proficiency. While significant improvements were observed in our training exercises for both the adaptive and non-adaptive groups, perhaps the performance threshold required for significant transfer to untrained tasks was not reached during the programme, thus explaining why significant transfer was not observed for most of the post-training assessments in our study. Therefore, future studies should consider the inclusion of a learning or performance criterion that must be reached as part of the aim of the training exercises. However, while this may be important for the comparison of different age groups, this would not be possible when comparing adaptive training to an active control group, as the point is for the adaptive training to remain challenging and the active control not to receive substantial training. Certainly, this would have been useful in our analyses which combined adaptive and non-adaptive groups, as the non-adaptive group was kept to low task difficulty and could therefore not reach performance levels that may have been required for transfer, however, this was not possible in our study as this was not part of our original design (i.e., training group vs. active control).

Furthermore, participants were not required to reach a performance criterion in the PAL task, and this may be a reason that improvements were not observed for the PAR exercise. If participants did not learn the paired-associates well enough in the PAL, then performance on the subsequent PAR memory task would not be expected to show improvements. The studies by Pfeifer et al. (2014; 2016) employed a learning paradigm for the PAL task in which participants were trained to a performance criterion to guarantee sufficient exposure to the pair-associates and satisfy subject-specific learning requirements. This was done to account for an age-related encoding deficit found in older adults (see Naveh-Benjamin, 2000; and Shing et al., 2010 for reviews), and to assess associative retrieval after participants had reached the same performance level. In the present experiment, the ANCOVA examining post-training PAR scores included post-training PAL performance as a covariate to mitigate this issue. Moreover, the PAR scores in our study were quite high in both the pre- and post-training sessions (*M* = 81% correct; *M* = 85% correct, respectively), indicating that the pair-associates were successfully encoded during the PAL task and that middle-aged adults likely do not have the same encoding deficit found in older adults.

With regards to the PAR and N-back tasks, participants in our study could potentially have responded to the target items using familiarity information rather than, or in addition to associative and working memory processes, leading to better scores (Oberauer, 2005; Schmiedek et al., 2009; Schmiedek et al., 2014; Emch et al., 2019). For the PAR task, we addressed this issue by using recombinations of same-set stimuli which constitutes a more powerful test of associative memory, requiring participants to retrieve the intact combination of pair-associates out of equally familiar stimuli rather than rejecting lures on the basis of their novelty (Mayes et al., 2007; Pfeifer et al., 2014; 2016). In the N-back task, lure items are non-target items that match an item earlier in the sequence but not at the current critical target position (Oberauer, 2005; Schmiedek et al., 2009; Schmiedek et al., 2014; Emch et al., 2019). Therefore, we used lure stimuli in the N-back to make the task more difficult and not possible to solve based solely on familiarity, although this does not completely eliminate the contribution of familiarity items to working memory performance in this task.

We must consider the limitations of using multiple assessment tasks to investigate transfer. The use of multiple assessments in a single session makes the study more susceptible to confounds such as participant boredom and exhaustion (Morrison & Chein, 2011). This means that the quality of performance on the transfer tasks may be diminished over the course of each session, whereby performance on the N-back is less reliable due to participants completing this assessment last. Indeed, this may have been the case for the 3-back task in our study, as indicated by a decrease in performance scores from pre- to post-training, whereas performance improved on the RAPM, PAL, and PAR. However, this seems unlikely given that there was significantly improved performance on the 4-back task.

Along similar lines, there are a number of other confounding variables that may have influenced transfer to the post-training assessments, or lack thereof. An individual's level of effort and investment in the assessment tasks, as well as expectancy concerning the benefits from training, have previously been shown to influence transfer (e.g., Carretti et al., 2011; Boot et al., 2013; Jaeggi et al., 2014; Linares et al., 2019). For example, when investigating placebo effects within cognitive training, Boot et al. (2013) observed that

participants expecting to perform better on a given assessment (due to beliefs that the training programme had enhanced their performance) display increased effort and motivation to do well in that assessment. Moreover, Jaeggi et al. (2014) found that transfer was enhanced for participants that believed intelligence was malleable, and for those that reported stable engagement and motivation levels throughout the programme. Thus, with respect to the 4-back task in our study, post-training increases in performance may have occurred as a result of motivation, effort, and beliefs, rather than the training itself. The reverse of this may also be possible. Specifically, participants in our study may have expected the training programme to have no effect, or believed that their cognitive abilities had not improved, therefore they may have been less motivated and effortful when completing the post-training transfer tasks and their performance would have been negatively affected, as demonstrated by the lack of significant transfer on the RAPM, PAL, PAR, and 3-back tasks. However, the fact that there was significant transfer to the 4-back task suggests that participants were motivated to do well on the tests. Nonetheless, in order for these variables to be ruled out as confounds in future studies, experiments should include a self-report measure of expectancy, effort, and motivation, as well as a measure of implicit beliefs about the malleability of intelligence, to show explicitly that these factors do not correlate with transfer assessments. This may also be useful for studies employing passive control groups, where transfer effects could be ascribed to such factors as increased motivation, effort, and expectancy rather than to the training itself.

Indeed, by combining the adaptive and non-adaptive groups for paired samples t-tests comparing pre- and post-training sessions, we essentially had a within-subjects study design without a control group. Therefore, as suggested above, the significant transfer effect found for the 4-back task was susceptible to non-specific factors such as test-retest effects, expectancy effects, and increased motivation. That is, performance may have improved not because of the training, but due to these other factors. However, this finding is supported by the correlation showing that better performance on the post-training 4-back task was related to improvements in working memory. This suggests that the working memory training specifically in this case may have led to the significant improvement in the 4-back. Furthermore, the same non-specific factors would have been

present for the RAPM, PAL, PAR, and 3-back, yet no significant improvements were found in these tasks. This strengthens the interpretation of the 4-back transfer effect as being training-related, rather than due to potential effects generated by general improvements in motivation or due to expectancy.

In addition, the study was single-blind in that participants did not know whether they were in the training group or in the active control group. However, the study was not double-blind and the experimenter knew which group participants belonged to. Thus, there was the potential for the researcher to treat the study groups differently and introduce the risk of various types of biases, such as observer bias or confirmation bias, or increased attention paid to one of the groups, which may have influenced performance (Landsberger, 1958; Collie et al., 2003; McCarney et al., 2007; Green & Bavelier, 2012). To mitigate this issue, participants in both groups were given the same written instructions, and in fact, most of the task instructions were delivered on the computer, thus, contact with the researcher was kept to a minimum. Indeed, we did not see any significant differences between the groups on any of the post-training transfer tasks, indicating that any possible differences in treatment by the experimenter did not translate to a benefit for one group over the other. Certainly, an optimal study design for future research would be double-blind and include an active control wherever possible. However, employing an active control group bears the risk of missing or underestimating the effects of training (von Bastian & Oberauer, 2014; Pappa et al., 2020). For this reason, there should be a dynamic balance between employing an active control group and a control group that does not receive any contact (von Bastian & Oberauer, 2014; Pappa et al., 2020).

4.4.6 Conclusions

Our study provides novel evidence that a course of cognitive training in healthy middle-aged adults can result in considerable improvements on the trained tasks, and transfer to untrained tasks. This was demonstrated by the significant gains in training task performance coupled with very large effect sizes, and by the significant transfer effect in the 4-back task. Therefore, we conclude that there is substantial cognitive plasticity and

behavioural improvement following training not only at younger age, but also in middle-age.

Furthermore, we found that the more process overlap between tasks, the more likelihood of transfer. Therefore, tasks that shared more processes with the training programme, such as the N-back task, showed transfer effects, while tasks that shared fewer processes with the training programme, such as PAR, PAL, and RAPM did not show transfer effects. Thus, although the variability of our training protocol may make the results more difficult to interpret, such that it is unclear which specific aspects of the training were effective, this was a key feature of our programme in order to train more processes and induce transfer, as well as to keep it interesting and motivating for participants. To be able to better identify factors that influence the effectiveness of the programme, future studies could also include groups that receive more specific training (e.g., only working memory tasks) (Schmiedek et al., 2010). However, practically speaking, in order for training to have an impact on everyday functioning and to prevent cognitive decline, we conclude that a varied programme targeting multiple processes would be more beneficial.

Having established that cognitive training in middle-aged adults improved performance substantially on the trained tasks and resulted in transfer to an untrained task, we next analysed diffusion and fMRI data in order to determine the neural mechanisms of these behavioural findings. An explanation for transfer is that the effects observed following training reflect plasticity in the neural system underpinning the particular function that has been trained; training might therefore lead to durable neuronal changes and improved neural efficiency which should extend to other activities that engage the same processes (Westerberg & Klingberg, 2007; Klingberg, 2010; Takeuchi et al., 2010; Astle et al., 2015; Barnes et al., 2016; Caeyenberghs et al., 2016; Salmi et al., 2018; Gathercole et al., 2019). With this in mind, in the next chapter, we examined the structural and functional neural correlates of cognitive training in middle-aged adults.

Chapter 5: Working memory, attention, and executive function training in middle-aged adults: MRI findings

5.1 Introduction

5.1.1 Cognitive training and neural plasticity

Given that decline in cognitive function is paralleled by neurochemical, structural, and functional changes in the aging brain, the study of cognitive training as an intervention to induce neural plasticity and slow down decline, has gained considerable interest from the research community (Bopp & Verhaeghen, 2005; Yang et al., 2006; Kundu et al., 2013; Blacker et al., 2017; Pergher et al., 2018). Although the degree of plasticity varies across studies, the potential of the brain to reorganise itself in response to environmental demands is observed across the lifespan (Craik & Salthouse, 2002; Bialystok & Craik, 2006; Yang et al., 2006; Heinzel et al., 2014; Lawlor-Savage & Goghari, 2016; Loosli et al., 2016; Pergher et al., 2018). Cognitive training is thought to improve different functions such as attention, perception, and memory in young and older adults by tapping into this plasticity to increase the efficiency of the neural system (Mahncke et al., 2006; Yang et al., 2006; Dahlin et al., 2008; Schmiedek et al., 2010; Lawlor-Savage & Goghari, 2016; Loosli et al., 2016; Salminen et al., 2016; Heinzel et al., 2017; Pergher et al., 2018). Therefore, following training on a cognitive task, the neural system's response to the training, such as improved cognitive performance, as well as functional and structural changes in the brain, are considered indications of plasticity (Lovden et al., 2010; Pappa et al., 2020). For example, brain plasticity has been demonstrated in response to working memory training with changes in functional activity in frontal and parietal cortex (e.g., Olesen et al., 2004; Klingberg, 2010; Jolles et al., 2013; Kundu et al., 2013; Caeyenberghs et al., 2016). Structural changes have also been found in response to cognitive training such as modified cortical thickness, grey matter volume changes, changes in white matter tracts, and changes in structural connectivity (e.g., Engvig et al., 2010; Takeuchi et al., 2010; Takeuchi et al., 2011; Caeyenberghs et al., 2016). It should be noted that the above functional changes were demonstrated on the trained tasks.

What are the neural mechanisms that might underlie transfer from cognitive training? The few studies that have assessed the neural effects of transfer by scanning both trained as well as untrained tasks at pre- and post-training sessions, have revealed that training-induced plasticity generalises across tasks that engage overlapping brain

areas (Dahlin et al., 2008; Schneiders et al., 2012; Schweizer et al., 2013; Heinzel et al., 2016; Flegal et al., 2019). The underlying assumption here is that if two different tasks show robust recruitment of a particular brain region, it is likely that they both engage the cognitive process(es) subserved by that region (Lustig et al., 2009). Therefore, improving the function of that brain region (and presumably that process) by inducing neural plasticity through training on Task A, should have beneficial effects for its use in Task B (Lustig et al., 2009). If neural overlap indicates functional (process) overlap, there is the potential for transfer of training between different cognitive domains (Persson & Reuter-Lorenz, 2008; Lustig et al., 2009). The principle that neural overlap predicts functional overlap is a critical one that may be key to effective transfer and the development of successful interventions (Persson & Reuter Lorenz, 2008; Lustig et al., 2009).

5.1.2 Cognitive training and functional imaging

In studies investigating plasticity with neuroimaging outcome measures for the trained tasks, there is no consensus regarding the pattern of training-induced functional changes (Dahlin et al., 2009; Brehmer et al., 2011; Salmi et al., 2018; Emch et al., 2019; Pappa et al., 2020). For example, activation increases and decreases have been reported, as well as functional reorganisation, and more complex dynamics of brain activity changes are also found over the course of training (Klingberg, 2010; Morrison & Chein, 2011; Hsu et al., 2014; Flegal et al., 2019). Activation increases in training studies are explained as added recruitment of brain regions or as response strengthening within a cortical region, and are thought to reflect increases in capacity (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020). Activation decreases, on the other hand, are thought to reflect neural efficiency, i.e., fewer resources are needed to perform the same task after training than before training (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020). This interpretation is consistent with the concept of plasticity in which the neural system responds to environmental demands (e.g., a continuously challenging cognitive task) that exceed functional supply (i.e., neural resources), with plastic changes leading to increases in capacity or increased neural efficiency (Lovden et al., 2010; Pappa et al., 2020).

A mix of activity increases and decreases over time have been reported in studies that employed three scanning sessions, i.e., pre-training, early training, and post-training (Hempel et al., 2004; Kuhn et al., 2013; Pappa et al., 2020). Studies such as these provide valuable insight into the pattern of training-related activation increases and decreases elapsing over time (Pappa et al., 2020). For example, Hempel et al. (2004) and Kuhn et al. (2013) reported initial increases in activity between sessions 1 and 2, i.e., pre-training and early training fMRI sessions, respectively, followed by decreases between sessions 2 and 3, i.e., from early training to post-training (Pappa et al., 2020). 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 increase at the right intraparietal sulcus and superior parietal lobe two weeks into a four-week training programme, and a subsequent decrease in these areas post-training (Pappa et al., 2020). Thus, some of the variability in the direction of activation changes in the literature 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 (Pappa et al., 2020).

As discussed in Chapter 3 (Perceptual-cognitive-motor training in middle-aged adults, pg. 78), Doyon and Ungerleider (2002) proposed a framework for interpreting the dynamic pattern of brain activation underlying motor skill training – including a fast early learning stage, and a slow later stage. Different changes in activity are observed in the cortico-striatal and cortico-cerebellar systems as well as in prefrontal and parietal regions at different stages in the motor learning process. If this motor learning model is applied to 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 (Lustig et al., 2009; Pappa et al., 2020). However, cognitive intervention studies rarely have the multiple assessments of brain activity needed to fully test whether the stages suggested by Doyon and Ungerleider apply to non-motor functions (Lustig et al., 2009), although the cognitive training studies by Hempel et al. (2004) and Kuhn et al. (2013) do provide some support for the hypothesis of early stage activity increases and late stage decreases (Pappa et al., 2020).

The above activation patterns are discussed with respect to training tasks. Training-related activity changes in transfer tasks have not been examined as extensively as for trained tasks (Pappa et al., 2020). Overall, studies that did investigate functional outcomes on transfer tasks reported activation increases (Dahlin et al., 2008; Backman et al., 2011; Schweizer et al., 2013; Salminen et al., 2016; Clark et al., 2017). For example, Dahlin et al. (2008) found post-training increases in striatum and frontal, parietal and temporal cortex when assessing a near transfer task. Salminen et al. (2016) found increased activity in the striatum, cuneus and calcarine gyrus for a near transfer task. Clark and colleagues (2017) found increased activity post-training in frontal areas, as well as in the precentral and postcentral gyrus for a far transfer task. This is consistent with working memory training meta-analyses by Salmi et al. (2018) and Pappa et al. (2020) reporting mostly frontal and striatum increases in transfer tasks.

A few studies have reported transfer task activity decreases after training (Heinzel et al., 2016; Miro-Padilla et al., 2020). For example, Heinzel et al. (2016) reported activity decreases in middle and superior frontal areas for a near transfer task. Miro-Padilla et al. (2020) reported activity decreases in dorsolateral prefrontal cortex (dPFC) for a far transfer auditory serial addition task after working memory training. Even though the study by Miro-Padilla et al. (2020) exhibited decreases in a far transfer task following N-back training, there were no significant behavioural transfer effects, and thus it is difficult to assign a meaningful interpretation to these neural findings (Pappa et al., 2020).

Other studies observed no significant changes in activity post-training for far transfer tasks (Dahlin et al., 2008; Schneiders et al., 2011; 2012; Opitz et al., 2014; Flegal et al., 2019). For example, the study by Flegal et al. (2019) examined subcortical ROIs that revealed no differences in activity changes between the adaptive training group and a non-adaptive, active control group. Opitz et al. (2014) found no changes for the training or active control group. These findings are not surprising given the lack of behavioural far transfer effects observed in the cognitive training literature.

Returning to the fast-early and slow-late stage model first applied to motor skill training (Doyon & Ungerleider, 2002), Pappa and colleagues (2020) suggest this can be extended to account for the commonly observed activation increases for transfer tasks

following cognitive training. Similar to the dynamic activation increases and decreases over time for training tasks scanned early and then again later in training (Hempel et al., 2004; Kuhn et al., 2013), activation profiles for transfer tasks may also follow the same pattern, but at a different rate reflecting their less frequent exposure to participants (Pappa et al., 2020). In other words, a post-training functional activity decrease would eventually occur if participants were repeatedly exposed to the transfer task, consequently approaching the slow-late learning stage. Thus, there is a hypothesised time-lag in the activation curve as a function of time for transfer tasks, compared to training tasks (Pappa et al., 2020).

In sum, repeated exposure to, and practice with the training task, is associated with functional changes observed as early-stage activity increases, followed by late-stage activity decreases that may represent neural efficiency resulting from training-induced plasticity (Pappa et al., 2020). Although participants have had repeated exposure to the training task, at post-training the transfer task is still relatively novel and challenging, thus, performance is still effortful—similar to a training task at the early stage of learning—and the activation change from baseline is observed as an increase representing the added recruitment of brain regions (Pappa et al., 2020). Therefore, neural changes associated with training follow a fast-early activity increase and a late-slow decrease in task-related regions, while those associated with transfer of training appear to follow the same pattern albeit with a lag (Pappa et al., 2020).

5.1.3 Cognitive training and structural imaging

Few studies to date have focused on structural changes after cognitive training (Pappa et al., 2020). Of those that have, changes in brain structure as a result of training have involved grey matter volume or cortical thickness in task-relevant regions, as well as white matter volume and architecture (Takeuchi et al., 2011; Colom et al., 2016; Melby-Lervag et al., 2016; Metzler-Baddeley et al., 2016). For example, one study reported reduced grey matter in frontal and parietal cortices following working memory training (Takeuchi et al., 2011), while another found both increases and decreases in cortical thickness in frontal areas (Metzler-Baddeley et al., 2016), and the study by Colom et al. (2016) found an increase in grey matter volume in the right temporal lobe, left posterior

cingulate cortex, and right cerebellum. Other studies found no significant training-related changes in grey matter volume, surface, or thickness (Heinzel et al., 2014; Lawlor-Savage et al., 2019; Biel et al., 2020; Pappa et al., 2020). However, microstructural techniques such as diffusion-weighted MRI are more likely to detect small-scale changes as a result of cognitive training than alternative structural MRI techniques (Kodiweera et al., 2016). Indeed, microstructural imaging biomarkers, such as those derived from diffusion tensor imaging (DTI), are potentially more sensitive and altered earlier than the traditional technique of volumetric analyses (Kodiweera et al., 2016).

Evidence from DTI studies indicates that cognitive training can modify grey and white matter microstructure (Takeuchi et al., 2010; Zatorre et al., 2012; Lovden et al., 2013; Wolf et al., 2014). For example, increased fractional anisotropy (FA) in the intraparietal sulcus and anterior corpus callosum has been demonstrated in response to working memory training (Takeuchi et al., 2010). Structural connectivity increases in the fronto-parietal network have also been reported following training (Takeuchi et al., 2010; Caeyenberghs et al., 2016; Roman et al., 2017; Pappa et al., 2020). In a study by Nazeri et al. (2017), better performance in a working memory task (spatial span) was significantly associated with higher white matter FA in the corpus callosum. Higher FA is thought to reflect greater white matter integrity, which may underlie the strengthened neural connections observed in brain networks following cognitive training (Lovden et al., 2010; Engvig et al., 2012; Metzler-Baddeley et al., 2017). Although frequently concluded that greater myelination in response to increased neuronal firing underpins training-induced FA changes, FA can be modulated by a variety of biological factors, including myelination, packing density, and diameter of the axonal fibres (Zatorre et al., 2012; Jones et al., 2013; Caeyenberghs et al., 2016). Indeed, a change in DTI indices such as FA and mean diffusivity (MD) cannot be attributed to specific changes in brain tissue (Pierpaoli et al., 1996; Zhang et al., 2012; Jones et al., 2013; Jelescu et al., 2016; Kodiweera et al., 2016). Thus, it is difficult to say which of these biological mechanisms may underlie training-induced structural plasticity in the brain.

Neurite orientation dispersion and density imaging (NODDI) provides measures of neurite density (NDI) and dispersion (ODI), thereby disentangling two key contributing

factors to FA and enabling the analysis of each factor individually (Zhang et al., 2012). These more specific indices can be used to assess axonal and dendritic organisation (Jespersen et al., 2007; Zhang et al., 2012; Nazeri et al., 2015) following cognitive training.

Studies to date have not used NODDI to assess training-induced brain plasticity. However, NODDI has previously been used to show age-associated changes to white matter (Kodiweera et al., 2016) and cortical grey matter (Nazeri et al., 2015). For example, Nazeri et al. (2015) investigated changes in microstructure across the adult lifespan (age range: 21– 84) and found a significant age-related deficit in grey matter ODI (most prominently in frontoparietal regions), whereas increased ODI was observed in hippocampus and cerebellum with advancing age. Notably, they demonstrated a significant association between frontal pole ODI and working memory/processing speed, independent of age. In addition, hippocampal ODI was shown to be significantly related to working memory/processing speed, independent of age.

A further study by Nazeri and colleagues (2017) demonstrated that better performance on a spatial working memory task (spatial span) was significantly associated with higher grey matter NDI in dPFC; orbitofrontal, medial prefrontal, superior temporal, and cingulate cortices; and temporal pole, insula, hippocampus, and striatum. In a study of Alzheimer's disease, cortical NDI and ODI indices were found to be reduced compared to healthy controls, and importantly this was correlated with performance on the mini mental state examination (Parker et al., 2018). Therefore, NODDI may provide more specific information about the underlying brain changes that can occur following cognitive training, and these microstructural alterations may be shown to be related to improved cognitive function.

Furthermore, neural mechanisms such as these may play important roles as mediators of transfer effects (Schmiedek et al., 2010). For example, experience-dependent plasticity resulting from training may occur in dendrites and axons, and this may have pronounced effects on the synchronous operations of brain regions that higher order cognition is highly dependent on (Fields, 2008; Scholz et al., 2009; Schmiedek et al., 2010). Cognitive training may therefore lead to durable changes in neural infrastructure supporting transfer of training, including to everyday functioning (Strenziok et al., 2014).

5.1.4 Experiment aims and design

The aim of this study was to investigate how the brain responds to cognitive training in healthy middle-aged adults (40-50 years old). We sought to characterise functional and structural plasticity as a result of training with task-based fMRI, and diffusion MRI including DTI and NODDI.

Training-induced functional changes were assessed with near transfer tasks. Near transfer following cognitive training has been widely reported for both young and older adults (e.g., Klingberg et al., 2005; Willis et al., 2006; Jaeggi et al., 2008; Mozolic et al., 2009; Schmiedek et al., 2010; Karbach & Verhaeghen, 2014; Emch et al., 2019). On the other hand, the consensus is that there is very little evidence of far transfer (e.g., Shipstead et al., 2012; Sonuga-Barke et al., 2013; Redick et al., 2015; Melby-Lervag et al., 2016; Simons et al., 2016; Soveri et al., 2017; Gathercole et al., 2019; Pappa et al., 2020). Indeed, far transfer to untrained tasks that share few cognitive processes with the training tasks is much less likely than near transfer, whereby training and transfer tasks both place demands on the same underlying processes and brain regions (Dahlin et al., 2009; Shipstead et al., 2012; von Bastian et al., 2013; Strenziok et al., 2014; Soveri et al., 2017; Gathercole et al., 2019; Pappa et al., 2020). Therefore, we did not expect far transfer as a result of training, and as such, we assessed neural outcomes solely on the near transfer tasks (N-back, PAR).

The N-back task was selected to test for training-related improvements in working memory. Age-related decline in working memory is well documented (e.g., Baddeley, 1986; Just & Carpenter, 1992; Verhaeghen & Salthouse, 1997; Park & Reuter-Lorenz, 2009; Au et al., 2015; Soveri et al., 2017; Emch et al., 2019; Pliatsikas et al., 2019). This decline is paralleled by neural changes in the frontoparietal regions of the aging brain (Bopp & Verhaeghen, 2005; Rajah & D'Esposito, 2005; Pergher et al., 2018). Therefore, a goal of our training programme was to induce plasticity in brain regions that would improve working memory and result in transfer to the N-back task. This task was specifically developed for measuring working memory (Kirchner, 1958; Mackworth, 1959), and has been shown to consistently activate lateral and medial premotor cortex, dorsal cingulate, dorsolateral and ventrolateral PFC, frontal pole, and the lateral and

medial posterior parietal cortex (Gevins et al., 1990; Owen et al., 2005; Pergher et al., 2018). These locations are largely consistent with regions known to be involved in working memory (i.e., fronto-parieto-cerebellar circuitry and subcortical regions such as parts of the basal ganglia) (Wager & Smith, 2003; Owen et al., 2005; Rottschy et al., 2012; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019). In particular, key regions forming the neural basis of working memory comprise the ventrolateral PFC (vPFC) including the inferior frontal gyrus (IFG) pars triangularis, and IFG pars opercularis; dorsolateral PFC (dPFC); precentral gyrus; posterior parietal cortex including the superior and inferior parietal lobules; inferior temporal cortex including the inferior temporal gyrus, fusiform gyrus, and parahippocampus; subcortical regions such as the basal ganglia involving the striatum (caudate and putamen); and cerebellum (Curtis & D'Esposito, 2003; Wager & Smith, 2003; Ranganath et al., 2004; Ranganath, 2006; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019; Pappa et al., 2020). Thus, the working memory training in our programme (CODING and DATEUP tasks) was expected to engage these areas, thereby inducing functional plasticity that would translate to an improvement on an untrained working memory task (N-back).

The PAR task was selected to test for training-related improvements in associative memory. Older adults are particularly impaired in this cognitive domain with known age-related decline in visual association networks (Iidaka et al., 2001; Sperling et al., 2003; Cowan et al., 2006; Cohn et al., 2008; Shing et al., 2008; Naveh-Benjamin et al., 2009; Edmonds et al., 2012). Therefore, a goal of the present experiment was to engender improvements in this particular function via training-induced plasticity in associative memory regions. In addition to a working memory component, the PAR task involves retrieval and recognition memory processes. The working memory component is thought to engage the regions discussed above (i.e., fronto-parieto-cerebellar circuitry and subcortical regions such as the striatum) (Wager & Smith, 2003; Owen et al., 2005; Rottschy et al., 2012; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019). Visual associative retrieval involves the dPFC, vPFC, frontal pole, hippocampus, entorhinal and perirhinal cortices, thalamus, caudate, cerebellum, inferior parietal regions, and visual cortex (Ranganath et al., 2000; Naya et al., 2001; Cabeza et al., 2002; Ranganath et al., 2004; Byun & Lee, 2010; Jo & Lee, 2010; Pfeifer et al., 2016). Associative recognition

memory during the PAR task involves hippocampus, middle frontal gyrus, vPFC, anterior cingulate cortex, putamen, postcentral gyrus, and superior, middle, and inferior temporal cortex (Ranganath et al., 2000; Cabeza et al., 2002; Ranganath et al., 2004; Pfeifer et al., 2016). Therefore, there is substantial overlap between regions involved in the working memory, retrieval, and recognition components of the PAR task (i.e., dPFC, vPFC, frontal pole, caudate, putamen, cerebellum, inferior parietal regions, and inferior temporal cortex). As such, our training programme should induce functional plasticity in working memory regions that may contribute to improved performance on an untrained associative memory task (PAR).

To further investigate the neural mechanisms involved in transfer of training gains, we used the NODDI technique in addition to traditional DTI. Thus, we examined the underlying microstructural alterations that may occur following cognitive training, thought to indicate experience-dependent plasticity that may support transfer of training (Schmiedek et al., 2010; Strenziok et al., 2014).

5.1.5 Experiment hypotheses

We tested two hypotheses for this experiment. First, if cognitive training induces functional plasticity in middle-aged adults, then we should see post-training changes in brain activity during the transfer tasks. Adaptive cognitive training is thought to promote the lasting neural changes required for transfer through sustained cognitive challenges (e.g., Holmes et al., 2009; Smith et al., 2009; Lovden et al., 2010; Brehmer et al., 2012; Rudebeck et al., 2012; Anguera et al., 2013; Heinzel et al., 2016; Flegal et al., 2019). Furthermore, studies that examined training-related brain changes for transfer tasks reported activation increases (Dahlin et al., 2008; Backman et al., 2011; Schweizer et al., 2013; Salminen et al., 2016; Clark et al., 2017; Pappa et al., 2020). At post-training, the transfer task is still relatively novel and challenging, thus, performance is still effortful and at the early stage of learning – as such, the activation change from pre-training is observed as an increase (Pappa et al., 2020). We therefore predicted that adaptive training in middle-aged adults would lead to increased activity in working memory regions common to both the training and transfer tasks. Specifically, we expected training-related increases in activity in dPFC, vPFC, frontal pole, superior parietal cortex, inferior parietal

cortex, striatum, inferior temporal cortex, and cerebellum during performance of the N-back and PAR tasks.

Second, if cognitive training induces structural plasticity in middle-aged adults, then we should see changes in microstructural indices following training. Specifically, we expected that DTI and NODDI indices indicating microstructural changes in dendrites and axons would be demonstrated for the adaptive training group. DTI studies have shown that cognitive training can modify grey and white matter microstructure (Takeuchi et al., 2010; Zatorre et al., 2012; Lovden et al., 2013; Wolf et al., 2014). Decreased MD and increased FA are thought to reflect greater structural integrity, which may underlie the strengthened neural connections observed in brain networks following cognitive training (Lovden et al., 2010; Engvig et al., 2012; Metzler-Baddeley et al., 2017). We therefore predicted that the adaptive group would show changes in grey and white matter microstructure as a result of training, specifically, decreased MD and increased FA.

Although NODDI has not been used to assess training-induced structural plasticity, it has been used to show significant associations between NDI and cognitive performance; and between ODI and cognitive performance (Nazeri et al., 2015, 2017; Parker et al., 2018). Higher levels of NDI indicate a greater density of axons in white matter and dendrites in grey matter (Zhang et al., 2012). Therefore, we expected increased NDI in both grey and white matter as a result of training. Lower ODI in white matter tracts indicates less axonal dispersion and high axonal coherence (Zhang et al., 2012). Whereas higher ODI in grey matter indicates areas that are rich in multi-directional dendritic structure (Dowell et al., 2019). As such, we predicted decreased ODI in white matter and increased ODI in grey matter as a result of training. Such results would provide evidence for training-induced microstructural plasticity in addition to the predicted functional changes – both neural mechanisms may support improved cognitive function and successful transfer.

5.2 Summary of methods

5.2.1 Participants

The same participants as in Chapter 4 were tested for the MRI part of the experiment. Details can be found in section 2.2.1. In sum, a total of 40 middle-aged adults completed the study. Of these, 20 were part of the adaptive (experimental) training group, and 20 were part of the non-adaptive (control) training group. One person (non-adaptive group) was excluded from the PAR fMRI analyses due to major artefacts found on the scan, leaving 39 data sets for analysis (adaptive: *n* = 20; non-adaptive: *n* = 19). One person (adaptive group) was excluded from the N-back fMRI analyses due to data corruption during transfer from the scanner, leaving 39 data sets for analysis (adaptive: *n* = 19; non-adaptive: *n* = 20). A single non-adaptive participant's diffusion data were corrupted during transfer from the scanner and therefore excluded, leaving 39 data sets for analysis (adaptive: *n* = 20; non-adaptive: *n* = 19).

5.2.2 Procedure

The procedure was the same as in Chapter 4. Details are described in section 2.2.2 and will be summarised here. The study involved two scanning sessions for each participant: a pre-training session and a post-training session. In the pre-training MRI session, participants first learned a set of 8 paired associates (PAL) outside of the scanner and were then tested on them during a memory task in the scanner (PAR). Following which they completed the N-back task, also in the scanner. Participants then completed 12 sessions of either the adaptive or non-adaptive training over 4-6 weeks (2-3 sessions per week). For the post-training scan, participants again completed the PAR and N-back tasks to measure possible changes in brain function and cognitive ability.

Each session included PAR task fMRI (13min), followed by a structural T1 scan (6min), then N-back task fMRI (11min), then quantitative magnetisation transfer (qMT) and associated DESPOT1 and b1 maps for 20min (data not reported in this thesis), and finally a NODDI/DTI scan (9min). Total scanning time per session was about 1 hour.

5.2.3 fMRI analyses

PAR task

We examined activation differences following training in regions of interest (ROI). The subject-specific contrast images were entered into separate 2 group (adaptive, non-adaptive) × 2 session (pre-training, post-training) x 3 period (cue, delay, target) mixed ANOVAs for each ROI. All main and interaction effects derived from the ANOVAs are reported using a statistical significance of $p < .05$ after False Discovery Rate (FDR) correction for multiple comparisons at the cluster level, clusters formed using $p < .001$ (Genovese et al., 2002; Chumbley & Friston, 2009).

ROI analyses were carried out based on areas that were thought to overlap between our cognitive training programme and the PAR task. In particular, we expected brain regions involved in working memory to be recruited during our training programme and during the PAR task. We specified 8 anatomical ROIs bilaterally that included dorsolateral PFC, ventrolateral PFC, frontal pole, superior parietal cortex, inferior parietal cortex, inferior temporal cortex (including inferior temporal gyrus, fusiform gyrus, and parahippocampal gyrus), striatum (including caudate and putamen), and cerebellum.

N-back task

We investigated activation differences following training in regions of interest (ROI). The subject-specific contrasts were entered into separate 2 group (adaptive, non-adaptive) × 2 session (pre-training, post-training) x 4 condition (0-, 1-, 3-, and 4-back) mixed ANOVAs for each ROI. All second level analyses were thresholded at cluster-wise FDR-correction $p < .05$ (cluster-forming threshold $p < .001$).

The N-back task was specifically developed as a test of working memory (Kirchner, 1958; Mackworth, 1959). Therefore, ROI analyses were carried out using the same working memory regions as used for the PAR task. We specified 8 anatomical ROIs bilaterally: dorsolateral PFC, ventrolateral PFC, frontal pole, superior parietal cortex, inferior parietal cortex, inferior temporal cortex (including inferior temporal gyrus,

fusiform gyrus, and parahippocampal gyrus), striatum (including caudate and putamen), and cerebellum.

5.2.4 Diffusion MRI analyses

Whole-brain parameter maps from session one were subtracted from whole-brain parameter maps from session two in order to obtain ODI, NDI, FA, and MD change from baseline for each participant. These difference maps (session two – session one) were entered into whole-brain voxel-wise one- and two-sample t-tests to identify effects of overall training, as well as adaptive versus non-adaptive training, on regional differences in NDI, ODI, FA, and MD parameters. A statistical significance threshold of $p < .05$ FWE-corrected at the cluster level was used, after clusters were formed with an uncorrected $p < .001$.

5.3 Results

5.3.1 PAR task fMRI

ROI analyses

Separate 2 × 2 x 3 mixed ANOVAs were computed for each ROI with group (adaptive, non-adaptive) as the between-subject factor, and session (pre-training, post-training) and period (cue, delay, target) as within-subject factors. We found a significant interaction between session and task period with the inferior temporal cortex mask, which included a cluster in right fusiform gyrus and right parahippocampal gyrus (Table 5.1). We examined the interaction further using the contrasts pre-training_cue > post-training_cue, post-training_cue > pre-training_cue, pre-training_delay > post-training_delay, post-training_delay > pre-training_delay, pre-training_target > post-training_target, and post-training_target > pre-training_target. We found a significant effect for post-training_target > pre-training_target in right fusiform gyrus and right parahippocampal gyrus (Table 5.1). We did not observe a significant interaction between session and task period in any other ROIs. In addition, we did not find a main effect of group, nor a main effect of session, and no main effect of task period in any of the ROIs.

Interactions between group and session, group and period, and group x session x period, were also not significant in any of the ROIs.

Table 5.1. ROI analysis for the PAR task: brain regions with a significant interaction between session and task period shown for the inferior temporal cortex mask. Specifically, there was increased activity during the post-training target period.

Brain region	MNI coordinates			*F*-value	Cluster size (voxels)	*P*-value FDR-corrected
	x	y	z			
Interaction: session x task period						
Right fusiform gyrus	22	-44	-12	16.39	120	.039
Right parahippocampal gyrus	20	-34	-12	9.22		
Post-training_target > pre-training_target						
				t-value		
Right fusiform gyrus	22	-44	-12	6.11	264	.005
Right parahippocampal gyrus	20	-34	-12	5.19		

A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, after clusters were formed with an uncorrected $p < .001$. *P* values are reported at the cluster level. The MNI coordinates refer to the peak *F*- and *t*-values. Local maxima that are more than 8 mm apart are shown for each cluster.

5.3.2 N-back task fMRI

ROI analyses

Separate 2 × 2 x 4 mixed ANOVAs were computed for each ROI with group (adaptive, non-adaptive) as the between-subject factor, and session (pre-training, post-training) and condition (0-, 1-, 3-, and 4-back) as within-subject factors. We found a significant main effect of session in right cerebellum (Table 5.2). We found a significant main effect of N-back condition bilaterally in dPFC, vPFC, oPFC, precentral gyrus, insula, right superior medial gyrus, right mid cingulate cortex, right anterior cingulate cortex, bilaterally in superior parietal cortex, inferior parietal cortex, angular gyrus, precuneus,

postcentral gyrus, right supramarginal gyrus, left inferior occipital gyrus, bilaterally in inferior temporal gyrus, fusiform gyrus, left lingual gyrus, and bilaterally in putamen, caudate, and cerebellum (Table 5.2). There was also a significant interaction between session and N-back condition in left superior parietal cortex, left precuneus, right caudate, right putamen, and bilaterally in cerebellum (Table 5.2). We examined the differences in session and N-back working memory load more closely using the contrasts pre-training_1-back > post-training_1-back, post-training_1-back > pre-training_1-back, pre-training_3-back > post-training_3-back, post-training_3-back > pre-training_3-back, pre-training_4-back > post-training_4-back, and post-training_4-back > pre-training_4-back (N.B., 0-back baseline activity was subtracted from the 1-, 3-, and 4-back conditions). We found a significant effect for the contrast post-training_4-back > pre-training_4-back in right cerebellum (Table 5.2).

Table 5.2. ROI analysis for the N-back task: brain regions organised by significant main effect and mask used for the analysis. Includes contrast showing increased activity during the post-training 4-back condition in cerebellum.

Brain region	MNI coordinates			*F*-value	Cluster size (voxels)	*P*-value FDR-corrected
	x	y	z			
Main effect of session						
Cerebellum ROI mask						
Right cerebellum (IV-V)	12	-50	-22	25.85	117	.031
Main effect of N-back condition						
dPFC ROI mask						
Left IFG (p. Triangularis)	-50	24	26	19.04	247	< .001
Left precentral gyrus	-44	12	30	18.07		
Left IFG (p. Opercularis)	-56	18	32	13.90		
Left middle frontal gyrus	-40	14	34	10.37		
Right superior medial gyrus	4	38	38	17.79	111	.011

Right mid cingulate cortex	6	38	34	17.46		
Right anterior cingulate cortex	4	44	22	8.50		
Right IFG (p. Opercularis)	48	16	28	21.24	85	.049
Right precentral gyrus	52	12	36	11.28		
Right IFG (p. Opercularis)	44	16	34	21.18	77	.049
Right middle frontal gyrus	44	24	34	8.71		
Right IFG (p. Triangularis)	52	28	20	13.35	63	.049
Left IFG (p. Triangularis)	-46	28	24	15.05	61	.049
Left middle frontal gyrus	-38	36	16	6.49		
vPFC ROI mask						
Right insula lobe	30	22	-10	30.98	361	< .001
Right IFG (p. Triangularis)	42	22	4	19.47		
Right IFG (p. Orbitalis)	42	22	-12	13.31		
Right IFG (p. Opercularis)	50	16	10	10.07		
Left insula lobe	-32	20	-6	34.07	191	.001
Left IFG (p. Orbitalis)	-46	18	-6	9.65		
Left IFG (p. Triangularis)	-48	24	8	9.47		
Left IFG (p. Triangularis)	-54	26	24	18.84	150	.011
Left IFG (p. Opercularis)	-60	6	16	12.24		
Right IFG (p. Orbitalis)	36	30	-6	12.94	64	.049
Inferior parietal ROI mask						
Left inferior parietal cortex	-30	-58	46	23.58	1341	< .001
Left angular gyrus	-34	-66	42	19.50		
Left postcentral gyrus	-50	-30	50	15.23		
Right supramarginal gyrus	58	-46	24	23.52	691	< .001
Right angular gyrus	44	-50	22	10.89		
Right angular gyrus	38	-68	48	21.90	579	< .001
Right postcentral gyrus	38	-32	44	17.24	194	.001
Right inferior parietal cortex	44	-34	48	10.86		
Superior parietal ROI mask						

Left inferior parietal cortex	-28	-68	44	32.12	820	< .001
Left superior parietal cortex	-30	-70	50	30.61		
Left precuneus	-6	-72	56	12.21		
Right angular gyrus	34	-70	44	25.10	605	< .001
Right superior parietal cortex	18	-58	60	14.37		
Right postcentral gyrus	22	-44	64	8.23		
Right precuneus	8	-72	56	7.03		
Inferior temporal ROI mask						
Left inferior temporal gyrus	-50	-56	-16	26.10	181	.001
Left inferior occipital gyrus	-50	-62	-16	24.65		
Left fusiform gyrus	-28	-60	-8	14.21	174	.001
Left lingual gyrus	-18	-46	-6	7.41		
Right inferior temporal gyrus	50	-56	-16	21.05	173	.001
Right fusiform gyrus	32	-48	-10	20.73	164	.011
Left inferior temporal gyrus	-46	-60	-6	19.90	89	.015
Left inferior occipital gyrus	-42	-68	-4	16.87		
Striatum ROI mask						
Right putamen	20	12	-10	33.34	425	< .001
Right caudate nucleus	16	12	-12	30.66		
Left putamen	-22	12	-6	28.41	372	< .001
Left caudate nucleus	-10	14	-6	18.66		
Cerebellum ROI mask						
Left cerebellum (Crus 1)	-28	-80	-22	38.70	8043	< .001
Cerebellar vermis (6)	6	-80	-16	33.64		
Left cerebellum (VI)	-4	-80	-16	30.54		
Left cerebellum (Crus 2)	-12	-80	-36	27.20		
Right cerebellum (Crus 2)	8	-78	-40	26.89		
Right cerebellum (VI)	30	-46	-26	26.15		
Interaction: session x N-back condition						
Superior parietal ROI mask						

Left superior parietal cortex	-22	-64	54	9.83	99	.017
Left precuneus	-8	-68	54	7.23		
Striatum ROI mask						
Right caudate nucleus	16	14	8	12.01	136	.003
Right putamen	22	18	0	8.60		
Cerebellum ROI mask						
Right cerebellum (VIII)	30	-66	-46	10.39	633	< .001
Right cerebellum (Crus 2)	58	-54	-42	10.29		
Right cerebellum (Crus 1)	38	-60	-38	10.02		
Right cerebellum (VI)	24	-60	-34	7.36		
Right cerebellum (VII)	44	-62	-54	7.29		
Left cerebellum (Crus 1)	-40	-48	-32	8.14	212	< .001
Post-training_4-back > pre-training_4-back						
Cerebellum ROI mask						
				t-value		
Right cerebellum (VII)	8	-78	-42	4.49	175	.006
Right cerebellum (VI)	30	-54	-36	4.25		
Right cerebellum (Crus 1)	34	-60	-32	3.98		
Right cerebellum (VIII)	14	-72	-40	3.67		

A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, after clusters were formed with an uncorrected $p < .001$. *P* values are reported at the cluster level. The MNI coordinates refer to the peak *F*- and *t*-values. Local maxima that are more than 8 mm apart are shown for each cluster. IFG = inferior frontal gyrus.

5.3.3 Diffusion MRI

Whole-brain analyses

To investigate whether there were any significant microstructural changes as a result of cognitive training, whole-brain one-sample *t*-tests were performed with the diffusion difference maps (combining the adaptive and non-adaptive groups, $N = 39$) for each of the NODDI and DTI indices (ODI, NDI, FA, and MD). We found a significant increase in ODI in grey and white matter of the left frontal pole post-training (Figure 5.1).

To investigate whether the type of training programme had an effect on microstructural change, whole-brain two-sample *t*-tests were performed comparing adaptive and non-adaptive difference maps for each of the four diffusion indices. No significant differences were found in ODI, NDI, FA, and MD difference maps between adaptive and non-adaptive groups.

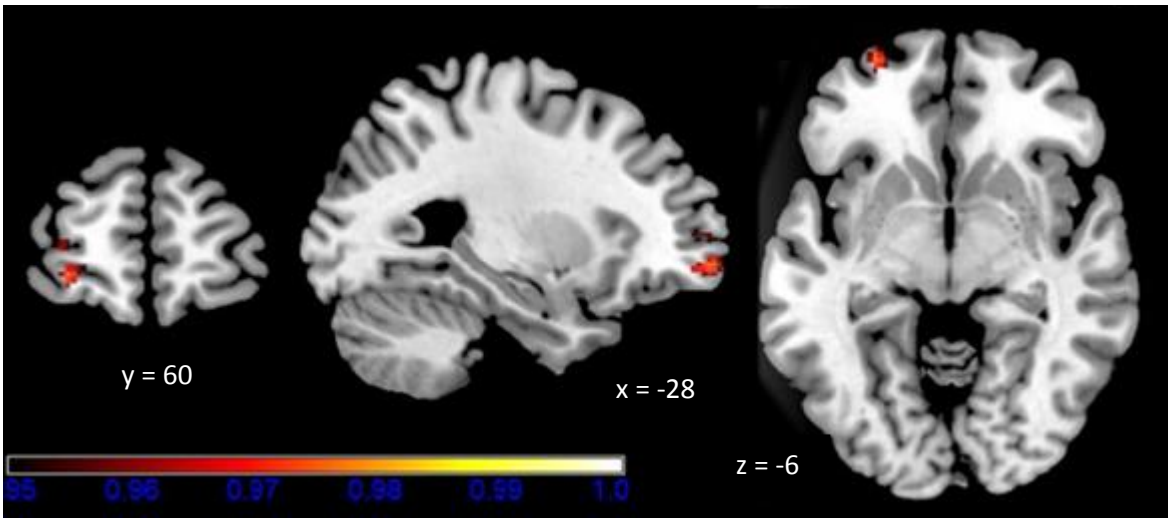


Figure 5.1. Whole-brain diffusion MRI analysis: significant increase in ODI in left frontal pole post-training. Results are shown using a statistical significance of $p < .05$ after FWE-correction at the cluster level, clusters formed using an uncorrected $p < .001$, $N = 39$.

5.4 Discussion

5.4.1 Summary of main findings

We assessed the neural effects of cognitive training in healthy middle-aged adults by scanning transfer tasks (PAR, N-back) at pre- and post-training sessions. In addition to task-based fMRI, we used DTI and NODDI to investigate structural plasticity as a result of training. Participants completed 12 sessions of the training programme which targeted working memory, attention, and other executive functions such as inhibition. We compared an adaptive training group to a non-adaptive, active control group.

We did not find any significant differences between adaptive and non-adaptive training on functional and structural imaging outcomes. We did, however, find significant differences between the pre- and post-training sessions for the combined groups (*N* = 39 for fMRI, *N* = 39 for DTI and NODDI). For the PAR task, we found a significant interaction between session and task period in right fusiform gyrus and right parahippocampal gyrus. Specifically, we found increased activity in these regions post-training for the target period, indicating training-induced plasticity in these regions for associative recognition memory. For the N-back task, we found a significant main effect of session in right cerebellum. We found a significant main effect of condition (0-, 1-, 3-, and 4-back) bilaterally in dPFC, vPFC, oPFC, precentral gyrus, insula, right superior medial gyrus, right mid cingulate cortex, right anterior cingulate cortex, bilaterally in superior parietal cortex, inferior parietal cortex, angular gyrus, precuneus, postcentral gyrus, right supramarginal gyrus, left inferior occipital gyrus, bilaterally in inferior temporal gyrus, fusiform gyrus, left lingual gyrus, and bilaterally in putamen, caudate, and cerebellum. There was also a significant interaction between session and condition in left superior parietal cortex, left precuneus, right caudate, right putamen, and bilaterally in cerebellum. Notably, we found increased activity post-training for the 4-back condition in right cerebellum, demonstrating training-induced plasticity in this region for a working memory task. We did not find any differences between pre- and post-training sessions for the DTI indices of FA and MD, nor for the NODDI index of NDI. We found a significant increase in ODI in grey and white matter of the left frontal pole post-training, providing evidence for training-induced microstructural change.

5.4.2 Adaptive vs. non-adaptive training

We found no significant differences between adaptive and non-adaptive training on any of the neuroimaging outcomes. This is contrary to studies that have shown that adaptive training provides sustained cognitive challenges resulting in neural changes that underlie transfer (e.g., Lovden et al., 2010; Brehmer et al., 2012; Rudebeck et al., 2012; Anguera et al., 2013; Heinzel et al., 2016; Flegal et al., 2019). As discussed previously, we found that participants in the non-adaptive group benefitted significantly from training as demonstrated by substantial improvement in performance for the training tasks. Our

non-adaptive training programme, although less challenging, is still repeatedly recruiting (to a lesser extent) the brain networks involved in working memory, attention, and executive function. Therefore, even the non-adaptive training programme has the potential to initiate neural plasticity in these networks and brain areas (Baltes & Lindenberger, 1988). As such, there were significant increases in training task performance for both adaptive and non-adaptive training groups, and no significant differences between them on functional and structural outcomes. Future studies might benefit from active control training that is done with a different set of tasks that do not engage the same brain areas as the experimental group. Comparing these groups at post-training should yield differences between them if the training programmes have induced neural plasticity in their respective brain regions.

5.4.3 PAR fMRI findings

For the PAR task, we found a significant interaction between session and task period in right fusiform gyrus and right parahippocampal gyrus. Specifically, we found increased activity in these regions post-training during associative recognition. This is in line with studies demonstrating increased activity on transfer tasks following cognitive training (Dahlin et al., 2008; Backman et al., 2011; Schweizer et al., 2013; Salminen et al., 2016; Clark et al., 2017). This is also consistent with working memory training meta-analyses by Salmi et al. (2018) and Pappa et al. (2020) reporting mostly activity increases in transfer tasks. The increased activity observed on the PAR task is in accord with the fast-early and slow-late stage model first applied to motor skill training (Doyon & Ungerleider, 2002), i.e., the post-training transfer task represents the fast-early learning stage of the model. For example, at post-training the PAR transfer task is still relatively novel and challenging, thus, similar to a training task at the early stage of learning, the activation change from pre-training is observed as an increase (Pappa et al., 2020). Activation increases following training have been explained as added recruitment of brain regions or as response strengthening within a cortical region, leading to increased capacity in the processes performed by these areas (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020). Therefore, in the present

experiment, it is possible that the increased activity post-training reflects an increased capacity in the processes performed by the fusiform and parahippocampal gyrus.

Studies in nonhuman primates demonstrate that visual associative memory requires sustained activity within inferior temporal areas (Miyashita, 1988; Miyashita & Chang, 1988; Sakai & Miyashita, 1991; Yakovlev et al., 1998; Naya et al., 2003). In humans, fMRI studies have reliably identified inferior temporal subregions that selectively respond to categories of objects (Aguirre et al., 1998; Haxby et al., 2001; Malach et al., 2002; Spiridon & Kanwisher, 2002; Ranganath et al., 2004). Activity in the fusiform and parahippocampal gyrus in particular is thought to indicate the activation of object representations during both the working memory and recognition phase of the PAR task (Ranganath et al., 2004; Pfeifer et al., 2016; 2019). Therefore, in the current experiment, activity in these regions reflects the object that is currently active in memory, in this case, the abstract fractal images encoded during the learning phase (PAL task – outside of scanner). In other words, the PAR task requires retrieval of the relationship between the cue object and its paired associate; the neural representation of the paired associate is activated in fusiform and parahippocampal gyrus in anticipation of the upcoming memory decision during the target period (associative recognition memory) (Rainer et al., 1999; Ranganath et al., 2004; Pfeifer et al., 2016; 2019). The increased activity in these regions in the post-training compared to the pre-training session may be the result of these areas being repeatedly recruited during our training programme, especially during working memory to reactivate object representations necessary for the current task goal. For example, representations of cars would need to be reactivated in working memory for successful completion of the CODING training task, while representations of butterflies would need to be reactivated in working memory for the DATEUP training task. Thus, repeated recruitment of the fusiform and parahippocampal gyrus during training may have resulted in increased capacity for object representations – an important function for the PAR task.

It should be noted that these training-related functional changes in fusiform and parahippocampal gyrus did not translate to improved performance on the PAR task. We predicted that training would lead to increased activity in working memory regions

common to both the training and transfer tasks, resulting in improvements on the untrained PAR task. However, successful associative retrieval draws on multiple cognitive mechanisms that include the binding of stimuli, bottom-up perception and top-down imagery, as well as attention, in addition to working memory (Curtis & D'Esposito, 2003; Ranganath, 2006; Ciaramelli et al., 2008; Albright, 2012; Pfeifer et al., 2016; 2019). As such, the PAR and training tasks may have differed on several processes and associated brain regions. Consequently, it may not have been sufficient for changes in fusiform and parahippocampal gyrus to result in significant improvements on the PAR task.

5.4.4 N-back fMRI findings

For the N-back task, we found a significant main effect of condition in several regions including the PFC, parietal cortex, inferior temporal cortex, striatum, and cerebellum, indicating that different areas were recruited dependent on task difficulty (i.e., working memory load). There was also a significant interaction between session and condition in parietal cortex, striatum, and cerebellum. Importantly, significant differences between the pre- and post-training sessions were found for the cerebellum, indicating a training effect in this region. Specifically, we found increased activity post-training for the 4-back task in right cerebellum. This is consistent with studies and meta-analyses demonstrating mostly increased activity on transfer tasks following cognitive training (Dahlin et al., 2008; Backman et al., 2011; Schweizer et al., 2013; Salminen et al., 2016; Clark et al., 2017; Salmi et al., 2018; Pappa et al., 2020).

The cerebellum is one of the key regions forming the neural basis of working memory (Wager & Smith, 2003; Owen et al., 2005; Rottschy et al., 2012; Nee et al., 2013; Salmi et al., 2018; Emch et al., 2019). During verbal working memory in particular, it has been suggested that cerebellar activity supports inner speech mechanisms to facilitate rehearsal of the to be maintained information (Desmond et al., 1997; Chein & Fiez, 2001; Chen & Desmond, 2005; Chang et al., 2007; Durisko & Fiez, 2010; Marvel & Desmond, 2012; Koziol et al., 2014). Neuroimaging studies have shown that during the encoding phase, when verbalisable content, such as letters, is visually presented to participants, cerebellar activity increases (Chein & Fiez, 2001; Chen & Desmond, 2005; Koziol et al.,

2014). Thus, the cerebellum may be involved in creating an internal code for motor sequences related to the vocalisation of information (Ravizza et al., 2006; Ackermann et al., 2007; Marvel & Desmond, 2010; Marvel & Desmond, 2012; Koziol et al., 2014). Furthermore, cerebellar activity can be modulated by increasing working memory demands. For example, following encoding, if information needs to be manipulated in some way (e.g., as required during the N-back task when continually updating the sequence of letters, and during the DATEUP training task when continually updating the location of the butterflies), cerebellar activity remains elevated relative to activity during straightforward (non-manipulated) rehearsal of information (Marvel & Desmond, 2012; Koziol et al., 2014). This pattern indicates that as long as the cerebellum is encoding new information, new motor traces continue to be created, and activity levels remain high (Marvel & Desmond, 2012; Koziol et al., 2014). Therefore, it seems that the more effortful a verbal working memory task is, the more one engages an inner speech neural mechanism (Marvel & Desmond, 2012; Koziol et al., 2014). In sum, the specific contribution of the cerebellum may be to temporally sequence inner speech information by creating internal motor traces that help maintain that information (Desmond et al., 1997; Chein & Fiez, 2001; Chen & Desmond, 2005; Chang et al., 2007; Durisko & Fiez, 2010; Marvel & Desmond, 2012; Koziol et al., 2014).

In the current study, it is likely that this process (i.e., rehearsing information verbally – inner speech neural mechanism) was practiced and used repeatedly during training as a strategy for keeping information in working memory, and thus, repeatedly engaged the cerebellum. Although this is speculative for our experiment, future studies could test this idea by scanning the training tasks to see if they did indeed engage the cerebellum, and also by administering a questionnaire to ascertain which strategies were used to help complete the tasks. Nonetheless, the possibly increased engagement of the cerebellum during training may have led to an increase in capacity for this process, as demonstrated by increased activity in this region post-training on the 4-back task, and notably, significantly improved performance for this untrained transfer task. In addition, increased working memory demand, as in the 4-back task (relative to the 1- and 3-back), would have benefitted most from increased cerebellar activity and capacity, and this was

certainly the case, which was demonstrated by the result only being found for the 4-back and not at any other level.

5.4.5 Diffusion MRI findings

We did not find any significant differences between pre- and post-training sessions for the diffusion MRI indices of FA, MD, and NDI. We did, however, find significantly increased ODI in the grey and white matter of the left frontal pole following training, indicating training-induced microstructural change in this region. According to Zhang et al. (2012), in white matter areas, an increase in ODI indicates a reduction in fibre coherence. In areas of crossing fibres or grey matter, however, an increase in ODI could indicate a change in axonal and dendritic morphology (Zhang et al., 2012). Critically, both a reduction in fibre coherence and a change in dendritic morphology may be the result of new neurite growth (Zhang et al., 2012). For example, both branching dendrites and axons may increase the orientation distribution of intracellular diffusion (Zhang et al., 2012). Therefore, in the present experiment, the increase in grey and white matter ODI may indicate new neurite growth in the left frontal pole as a result of the cognitive training programme.

The frontal pole, or Brodmann's area 10, is a hyperconnected anterior region of the prefrontal cortex that plays a critical role in higher order cognition such as executive control and decision-making (Pandya & Yeterian, 1996; Burgess et al., 2007; Orr et al., 2015). Anatomically, the frontal pole is connected to regions of cognitive processing, social emotion, and default mode networks (Liu et al., 2013; Orr et al., 2015). Specifically, the dorsal regions are connected to other prefrontal regions that process goals and action plans, medial regions are connected to other areas that monitor action outcomes and motivate behaviours, and ventral regions connect to brain regions that process information about stimuli, values, and emotion (Orr et al., 2015). Because of this broad array of structural connections, the frontal pole is well equipped to guide attention and behaviour in relation to current goals, motivations, and values, while storing and updating current task information (Orr et al., 2015). This function of selecting and guiding actions in line with goals and motivations, and more explicitly storing alternative task information

ready for retrieval and execution upon completion of the current task, is known as cognitive branching (Koechlin et al., 2000; Koechlin & Hyafil, 2007; Koechlin, 2011). Cognitive branching contains a large working memory component and is hypothesised to be the core function of the frontal pole region (Koechlin et al., 2000; Koechlin & Hyafil, 2007; Koechlin, 2011). Indeed, recent functional characterisations of the frontal pole emphasize its role in using higher-order task representations to direct the selection and maintenance of relevant information in working memory (Braver et al., 2003; Bunge et al., 2003; Sakai & Passingham, 2003; Ramnani & Owen, 2004; Ranganath et al., 2004; Koechlin & Hyafil, 2007; Koechlin, 2011). Importantly, this means that the frontal pole is heavily involved in working memory processes, which were trained in our study's programme. It is possible that repetitively exercising working memory processes resulted in repeated and sustained stimulation of the frontal pole, and therefore neural plasticity in this region.

Furthermore, Nazeri et al. (2015) demonstrated a significant association between frontal pole ODI and performance on tests of working memory/processing speed. Specifically, higher levels of frontal pole ODI were related to better performance on tests of cognitive function (Stroop Test, Trail-Making Test B, Letter-Number Sequencing Test). As such, frontal pole neurite growth as a result of training may have benefitted working memory abilities, and would therefore be reflected by higher scores in the PAR and N-back tasks post-training. This was certainly the case for the 4-back task in which performance significantly improved post-training. However, we did not see a behavioural effect for the PAR task. The functional and structural changes might simply not have been sufficient to result in a measurable behavioural change for this task.

All results reported in this chapter were corrected for multiple comparisons. It is possible that using an exploratory uncorrected threshold would have yielded more positive findings. However, while it was deemed appropriate to use an exploratory uncorrected threshold for the results from the sensorimotor training, reported in Chapter 3 (Perceptual-cognitive-motor training in middle-aged adults, pg. 89), this was not deemed appropriate for this cognitive training study. This was because training was for a relatively short period of 31 minutes in the first experiment, which may have resulted in

small-scale changes that would be difficult to detect with a strict correction for multiple comparisons (Jueptner et al., 1997; Doyon et al., 2002; Orban et al., 2010; Steele & Penhune, 2010). Training for the second experiment was of a longer duration of 10 hours over 4-6 weeks, and therefore, effects were expected to be large enough to be detected with a correction for multiple comparisons. However, it is possible that training may still have been too short of a duration to result in a greater number of effects reaching the threshold for significance, thus explaining the small number of statistically significant outcomes.

Indeed, the duration of our training programme may not have been sufficient to induce changes in the diffusion indices of FA, MD, and NDI. Structural alterations in response to training such as white and grey matter plasticity take time to develop (Scholz et al., 2009; Metzler-Baddeley et al., 2017). For example, Scholz et al. (2009) found that grey matter density (as measured by voxel-based morphometry) in medial occipital and parietal regions continued to increase 4 weeks after a 6-week training programme on a novel visuo-motor skill had ended. Notably, this grey matter change correlated with cumulative improvement on the visuo-motor task (juggling), meaning both neural and behavioural effects of training were still developing ten weeks after the programme began and during the four week period without juggling. Thus, while our programme consisted of 12 sessions spread over 4-6 weeks, this may still have been too short a timescale for significant microstructural changes to occur. This may explain the absence of microstructural changes observed post-training as measured by FA, MD, and NDI parameters, as well as the confinement of ODI changes to the left frontal pole only. This may also explain the lack of functional changes in frontal (dPFC, vPFC, frontal pole) and striatal (caudate, putamen) regions that we expected to show plasticity as a result of training. For example, a recent meta-analysis of fMRI studies looking at working memory training by Salmi et al. (2018) has shown that modulation of frontostriatal activity may not emerge until some time after training. Indeed, longer programmes (> 10 hours) allow more time for training-induced changes to the frontostriatal system that, critically, are thought to mediate near transfer to untrained tasks (Salmi et al., 2018). Therefore, future studies should aim to utilise training programmes with more than 12 sessions and with a duration of longer than ten weeks.

Furthermore, our sample size can be considered relatively small (Nazeri et al., 2017). As such, it is possible that this study was underpowered and did not allow for the reliable detection of small-scale brain changes. Although a limited number of significant training-induced changes in brain microstructure and function were demonstrated in middle-aged adults, additional studies with larger sample sizes may detect effects in other brain regions, as well as any subtle effects which may have resulted from an insufficient duration of training.

As discussed previously, we must also consider that the greater number of negative findings may be due to our training programme not engaging the same cognitive processes and brain regions as our transfer tasks. Including a session to scan the training tasks might have confirmed that the training and transfer tasks did indeed engage overlapping brain regions, thought to be required for successful transfer (Dahlin et al., 2008; Lustig et al., 2009; Shipstead et al., 2012; von Bastian et al., 2013; Strenziok et al., 2014; Soveri et al., 2017; Pappa et al., 2020). However, regions involved in working memory are well established in the literature, and therefore, previous research still provided us with strong a-priori knowledge about which areas would overlap between our training and transfer tasks. Thus, our training programme was expected to engage areas involved in working memory, thereby inducing functional plasticity that would translate to changes in activity on the N-back and PAR transfer tasks. We did, indeed, find a significant post-training increase in activity in the cerebellum for the 4-back task, as well as in the fusiform and parahippocampus for the PAR task; all are regions that have been shown to be involved in working memory (e.g., Ranganath et al., 2004; Owen et al., 2005; Ranganath, 2006; Rottschy et al., 2012; Emch et al., 2019). This provides evidence for function and brain region overlap between our training and transfer tasks, and it is more likely that the negative findings in this experiment stem from low power to detect statistically significant changes, or from an insufficient duration of training.

5.4.6 MRI findings in the middle-aged compared to young and older adults

5.4.6.1 fMRI comparisons between age groups

Overall, the few studies that have investigated functional outcomes on near transfer tasks reported activation increases for young adults, and decreases or no change for older adults (Dahlin et al., 2008; Backman et al., 2011; Heinzel et al., 2016; Salminen et al., 2016). For example, Dahlin et al. (2008) found post-training increases in striatal, frontal, parietal, and temporal regions when assessing a near transfer task in young adults (age range: 20-31), while no significant changes were reported for the older adults (age range: 65-71). Backman and colleagues (2011) demonstrated near transfer following working memory training and increased activity in striatum in young adults (age range: 19-33). Salminen et al. (2016) found increased activity in the striatum, cuneus and calcarine gyrus for a near transfer task in young adults (age range: 20-32). And finally, Heinzel et al. (2016) reported activity decreases in middle and superior frontal regions for a near transfer task in older adults (age range: 60-75). Findings in the middle-aged participants in our study corroborate what is found in the young adults with increases in activity shown for the PAR task in fusiform and parahippocampal gyrus, and increases in activity for the 4-back task in cerebellum. This is in contrast to the decreases in activity found for older adults in the study by Heinzel et al. (2016), and no change in the study by Dahlin et al. (2008).

Older adults often exhibit greater activation compared to young adults and one explanation for this is a compensatory use of neural circuits (Grady et al., 1994; Cabeza, 2002; Reuter-Lorenz et al., 2000; Reuter-Lorenz & Cappell, 2008; Pappa et al., 2020). It is suggested that older adults reach a peak in functional activity at lower difficulty levels than young adults, and therefore may reach maximum capacity in the pre-training session (Reuter-Lorenz & Cappell, 2008; Pappa et al., 2020). As a result of overactivation at the pre-training session, improvement from training leads to a decrease in activation for the post-training session (i.e., fewer resources needed to perform the task after training). For young adults that have not reached maximum capacity at the pre-training session, training leads to an increase in activity in the post-training session (i.e., an increase in capacity). In other words, for the young adults, there is a post-training shift in the peak

activation via training-induced plasticity, i.e., neural resources reach maximum capacity at higher difficulty levels than before the intervention, which would in fact produce relative increases in activity (Iordan et al., 2020; Pappa et al., 2020). Therefore, the middle-aged adults in the present experiment may have shown increases in activity and an increase in capacity similar to the post-training shift in peak activation reported for transfer tasks in young adults. However, this interpretation needs to be treated with caution as there are very few studies examining functional outcomes on transfer tasks, and further research is needed to compare patterns of activity between young, middle-aged, and older adults.

5.4.6.2 DTI comparisons between age groups

In general, studies assessing training-induced microstructural plasticity have been investigated in young adults (Scholz et al., 2009; Takeuchi et al., 2010; Sagi et al., 2012; Hofstetter et al., 2013; Caeyenberghs et al., 2016; Roman et al., 2017). For example, Sagi et al. (2012) used DTI to examine grey matter microstructure in young adults (age range: 20-36) before and after training on a spatial learning and memory task. Analysis revealed significant decreases in MD in the left hippocampus and right parahippocampus following training. Using the same spatial navigation task, Hofstetter et al. (2013) used DTI to investigate white matter microstructure in young adults (age range: 20-38) and found reductions in FA and MD in the fornix after training. In contrast, increased FA in the intraparietal sulcus and anterior corpus callosum has been demonstrated in young adults (mean age: 21.7 years) in response to working memory training (Takeuchi et al., 2010). The study by Roman et al. (2017) revealed enhanced connectivity in a younger cohort of women (age range: 17-22) following a working memory intervention. Likewise, Caeyenberghs et al. (2016) reported structural connectivity increases in a fronto-parietal network following training in a group of younger adults (age range: 19-40).

Studies of training-induced microstructural plasticity in older adults are scarce, although there are a few investigations that have examined associations between DTI indices and training outcome (Bennett et al., 2011; Wolf et al., 2014). For example, Wolf and colleagues (2014) investigated the transfer of logical reasoning training to a measure of fluid intelligence in a group of older adults (age range: 60-85). Long-term transfer

(3-months after a 4-week training intervention) was associated with increased structural integrity (i.e., higher FA values) in the corpus and genu of the corpus callosum. Contrary to the DTI studies of young adults, we did not find any changes in FA or MD in the middle-aged adults in our study, and consequently, we did not test for any relationships between the indices and training outcome as was done in the older adult studies. It is possible that the lack of change in FA, MD, and NDI indicates less neuroplasticity in middle-aged adults compared to young adults. However, as stated previously, comparisons are difficult to make across studies, and in order to assess possible similarities and differences in plasticity, young, middle-aged, and older adults would need to be included within the same study. Indeed, this is the first study to examine training-related functional and structural neuroplasticity in a group of middle-aged adults, and research in this area is not only lacking for the middle-aged, but also for older and young adults.

5.4.6.3 NODDI comparisons between age groups

Studies to date have not used NODDI to assess training-induced brain plasticity in any age group. However, NODDI has previously been used to show age-related changes to white matter (Kodiweera et al., 2016) and cortical grey matter (Nazeri et al., 2015). For example, Nazeri et al. (2015) found a significant age-related deficit in grey matter ODI, most prominently in frontoparietal regions. Furthermore, associations have been demonstrated between grey and white matter microstructure and cognitive function (Nazeri et al., 2015; 2017; Parker et al., 2018). As stated above, in the study by Nazeri et al. (2015), higher levels of frontal pole ODI were related to better performance on tests of working memory/processing speed. These findings are of particular interest as we demonstrated a significant increase in ODI in the frontal pole following training in middle-aged adults. Therefore, training-induced plasticity is possible for this age group, and may be especially important in the frontal pole given that age-related deficits in grey matter ODI have been found in this region, and given that higher levels of frontal pole ODI are associated with better cognitive performance.

5.4.7 Limitations

There were no significant differences in function and structure between the adaptive and non-adaptive training groups. Thus, MRI results are reported for both groups combined, and in effect, we have one training group for which we examined pre- and post-training sessions with no corresponding control group (i.e., a within-subjects study design). This makes it difficult to interpret the brain changes found during the post-training session as being due solely to the cognitive training programme, and not due simply to performing the transfer tasks for a second time (i.e., the increased activity in the PAR and 4-back tasks could reflect practice on the transfer tasks themselves). However, it seems unlikely that these increases in activity would occur after such a short amount of practice, just 13 minutes for the PAR task and 11 minutes for the N-back task. Indeed, as discussed in Chapter 3 (Perceptual-cognitive-motor training in middle-aged adults, pg. 112), relatively short-term training (e.g., 31 minutes with the PCM task) might only result in small functional brain changes that would be difficult to detect with a stringent correction for multiple comparisons. Moreover, in motor skill learning studies, training is relatively longer and ranges from 60 – 120 minutes for the early learning stage, and even with this duration, researchers did not correct for multiple comparisons in order to reveal the possibly small effects (e.g., Jueptner et al., 1997; Doyon et al., 2002; Orban et al., 2010; Steele & Penhune, 2010). Thus, as the results for the PAR and 4-back tasks did pass a more stringent threshold for significance, this likely indicates larger or stronger effects as a result of longer-term practice on the training programme, rather than effects from 11-13 minutes of practice on the transfer tasks.

With regards to the change in microstructure, i.e., increase in frontal pole ODI, it is even less likely to be the result of practice on the PAR and N-back tasks instead of the training programme. Certainly, one would not expect training-induced changes in diffusion metrics with 11-13 minutes of practice. Currently, there are very few studies that have demonstrated training-related changes in diffusion metrics with short-term training (Sagi et al., 2012; Hofstetter et al., 2013; Marins et al., 2019). In comparison to the 11-13 minutes of practice on our transfer tasks, participants in these studies trained for 1-2 hours. For example, Marins and colleagues (2019) trained healthy individuals with

a motor imagery task, and after 1 h of training, participants showed increased FA in the sensorimotor segment of corpus callosum. In the studies by Sagi et al. (2012) and Hofstetter et al. (2013), participants trained for 2 hours on a spatial working memory task and demonstrated changes in FA and MD in grey and white mater. In fact, in the study by Hofstetter et al. (2013), results were not corrected for multiple comparisons as the changes in white matter were expected to be small after just 2 hours of training. Therefore, in our experiment, it is highly likely that the change in frontal pole ODI was due to the longer-term cognitive training programme and not due to 11-13 minutes of practice on the transfer tasks. Therefore, although we cannot say for certain that it is the training that resulted in the observed brain changes because we did not see differences between the groups, we can nevertheless, with relative confidence, interpret the findings as true training-induced effects, as it is very unlikely that such a short duration of practice on the transfer tasks would lead to the significant functional and microstructural plasticity observed in our study.

Our experiment investigated the neural effects of training exclusively on scanned transfer tasks. Notably, we provided evidence for training-induced increases in activity, interpreted as increases in capacity (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020), which may be a mechanism by which transfer occurs. However, it was not possible to assess the hypothesis that increased neural efficiency (i.e., decreases in activity) may also be a mechanism underlying transfer of training gains (Lustig et al., 2009; Lovden et al., 2010; Schmiedek et al., 2010; Strenziok et al., 2014; Flegal et al., 2019; Pappa et al., 2020). Increased neural efficiency has been demonstrated for trained tasks (Lustig et al., 2009; Klingberg, 2010; Morrison & Chein, 2011; Hsu et al., 2014; Salmi et al., 2018; Flegal et al., 2019; Pappa et al., 2020), however, as in our experiment, studies examining scanned transfer tasks typically reveal increases in activity (Dahlin et al., 2008; Backman et al., 2011; Schweizer et al., 2013; Salminen et al., 2016; Clark et al., 2017). This may be because the transfer tasks are at the fast-early stage of learning (Doyon & Ungerleider, 2002; Lustig et al., 2009; Pappa et al., 2020), and thus, only training-induced increases in capacity are likely to be detected. In order to see possible decreases in activity, a training task would need to have been scanned as well.

Indeed, both mechanisms may be involved in successful transfer, however, we were only able to provide evidence for one (i.e., training-related increases in capacity).

Furthermore, if increased neural efficiency is proposed as a mechanism for transfer, then one needs to question why increases in activity were observed in our transfer tasks as well as in other studies (Dahlin et al., 2008; Backman et al., 2011; Schweizer et al., 2013; Salminen et al., 2016; Clark et al., 2017). In other words, if decreases are consistently demonstrated on scanned training tasks indicating increased neural efficiency (Lustig et al., 2009; Klingberg, 2010; Morrison & Chein, 2011; Hsu et al., 2014; Salmi et al., 2018; Flegal et al., 2019; Pappa et al., 2020), why are these decreases not demonstrated in the regions thought to overlap in the transfer tasks? Thus, it might be reasonable to expect decreases in the post-training session for the transfer tasks as well. As there are few cognitive training studies examining scanned transfer tasks, further research is needed including both scanned training and transfer tasks to address this question.

A further limitation of our study is that we did not assess the cognitive function of our sample with standardised tests prior to training, such as the Mini Mental State Exam (MMSE; Folstein et al., 1975). However, we investigated a group of healthy middle-aged adults, which should have minimised the influence of relevant age-related changes, such as atrophy or amyloid plaques, while maximising the usefulness of the training with regard to training gains (Emch et al., 2019). Furthermore, individuals had no self-reported history of neurological and psychiatric disorders, or brain injuries. Nonetheless, we cannot be certain that participants with cognitive impairments were excluded from the study.

Our study compared images taken from different scanning sessions. In experimental studies, there are concerns about whether scans taken at different timepoints in the study (e.g., pre- and post-training) have been properly co-registered, and other sources of variability in image acquisition that can distort results (see Littmann et al., 2006; Lustig et al., 2009; and Lovden et al., 2013 for discussion). Issues include time-related changes in the positioning of subjects, and scanner stability over time (i.e.,

scanner drifts), such that differences between the sessions could stem from these time-related effects (Lovden et al., 2013). To mitigate these issues, we used state of the art preprocessing techniques including alignment across scans and sessions of all EPI data using an affine transformation with the FLIRT tool in FSL (version 5.0.7, Oxford, UK). In addition, high pass temporal filtering (128s) was applied to remove low frequency signals relating to scanner drift. Furthermore, several studies have reported an intersession variability in the BOLD response (e.g., Poellinger et al., 2001; Fischer et al., 2003; Coynel et al., 2010), and in the activation detected in brain regions involved in a task (e.g., Loubinoux et al., 2001; Marshall et al., 2004; Kübler et al., 2006; Coynel et al., 2010). This can be explained by a habituation of the participant to the fMRI context, as well as to the execution of a task, and stresses the importance of having both experimental and control groups when designing a training protocol over a longer period of time (Coynel et al., 2010). However, it's important to note that we did not find any decreases in activity, which would have been expected if habituation resulted in the brain changes observed in our study.

We demonstrated increased activity in areas thought to overlap between our training and transfer tasks. This suggests that training-related increased capacity of these regions may be one mechanism underlying the observed transfer to untrained abilities. However, we did not correlate scores from the task that showed transfer effects (i.e., 4-back) with the changes in functional and structural measures. Therefore, we have not demonstrated a direct link between training-related brain changes and training-related performance improvements in transfer tasks. Showing this link is important because it provides further evidence for the importance of neuroplasticity in transfer of training to untrained tasks (Strenziok et al., 2014). That the increased activity and microstructural change was revealed in regions known to be important for working memory, i.e., cerebellum and frontal pole (Wager & Smith, 2003; Ranganath et al., 2004; Owen et al., 2005; Koechlin & Hyafil, 2007; Rottschy et al., 2012; Nee et al., 2013; Emch et al., 2019), provides support for the notion that plasticity in these areas due to the working memory component of our training programme resulted in transfer to the 4-back task. Nonetheless, to strengthen this interpretation, a next step would be to test for associations between these brain changes and post-training 4-back performance.

It should also be noted that diffusion indices provide only an indirect marker of microstructural properties, and are difficult to relate unambiguously to underlying biology (Sagi et al., 2012; Zatorre et al., 2012; Hofstetter et al., 2013; Sampaio-Baptista et al., 2013; Caeyenberghs et al., 2016). Indeed, they are complex measures that are sensitive to manifold properties of tissue (Beaulieu, 2002; Johansen-Berg et al., 2007; Beaulieu, 2009; Jeurissen et al., 2013; Jones et al., 2013; Caeyenberghs et al., 2016). Grey matter changes that influence MRI signals may include neurogenesis, synaptogenesis, and changes in neuronal morphology (Zatorre et al., 2012). In white matter, changes in the number of axons, axon diameter, the packing density of fibres, axon branching, axon trajectories, and myelination can influence these metrics (Zatorre et al., 2012). Extra-neuronal changes can also affect these indices such as increases in glial cell size and number (Zatorre et al., 2012). Importantly, the NODDI index of ODI provides more specific information than metrics produced by other diffusion models. Therefore, we can with confidence say that the observed change in frontal pole ODI following training indicates a change in the dispersion of axons and dendrites. It is likely that this increase in dispersion is the result of neurite growth in this area, however, we cannot be certain that this is the cause of this change. Ultimately, histological studies are required to make direct links between changes in imaging measures such as ODI and underlying biological mechanisms (Sagi et al., 2012; Zatorre et al., 2012; Hofstetter et al., 2013; Sampaio-Baptista et al., 2013).

5.4.8 Conclusions

Our study provides novel evidence for training-induced functional and structural plasticity in healthy middle-aged adults. This was demonstrated by the significant increases in activity in fusiform and parahippocampus on the PAR transfer task following training; by the significant increases in activity in the cerebellum on the 4-back transfer task following training; and finally, by increased ODI in the frontal pole following training. Therefore, we conclude that cognitive training can successfully promote neuroplasticity in middle-aged adults as exhibited by changes in the function and structure of the brain post-training.

The increases in activity in the cerebellum following training, and the improved performance on the 4-back task, suggests that increases in capacity may be one mechanism by which transfer of training occurs to untrained tasks. We did not find evidence for the notion that increased neural efficiency underlies transfer as we did not find decreases in activity on the transfer tasks. In addition, the frontal pole is thought to have a critical role in working memory (Braver et al., 2003; Bunge et al., 2003; Sakai & Passingham, 2003; Ramnani & Owen, 2004; Ranganath et al., 2004; Koechlin & Hyafil, 2007; Koechlin, 2011), thus, the structural change observed in this area may also have contributed to transfer in the 4-back task. Therefore, the observed brain changes following training may underlie the improved performance on the untrained 4-back task. In conclusion, training-induced neuroplasticity may have benefits that transfer to untrained tasks. This may have important implications with regards to preventing cognitive decline in later life, i.e., training may result in brain changes that improve general cognitive function. Thus, investigating the neural mechanisms of transfer effects is an important avenue for further research.

Chapter 6: General discussion

6.1 Key findings and contributions of the present work

This thesis investigated the behavioural effects and neural correlates of cognitive training in healthy middle-aged adults (40-50 years old). In Chapters 3 - 5, we tested the effectiveness of training in inducing neuroplasticity and improving cognitive function, including general functioning. We assessed a range of different cognitive domains and processes including working memory, attention, inhibition, fluid intelligence, associative encoding, retrieval, and recognition. Brain changes following training were assessed using functional and structural MRI techniques.

In chapter 3, we examined the neural correlates of short-term training on a novel and complex perceptual-cognitive-motor (PCM) task in middle-aged adults. We sought to characterise functional plasticity at the early stage of training, and as such, we used functional magnetic resonance imaging (fMRI) to investigate changes in activation over 1 session. In addition, we sought to link functional plasticity as a result of training, with underlying structure. Thus, we used both diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) to analyse microstructural variation in relation to training outcome. We found that the number of successful trials significantly increased from pre- to post-training for the PCM task, and the effect size was large and positive. This indicates that within a relatively short space of time (31 minutes of training), middle-aged adults were able to greatly improve their performance. Furthermore, we observed post-training changes in activity in both cortical and subcortical regions including the prefrontal cortex, parietal cortex, M1, premotor cortex, SMA, preSMA, anterior cingulate cortex, striatum, hippocampus, parahippocampus, and cerebellum. These findings demonstrate training-induced functional plasticity in this age group. We found that post-training increased activity in the putamen and anterior cingulate was significantly and positively correlated with learning outcome, demonstrating a direct link between changes in brain function and improved performance following training. And finally, we found significant associations between microstructural indices and PCM training outcome. Specifically, training outcome was correlated with MD in the cerebellum and hMT+/V5; and with FA and ODI in the SMA. These results provide strong evidence for a relationship between brain structure and learning outcome, suggesting that structural variation has functional consequences. We

did not find a significant association between NDI and training outcome. Therefore, neurite density may not have played a significant role in learning ability in the present experiment.

In chapter 4, we investigated the behavioural effects of longer-term cognitive training (4-6 weeks) in middle-aged adults. Participants in the experimental condition completed an adaptive cognitive training programme, while the active control group completed a non-adaptive version of the training. The training programme targeted working memory, attention, and other executive functions such as inhibition. To test for training-related improvements in cognitive function we examined performance on the training tasks. To test for a general improvement in cognitive ability we assessed untrained transfer tasks (RAPM, PAL, PAR, and N-back). Adaptive participants showed substantial improvements over the course of training, as indicated by significant increases in performance for all training tasks. The non-adaptive group also showed significant increases in performance for the training tasks. Indeed, effect sizes were very large for both groups. This demonstrates considerable cognitive plasticity in this age group. We did not find any significant differences between adaptive and non-adaptive training, indicating that type of training programme did not have an effect on transfer. However, when combining both training groups, we found a significant improvement on the 4-back transfer task and the effect size was moderate. This demonstrates that the cognitive training was successful and resulted in transfer to an untrained task. There were no significant differences comparing pre- and post-training scores for the RAPM, PAL, and PAR tasks, indicating no transfer to these untrained domains.

In Chapter 5, we assessed the neural effects of cognitive training in middle-aged adults. We sought to characterise functional plasticity as a result of training with task-based fMRI. In particular, training-induced functional changes were assessed on the near transfer tasks (PAR, N-back). To further investigate the neural mechanisms involved in transfer of training gains, we used DTI and NODDI. Thus, we examined the microstructural alterations that occurred in the brain following cognitive training. We did not find any significant differences between adaptive and non-adaptive training on the neuroimaging outcomes. Therefore, we combined the groups to test for training-induced

neuroplasticity. For the PAR task, we found significantly increased activity in the fusiform and parahippocampal gyrus following training. For the 4-back task, we found significantly increased activity in the cerebellum post-training. These findings demonstrate training effects in these regions in middle-aged adults, and indicate the transfer of training-induced plasticity to untrained tasks. Furthermore, we found a significant increase in ODI in the left frontal pole post-training, providing evidence for training-induced microstructural change in this region. We did not find any significant differences between pre- and post-training sessions for the diffusion MRI indices of FA, MD, and NDI. It is possible that the duration of our training programme was not sufficient to induce changes in these indices.

Taken together, these results demonstrate that cognitive training in middle-aged adults was effective at improving cognitive function, and induced functional and structural changes in the brain. Moreover, this neuroplasticity and improved cognitive function generalised to untrained abilities, indicating the potential for gains to transfer beyond the practiced tasks to everyday functioning. In the following sections, conclusions from all the experiments are discussed in a broader context.

6.2 Implications

The work contained within this thesis has potential impact both at theoretical and practical levels. First, it seems important to discuss adaptive cognitive training and the Lovden et al. (2010) theoretical framework for plasticity and transfer.

6.2.1 Adaptive vs. non-adaptive training

We found no significant differences between adaptive and non-adaptive training. According to a recent theoretical model (Lovden et al., 2010; Flegal et al., 2019), transient cognitive challenges are only sufficient to promote task-specific gains, sustained challenges are required to elicit the lasting neural changes thought to underlie transfer and improvement of general cognitive function. It is suggested that raising the level of maximum function requires a prolonged mismatch in which environmental demand exceeds functional supply. Based on this framework, it is proposed that adapting the difficulty of training tasks to an individual's current level of ability would provide the

necessary prolonged mismatch, thereby driving cognitive and neural plasticity leading to broader transfer. It is possible that our adaptive training protocol, in which the level of difficulty was capped, may have been insufficient to induce plasticity that is associated with transfer.

However, we have demonstrated that both adaptive and non-adaptive groups significantly improved their performance on the trained tasks. Thus, it is likely that the non-adaptive participants in our study benefitted from the training programme. This finding is important because, while previous studies conclude that adaptive training may be key to transfer and that optimal designs should use this form of training (Holmes et al., 2009; Smith et al., 2009; Jaeggi et al., 2010; Brehmer et al., 2012; Rudebeck et al., 2012; Anguera et al., 2013; Heinzel et al., 2016; Flegal et al., 2019), we suggest that even non-adaptive training can have substantial positive effects on cognitive function. Therefore, in contrast to the Lovden et al. (2010) model, our findings suggest that adaptively increasing training task difficulty is neither necessary nor sufficient to promote transfer. Indeed, we propose that our non-adaptive training programme, although less challenging, is still repetitively engaging brain networks involved in working memory, attention, and executive function, and thus, may have induced neural plasticity in these networks. In terms of training interventions, this means that even less challenging forms of training may have the potential to initiate neural plasticity leading to cognitive enhancements.

6.2.2 Process-based training

We found a significant transfer effect to the untrained 4-back task. This task is considered to be in the cognitive domain of working memory, which was trained by two tasks in our programme. This provides support for the notion that transfer occurs when trained and untrained tasks share the same underlying cognitive processes (Jonides, 2004; Dahlin et al., 2008; 2009; Schmiedek et al., 2010; Shipstead et al., 2012; Flegal et al., 2019). Indeed, the 4-back task involves working memory, inhibitory control, and attention – all were processes trained in our programme. On the other hand, there were no significant differences comparing pre- and post-training scores for the RAPM, PAL, and PAR transfer tasks. These transfer tasks were in the cognitive domains of fluid intelligence, associative learning, and associative memory, respectively. Therefore, they

differed from the cognitive domains that were the focus of our training programme (i.e., working memory, attention, and inhibition). Hence, they differed on several component processes and perceptual features, and as such, transfer of training gains did not occur to these tasks.

Process-based theories suggest that rather than expanding the fundamental capacity of a particular cognitive domain in an undifferentiated manner, training enhances the specific processes within the domain that are engaged by the training tasks (Dahlin et al., 2008; Holmes et al., 2009; Shipstead et al., 2012; Sprenger et al., 2013; Dunning & Holmes, 2014; von Bastian & Oberauer, 2014; Minear et al., 2016; Soveri et al., 2017; Gathercole et al., 2019). This accounts for the absence of transfer even across paradigms in the same domain, by assuming that training results in increases in the efficiency of individual processes that are engaged by some, but not all tasks in a particular domain (Dahlin et al., 2008; Minear et al., 2016; Gathercole et al., 2019). Therefore, the more similar the tasks are, the more component processes they share, and thus, transfer is more likely to occur.

While we provide evidence for process-based models of transfer, this does mean that designing effective intervention programmes is quite a formidable task. Indeed, training various processes with a variety of tasks should lead to more transfer. This was evident in our N-back result where processes involved in this task were trained by two working memory tasks (CODING, DATEUP), and also by the attention (DIVID) and inhibition (HIBITR) tasks; whereas our training programme may not have been extensive enough to result in transfer to the RAPM, PAL, and PAR tasks. This suggests that in order for training to have an impact on everyday functioning and to prevent cognitive decline, a varied programme targeting multiple processes would be beneficial, although we acknowledge that designing such a programme is a challenging task. Taking this into account, it may be that multidomain approaches (e.g., videogames) would be more efficient at targeting more processes within one task. Thus, training a whole host of perceptual, cognitive, and motor functions for 1 hour during a session becomes possible. Whereas training particular functions for 10 minutes each during a 1-hour session is not as efficient. Multidomain approaches have been used with success in both younger and

older adults (e.g., Green & Bavelier, 2003; Basak et al., 2008, 2011; van Muijden et al., 2012; Strenziok et al., 2014). Certainly, we found positive effects of multidomain training with the PCM task in our first experiment. However, it remains to be seen whether PCM training would transfer more extensively to untrained tasks, although the results from our first study were promising.

6.2.3 Cognitive plasticity in middle-aged adults

Our findings suggest that even with short-term practice on a PCM task, middle-aged adults show significant plasticity in cognitive and motor abilities as indicated by the training gains made on the task. The effect size was large and shows that PCM training had a substantial positive outcome. Furthermore, in the second study, both adaptive and non-adaptive participants showed significantly improved performance on the training tasks, and effect sizes were very large, indicating considerable levels of plasticity in this age group.

We also found a significant improvement on the 4-back transfer task. This demonstrates that training-related gains transferred to an untrained task. Moreover, there was a significant positive relationship between working memory training outcome and post-training 4-back scores, providing evidence that improvements in working memory in particular transferred to an untrained task requiring the same ability. Working memory is a cognitive resource of significant importance for countless demands in everyday life (Baltes et al., 1999; Schmiedek et al., 2010; Gathercole et al., 2019). Our demonstration that this ability can be improved through training is an important step towards designing large-scale interventions that can have a positive impact on cognitive development (Schmiedek et al., 2010). Indeed, these findings are important because they establish that training-induced improvements in cognitive function (as evidenced by gains on the training tasks) transferred to untrained tasks (as evidenced by improvement on the 4-back task) in middle-aged adults. Therefore, cognitive training gains may have the potential to transfer to general cognitive functioning, and thus, prevent age-related decline.

While both younger and older adults show considerable gains on trained tasks, younger adults consistently show the greatest improvements on transfer tasks, suggesting that cognitive intervention is more effective in earlier than in later adulthood, and that cognitive plasticity declines in older age (e.g., Brehmer et al. 2007; Dahlin et al., 2008; Shing et al., 2008; Schmiedek et al., 2010; Brehmer et al., 2012; Borella et al., 2014; von Bastian & Oberauer, 2014; Zinke et al., 2014). Some studies dispute this finding, showing greater effects for older adults (Owen et al., 2010; Corbett et al., 2015). This is possibly because there is more room for improvement in older adults, and less scope for significant effects in younger adults who are already performing at peak levels.

Furthermore, motivational factors may also play a role in cases where training effects are greater for older compared to younger adults. For example, in the study by Corbett et al. (2015), the older cohort chose to complete more sessions than a younger group undertaking the same programme (Owen et al., 2010), such that the older adults completed more than double the number of cognitive training sessions than their younger counterparts, suggesting that the older group may have been more motivated to improve their cognitive fitness. This issue is of particular importance because recent work has identified motivation as a key condition for transfer to occur (Green & Bavelier, 2008; Jaeggi et al., 2014). We have demonstrated that cognitive training in middle-aged adults also produces transfer effects as shown by the 4-back result. Thus, the findings from our study suggest that middle-aged adults respond to cognitive training with improved performance on both trained and untrained tasks. This strengthens our arguments for the implementation of intervention programmes before older age. Indeed, middle-age presents an ideal time to implement cognitive training programmes – this age group are not performing at their peak and may be more motivated to undertake training as a way to prevent cognitive decline than younger adults, as well as potentially having more plasticity than older adults. Although it should be noted that a study design comparing all three age groups on training and transfer would be needed to confirm these conclusions.

6.2.4 Neuroplasticity in middle-aged adults

In our first experiment, we observed changes in activity in both cognitive and motor networks following PCM training, indicating training-induced functional

neuroplasticity in middle-aged adults. The prefrontal cortex and frontostriatal network demonstrate the highest age-related decline (see Cabeza, 2001 for an overview), with decreased volume in the frontal cortex as well as the caudate and putamen (Raz et al., 2003, 2005; Allen et al., 2005; King et al., 2013), and degradations in the white matter tracts connecting the striatum to the frontal cortex (Bennett et al., 2011; King et al., 2013). Thus, these areas would be ideal targets for a cognitive training programme aimed at preventing decline. Notably, we demonstrated functional plasticity in several regions including the prefrontal cortex, anterior cingulate, caudate, and putamen with training on the PCM task. Therefore, we have shown that the PCM task has promise for use in training programmes aimed at preventing cognitive and motor decline, as regions known to display age-related deficits showed plasticity with training on this task. Furthermore, we found that post-training increased activity in the putamen and anterior cingulate was associated with better training outcome, indicating a direct link between changes in brain function and improved performance following training. Therefore, we provide evidence of a relationship between training-induced brain changes and cognitive function, demonstrating the potential usefulness of interventions aimed at inducing neuroplasticity.

We found significant associations between microstructural indices and PCM training outcome, thus, inter-individual variation in brain structure was related to learning ability. Specifically, training outcome was correlated with MD in the cerebellum and hMT+/V5; and with FA and ODI in the SMA. Quantifying neurite morphology in terms of its density and orientation distribution provides a window into the structural basis of brain function (Zhang et al., 2012). Indeed, the structure and training outcome relationships that we found were colocalised to regions within which functional alterations occurred following training on the PCM task. For example, we observed increased activity post-training on the PCM task in cerebellum and SMA. Moreover, functional MRI studies have shown that these regions (i.e., cerebellum, SMA, and hMT+/V5) become consistently activated during visuomotor tasks (e.g., Jenkins et al., 1994; Sakai et al., 1999; Doyon et al., 2003; Oreja-Guevara et al., 2004; Floyer-Lea & Matthews, 2005; Steele & Penhune, 2010; van Kemenade et al., 2014). Thus, the structure-behaviour correlations were found within the same cortical regions that

functional plasticity occurred in, and in regions with functional significance for the PCM task. This provides evidence that morphological variation contributes to cognitive function. This means that cognitive training could potentially alter brain structure which may lead to improved cognitive performance.

Notably, in the following experiment, we were able to demonstrate structural change in the brain as a result of training. Specifically, we found a significant increase in ODI in the frontal pole post-training. The increase in grey and white matter ODI may indicate new neurite growth (Zhang et al., 2012) in this region as a result of the cognitive training programme. This is an important finding because, as discussed previously, Nazeri et al. (2015) found a significant age-related deficit in grey matter ODI in frontoparietal regions. Furthermore, they demonstrated that higher levels of frontal pole ODI were related to better performance on tests of working memory/processing speed. Moreover, past research suggests that the frontal pole plays an important role in mediating neuronal compensation (Marioni et al., 2012; Valenzuela et al., 2012). Therefore, demonstrating training-induced plasticity in this area may be especially significant given that age-related deficits in ODI have been found in this region, given that higher levels of frontal pole ODI are associated with better cognitive performance, and given this area's role in neuronal compensation. Thus, targeting the frontal pole with appropriate training interventions in middle-aged adults could be particularly beneficial in improving cognitive function and preventing decline in later life.

In addition to training-induced structural change in the brain, our second study also demonstrated functional plasticity in middle-aged adults. We found significant increases in activity in fusiform and parahippocampus on the PAR transfer task following training; and significant increases in activity in the cerebellum on the 4-back transfer task following training. Activation increases have been explained as added recruitment of brain regions or as response strengthening within a cortical region (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020). These mechanisms are thought to result in increased capacity in the processes performed by these areas (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Flegal et al., 2019; Pappa et al., 2020). Decreases in activity are thought to indicate increased neural

efficiency (Kelly & Garavan, 2005; Lustig et al., 2009; Lovden et al., 2010; Schmiedek et al., 2010; Strenziok et al., 2014; Flegal et al., 2019; Pappa et al., 2020).

Our findings of increased activity during the transfer tasks provides support for the notion that increases in capacity can transfer to untrained tasks requiring the same processes as the trained tasks. That is, the tasks in our training programme were thought to engage overlapping working memory regions with the PAR and N-back tasks. Thus, engaging these areas during the training may have led to increased capacity for processes subserved by these regions. This increased capacity may have transferred to the PAR and N-back tasks as demonstrated by increased activity in these regions, and by improved performance on the 4-back task. Therefore, we provide evidence for the hypothesis that transfer occurs when overlapping brain regions are engaged by the training and transfer tasks. We did not find evidence for the hypothesis that increased neural efficiency underlies transfer as we did not find decreases in activity on the transfer tasks. Thus, these findings suggest that training results in increased capacity of cognitive processes and this can transfer to untrained tasks that also require these processes. That increased capacity transferred to an untrained task (4-back) as demonstrated by significantly improved performance on this task, indicates that cognitive training can potentially have a big impact on everyday functioning if increased capacity in several processes transfers.

Furthermore, it's important to note that while this thesis is concerned with cognitive training as an intervention to prevent age-related decline, our findings also have implications for clinical use. For example, we have demonstrated that training-induced neuroplasticity can transfer to untrained tasks as demonstrated by increased activity during the transfer tasks, as well as significantly improved performance on the 4-back task. Moreover, neuroplasticity and significant training gains were demonstrated for the PCM task. Therefore, cognitive training programmes, as well as PCM training, may be useful for neurorehabilitative interventions for individuals with movement disorders or neurological injuries (e.g., Celnik & Cohen, 2004; Ertelt et al., 2007; Celnik et al., 2008, 2009; King et al., 2013). Further research with patient populations is needed to test this possibility.

6.3 Limitations and future directions

The findings in this thesis should be considered in light of several constraints. The primary methodological issues we identified for the overall study include issues common to within-subjects study designs, such as no control group. For our first experiment, we compared pre- and post-training performance of the training group against no control. In addition, for our second experiment, we combined the adaptive and non-adaptive groups to compare pre- and post-training sessions. Thus, we also had a within-subjects study design without a control group for the second experiment. Designs employing no control conditions make it more difficult to discern whether the effects stem from true training gains, or perhaps are mediated by other factors (Shipstead et al., 2012; Strenziok et al., 2014; Dougherty et al., 2016; Melby-Lervag et al., 2016; Pappa et al., 2020). Therefore, our lack of control groups somewhat limited interpretation of the findings, such that improvements on the tasks were susceptible to non-specific factors such as test-retest effects, expectancy effects, increased motivation, and the Hawthorne effect (Landsberger, 1958; Collie et al., 2003; McCarney et al., 2007; Green & Bavelier, 2012; Gathercole et al., 2019; Pappa et al., 2020). That is, performance may have improved not solely because of the training, but due to these other factors as well. Furthermore, this design makes it more difficult to interpret the post-training brain changes as being due solely to the training programme, and not due to additional factors such as habituation of the participant to the fMRI context, as well as to the execution of the tasks. This stresses the importance of having both experimental and control groups when designing a training protocol over a longer period of time (Coynel et al., 2010).

Indeed, an optimal study design for future research should be between-subjects, such that a training condition is compared to an active control treatment to ensure that any differences observed from pre- to post-training cannot be attributed to non-experimental variables. However, employing an active control group bears the risk of missing or underestimating the effects of training (von Bastian & Oberauer, 2014; Pappa et al., 2020). Certainly, in our study, we found no significant differences between adaptive and non-adaptive (i.e., active control) training on any of the transfer tasks, nor on the neuroimaging outcomes. However, it is likely that our active control was too stringent and

non-adaptive participants benefitted substantially from training. This is supported by the finding that significant improvements in performance and very large effect sizes for the training tasks were found not only for the adaptive group, but also for the non-adaptive group. As discussed by Morrison and Chein (2011), small effect sizes with regards to training may represent either little adaptive training-induced benefit, or unexpected cognitive enhancements related to the non-adaptive control training. To make sure that training conditions were the same for both our groups, participants in the experimental condition completed an adaptive cognitive training programme, while the active control group completed a non-adaptive version of the same training. Therefore, our non-adaptive training programme, although less challenging, is still repeatedly recruiting the brain networks involved in working memory, attention, and executive function. Thus, even the non-adaptive training programme has the potential to initiate neural plasticity in these networks and brain areas (Baltes & Lindenberger, 1988). As such, there were significant improvements in training task performance for both adaptive and non-adaptive training groups, and no significant differences were detected between them on transfer tasks, and on functional and structural outcomes.

With this in mind, future studies would benefit from active control training that is done with a different set of demanding tasks that do not engage the same processes and brain areas as the experimental group. Comparing these groups at post-training should yield differences between them if the training programmes have induced neural plasticity in their respective brain regions, thus resulting in a double-dissociation design. For example, if training programme A is designed to train processes tested by transfer task A, and training programme B is designed to train processes tested by transfer task B, then training programme A should result in improved performance on transfer task A but not on transfer task B, and training programme B should result in improvements on transfer task B but not on transfer task A. Furthermore, the inclusion of a passive control group could be employed to assess non-specific factors such as test-retest effects. In addition, future studies could include a self-report measure of expectancy, effort, and motivation, as well as a measure of implicit beliefs about the malleability of intelligence, in order to explicitly model these factors as covariates when assessing task performance.

A further limitation of our study is that the sample sizes in our experiments can be considered relatively small. Our second study in particular was underpowered, such that post-hoc power calculations demonstrated that achieved power for the analyses was very low. Although significant training-induced changes in brain microstructure and function were demonstrated in middle-aged adults, additional studies with larger sample sizes may detect effects in other brain regions, as well as possible smaller effects. Indeed, our first study may have benefitted from a larger sample as well, as relatively small effects may have resulted from just 31 minutes of training. As such, future research in this area should focus on investigating the effects of training on large-scale samples. Information from such large-scale samples will prove vital in determining the effectiveness of utilising cognitive training in middle-age to improve cognitive function, and prevent age-related decline.

An important issue that has been overlooked in the first experiment is whether benefits of training with the PCM task can transfer to untrained tasks. It would be important to test if training with the PCM task leads to a general improvement in the level of cognitive functioning and motor control. Interventions targeting age-associated cognitive decline should be trying to maximise the transfer of skills as much as possible. Identifying tasks that can lead to improvement in untrained tasks is crucial and recommends investigation of transfer effects. Moreover, we only examined short-term training with the PCM task. Although a detailed characterisation of the initial acquisition of a motor skill is critical to our understanding of motor learning, it is equally important to understand how the retention of newly acquired abilities occurs over longer periods of time (King et al., 2013). A study of longer-term training would be needed to see if further gains could be observed and indeed, to establish whether the PCM task would be useful in cognitive training regimes.

Our results provide support for the notion that cognitive training can be used beneficially in middle-aged adults with the potential to prevent cognitive decline in later life. However, in the context of implementing interventions designed to prevent or ameliorate age-related declines in cognitive performance, improvements in cognitive functioning must be maintained beyond the conclusion of the training sessions (King et

al., 2013). Therefore, a limitation of the present study is that we did not assess the durability of the training and transfer effects. In order to investigate whether our cognitive training programme can maintain these changes into late-life, a long-term follow-up study with the same participants looking at cognitive performance and brain function and structure would be necessary. Additionally, it would be interesting to see whether these brain changes persist with or without the aid of further, less rigorous, cognitive training (i.e., booster sessions), and for how long. Indeed, there are studies that have noted performance improvements that persist months or years after training (e.g., Schaie & Willis, 1986; Ball et al., 1988; Emery et al., 1992; Willis et al., 2006; Lustig et al., 2009). A possible explanation is that participants continue to use, and thus maintain, the trained processes in their everyday lives (Lustig et al., 2009). On a practical level, intensive training for short periods followed by periodic reassessments and booster sessions may be a useful method for preserving training benefits with minimal burden to the participant (Lustig et al., 2009).

A further limitation of our study is that we did not assess measures of everyday function, and therefore we cannot be certain of the training impact on daily living. Certainly it would be important to show that the training programme has the ability to improve everyday functioning. We have demonstrated transfer from the trained tasks to an untrained task and this is a promising indicator for taking the next step, i.e., transfer to everyday activities (Lustig et al., 2009). However, it remains to be seen whether these tasks can be used in practice to enhance everyday cognitive functioning (Strenziok et al., 2014; Pergher et al., 2018). It is important to note that this might be a challenging endeavour as many current standardised measures were originally designed for clinical populations, and often do not produce a sufficient range of performance in healthy adults to allow an adequate assessment of training effects (Lustig et al., 2009).

The findings from our study indicate that middle-aged adults respond to cognitive training with improved performance on both trained and untrained tasks, and with structural and functional plasticity. We have suggested that this strengthens our arguments for the implementation of intervention programmes before older age. Middle-aged adults may be more motivated to undertake training as a way to prevent cognitive

decline than younger adults, as well as potentially having more plasticity than older adults. However, the extent to which plasticity varies with age could not be considered with the present study and could only be assessed if younger and older adults were included within the same experiment. Although numerous studies suggest that younger adults benefit more from training than older participants and the capacity for plasticity declines with age (e.g., Nyberg et al., 2003; Dahlin et al., 2008; Li et al., 2008; Lustig et al., 2009; Brehmer et al., 2012; Emch et al., 2019), we do not know if this means that initiating training programmes in midlife would be more beneficial than starting in older age. Future research would require a study design comparing all three age groups on training and transfer effects, as well as brain structure and function in order to confirm these conclusions.

6.4 Conclusion

This thesis contributes new findings to the cognitive training literature. We found that short-term training on a perceptual-cognitive-motor task induced functional neuroplasticity in healthy middle-aged adults. Furthermore, this training resulted in significant improvement on the task, and extent of improvement was related to underlying brain structure and function. Furthermore, we found that longer-term training with working memory, attention, and inhibition tasks resulted in functional and structural plasticity in this age group. Substantial improvements were found for the training tasks, and training gains transferred to an untrained task. Taken together, these findings demonstrate considerable cognitive, motor, and neural plasticity in middle-aged adults. Moreover, neuroplasticity in this age group was demonstrated in areas that that have relevance for age-associated cognitive decline such as the prefrontal cortex, anterior cingulate, caudate, putamen, and frontal pole. Therefore, we conclude that cognitive training can successfully promote plasticity in middle-aged adults, and this may have a significant potential impact with regards to improving cognitive function and preventing age-related decline in later life.

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Appendices

I. PCM task instructions for participants

Task instruction

- During this task, you will see a white ball, a red target ball, and green balls. You will control the white ball with the MRI mouse, and try to move it to the red target.
- The green balls will move around on the screen. Your white ball must avoid the green balls. If your white ball touches a green ball, that trial will end. And the next trial will start.
- You will have 2 starting positions for your white ball, bottom left and right of screen. The starting positions will change randomly. Before the beginning of every attempt, you will see which corner you will start in and you can get ready by moving the mouse to that position.
- When the green balls start to move, that's the start of the trial and you will be able to move the white ball freely.

** Mouse will fail sometimes: go off the screen or can't move – don't worry about it. Tips: smooth movements, will sometimes need to lift mouse off of pad, keep left hand off of pad – maybe keep at side of box.

- There will be 4 phases of the task:

  First: **habituation** to scanner and MRI mouse = 8 trials, ~1min, no scanning.

  Second: **learning** phase = 80 trials, ~15min, fMRI scanning.

  Third: **practice** phase divided into two sections (break in b/w) = 24 trials, ~5min, structural scan and 48 trials, ~10min, diffusion scan.

  Fourth: **test** phase = 80 trials, ~15min, fMRI scanning.

II. N-back task instructions and visual example for participants

N-back task (in the scanner):

You will see a series of letters presented on a screen one at a time. Your task is to respond with a button press when the current letter on the screen matches one that was presented a certain number back in the sequence. This number will vary throughout the task.

For example, you may be asked to look for a match **1-back** in the sequence: you will need to press the button when the letter on the screen is the same as the previous letter. Both upper and lowercase of the same letter would be correct.

Or you may be asked to look for a match **3-back** in the sequence: you will need to press the button when the letter on the screen is the same as the letter that was presented 3 places before. Both upper and lowercase of the same letter would be correct.

Or you may be asked to look for a match **4-back** in the sequence: you will need to press the button when the letter on the screen is the same as the letter that was shown 4 places before. Both upper and lowercase of the same letter would be correct.

There will also be a task, in which you will be given a **target letter** to respond to each time it is on the screen. Every time that particular letter is on the screen, whether it is uppercase or lowercase, you will need to press the button.

The instruction for whether a particular series of letters is a target letter, 1-back, 3-back, or 4-back task, will be presented on the screen before the series starts.

** *Some of the N-back tasks will be difficult, but try to respond as quickly and accurately as possible.*

Target letter

Target: d/D	c	v	d	g	y	d	l	w	t	f

Here you would just respond to every ‘d/D’ in the sequence because you are looking out for the letter ‘d’ as given by the instructions.

In this version of the task you will always be told what letter you are looking for, for that particular set of letters.

1-back

1-back	s	f	W	w	s	b	B	g	j	s

Here you would respond to ‘w’, because it matches the ‘W’ before (one back in the sequence).

You would also respond to ‘B’, because it matches the ‘b’ just before (one back in the sequence).

3-back

3-back	t	h	s	t	q	d	v	b	d	k

Here you would respond to ‘t’, because it matches the other ‘t’ three letters back in the sequence.

You would also respond to the ‘d’, because it matches with another ‘d’ three letters back in the sequence.

4-back

4-back	z	s	h	f	z	y	H	k	l	t

You would respond to the ‘z’, because it matches the ‘z’ four letters back in the sequence.

Here you would also respond to the ‘H’, because it matches the ‘h’ four letters back in the sequence.

- Both upper and lowercase of the same letter would be correct

III. PAL and PAR task instructions and visual examples for participants

Learning task (NOT in the scanner):

You will be asked to learn eight pairs of abstract pictures that you will be given a memory test on in the scanner. Firstly, you will be presented with the eight pairs, one at a time on the screen for a few seconds, and we ask that you try and memorise the pairs. You will then have more time to learn the pairs in part 2 of the task. In part 2, you will be presented with one of the pictures above 4 other pictures, and the task is to match the picture to one of the 4 possibilities. You will be asked to respond with the keys 1-4 (corresponding to the four pictures from left to right). You will receive feedback as to whether you have chosen the correct or incorrect pairing after each attempt. Use this feedback to help you learn the correct pairings.

*** Try to respond as quickly and accurately as possible, 3 seconds to respond*

*** 8 trials/problems per run, score out of 8 at the end of each run, there are 16 runs*

*** The task takes about 12min*

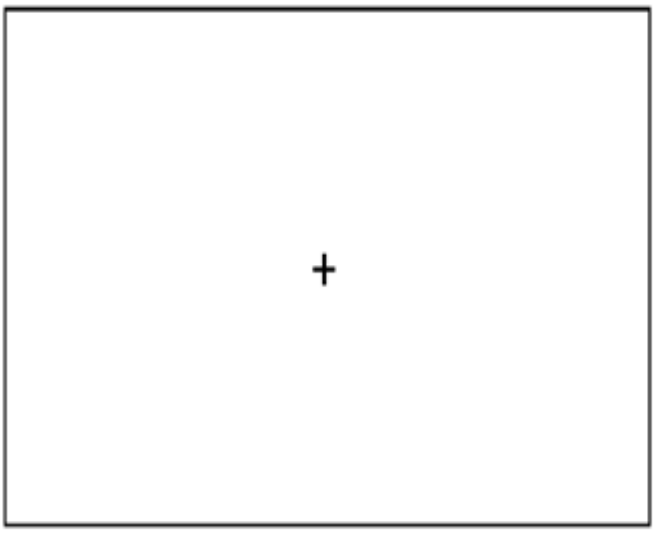
Memory task (in the scanner):

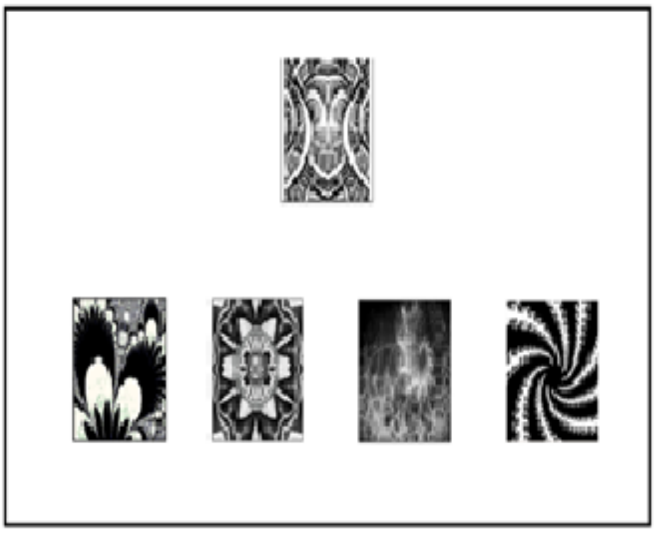
You will be presented with a picture from one of the pairs that you learned earlier. When you see this first picture, we ask that you try to remember its partner picture and hold this image in your mind for a few seconds. Then a second picture will be presented. You will be asked whether the second picture is the correct pair match to the first picture or not. If it is a match you will press button 1, if it is not a match you will press button 2.

*** Try to respond as quickly and accurately as possible, 3 seconds to respond*

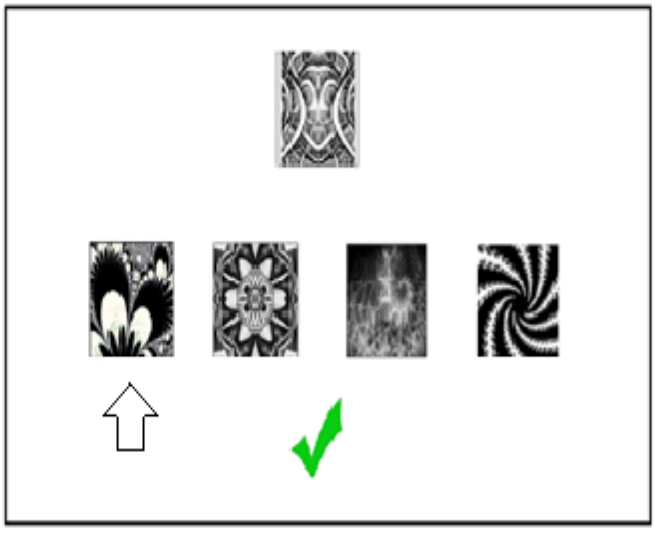
*** There will be no feedback for this task*

Learning task

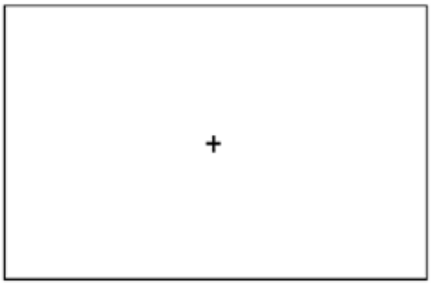


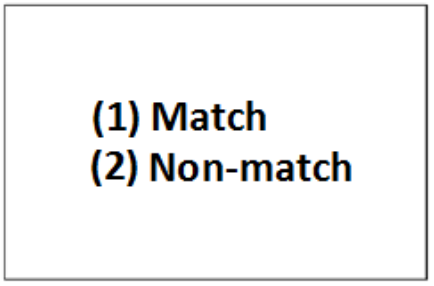


3 seconds to respond

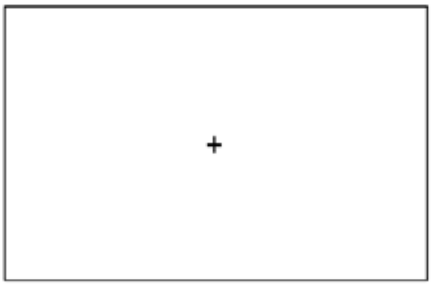


Memory task





3 seconds to respond



IV. CogniPlus task instructions for participants

CogniPlus training

Over the course of 4-6 weeks you will engage in a series of brain training tasks for 1 hour per day, 2-3 times per week. The training will consist of 5 tasks, each of which will last for 10 minutes. For the first 1 or 2 sessions you may practice the task before starting it. Sometimes the tasks will get harder as you go along, sometimes they will stay the same, and sometimes they may get easier. One of the tasks has a few different subtypes and you have a choice as to how you proceed with the training. You can adjust the volume at the beginning of the training session.

*** Try to respond quickly and accurately.*

*** Pressing the ESC and F5 keys at the same time pauses the training.*

*** For the first task, when someone's name is called on the intercom you may press the button right away, you do not need to wait until they finish calling the person's name.*

V. Chapter 3: figures for tests of assumptions

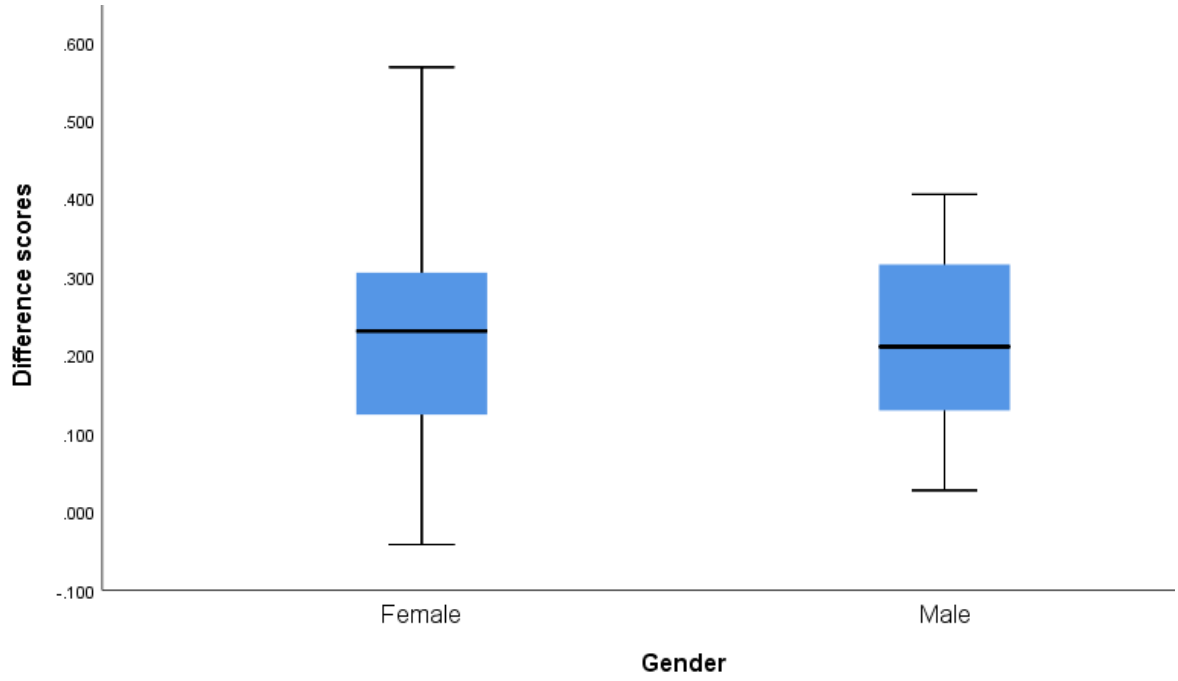


Figure V.1. Boxplots showing no outliers for female and male normalised difference scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

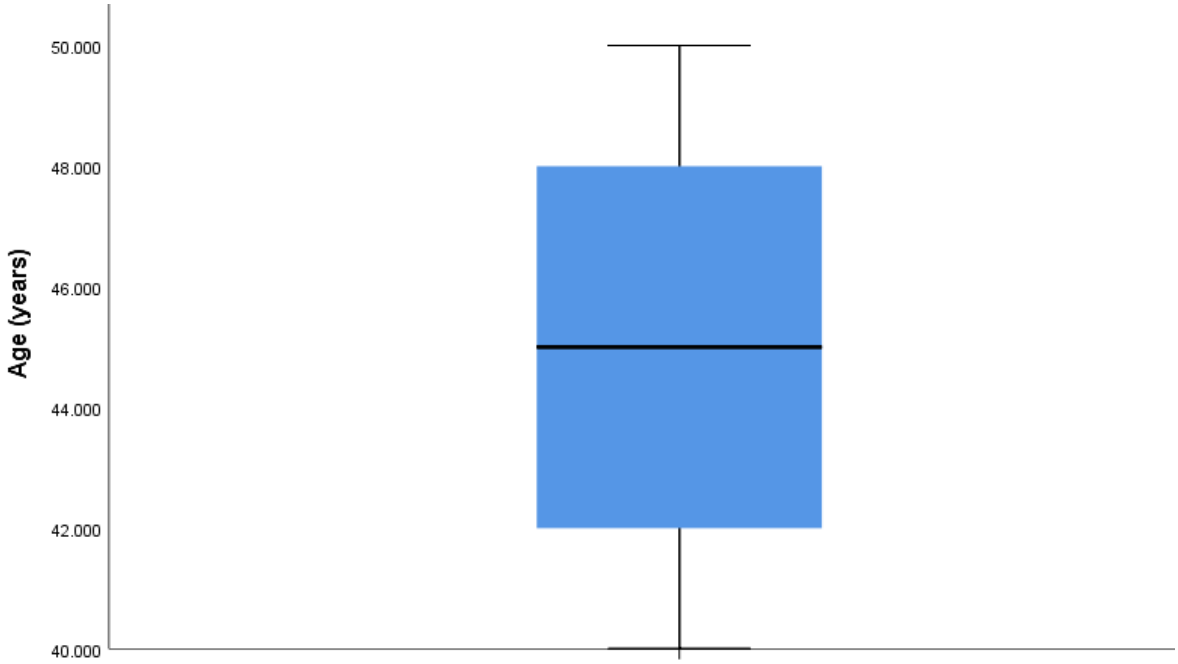


Figure V.2. Boxplot showing no outliers for age (years). The box represents the interquartile range which contains the middle 50% of ages. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

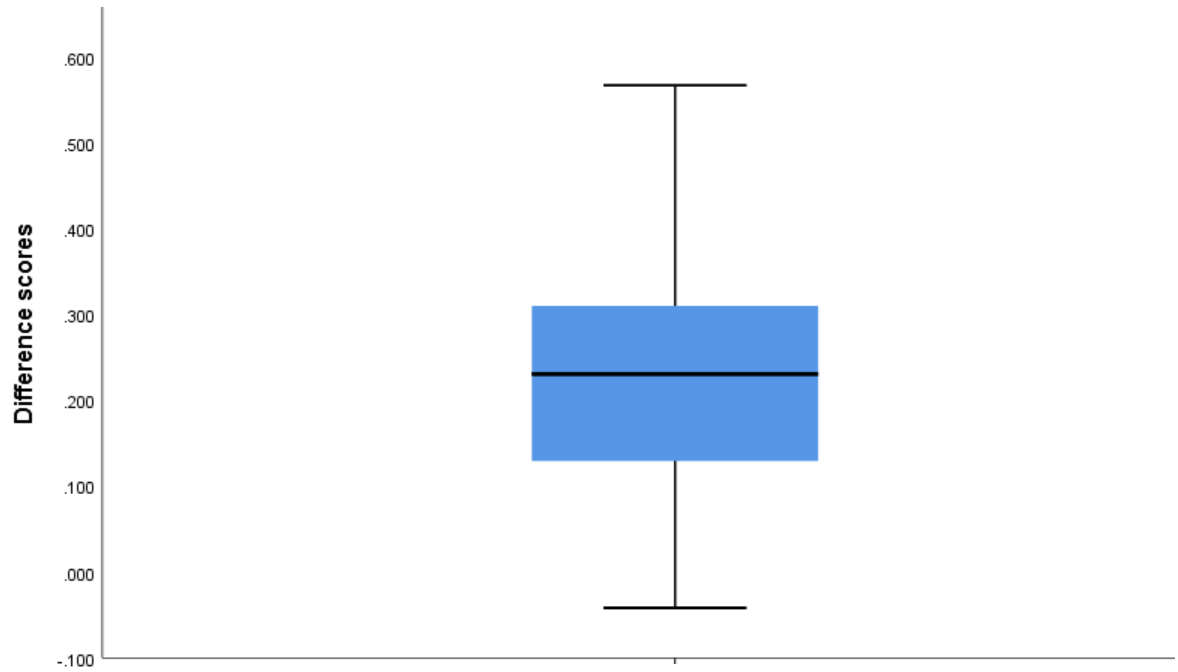


Figure V.3. Boxplot showing no outliers for normalised difference scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

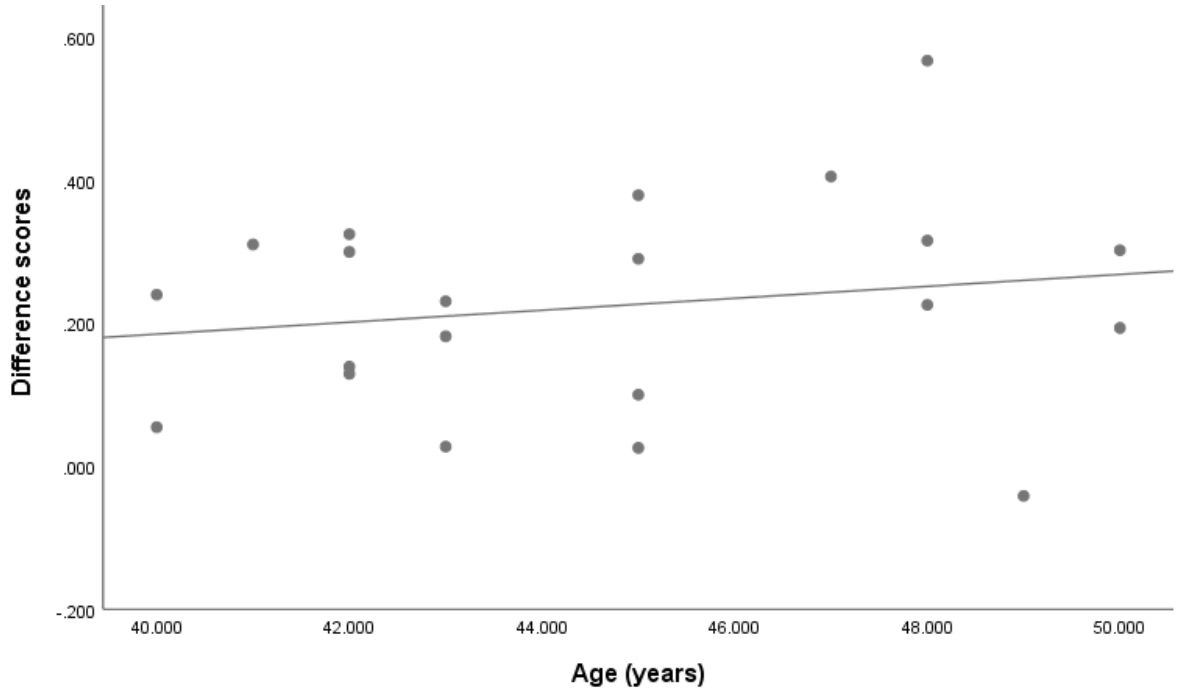


Figure V.4. Scatterplot of age (years) x normalised difference scores. The linear regression line is y = -0.15+8.36E-3*x, R^2 = 0.034.

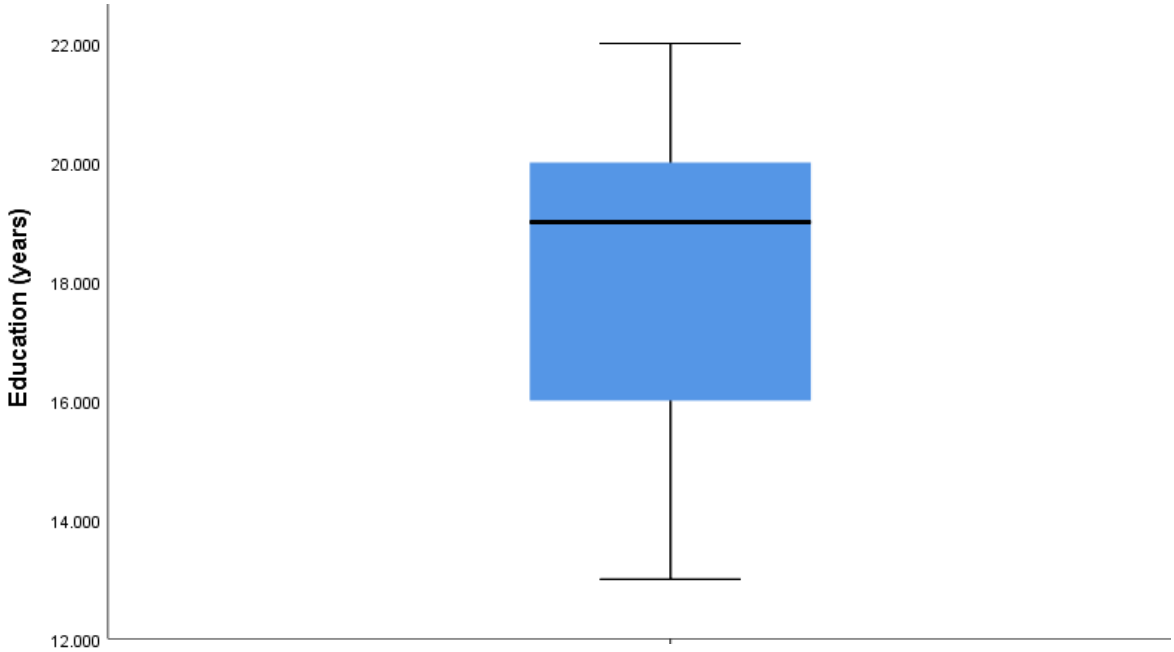


Figure V.5. Boxplot showing no outliers for education (years). The box represents the interquartile range which contains the middle 50% of values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

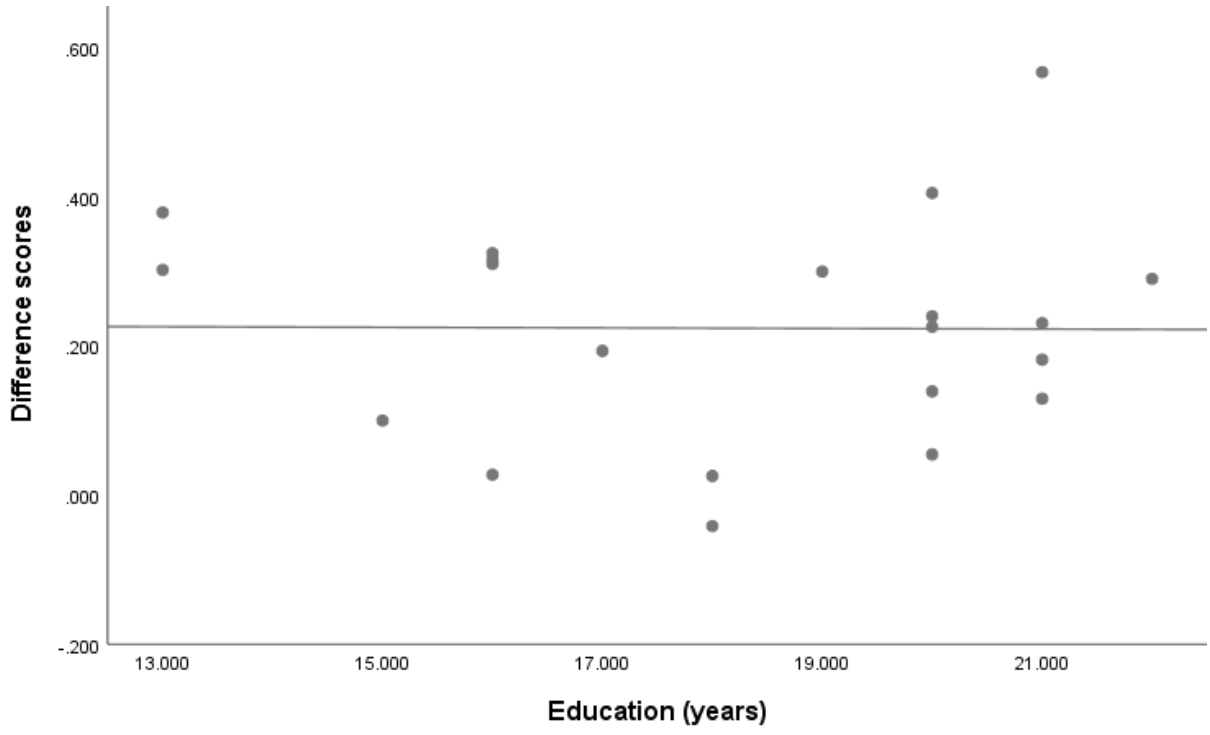


Figure V.6. Scatterplot of education (years) x normalised difference scores. The linear regression line is y = 0.23-3.91E-4*x, R^2 = 5.255E-5.

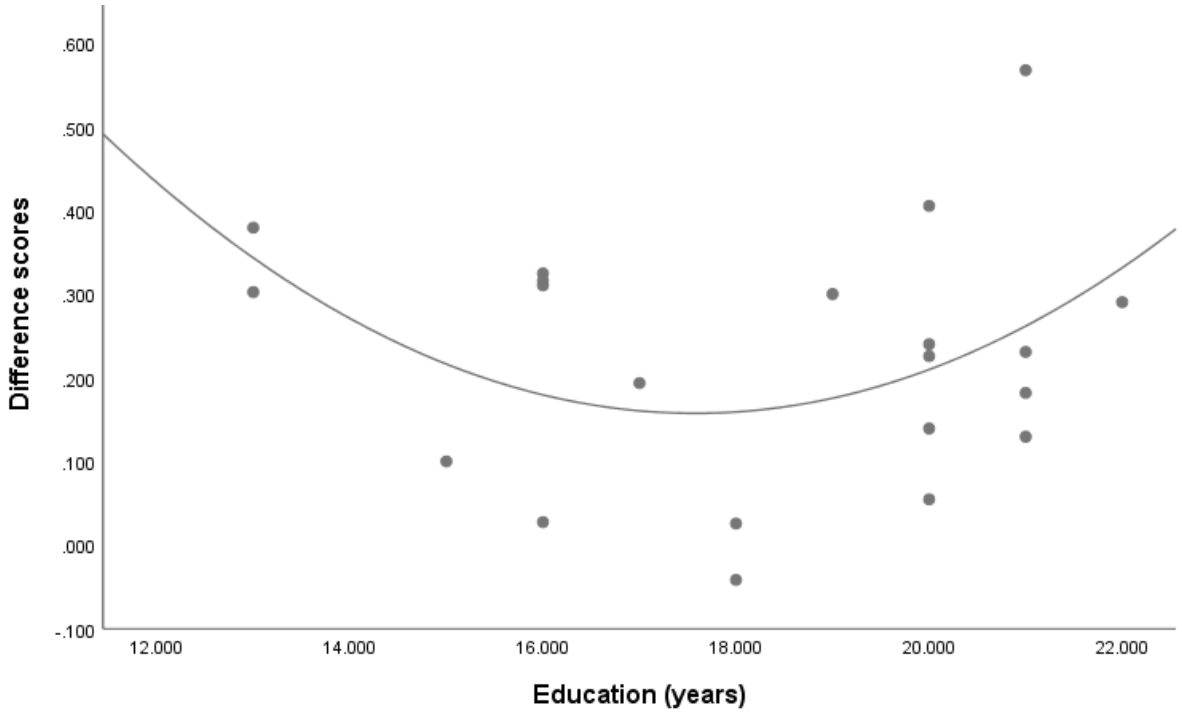


Figure V.7. Scatterplot of education (years) x normalised difference scores. Quadratic regression line is y = 2.9-0.31*x+8.88E-3*x^2, R^2 = 0.162.

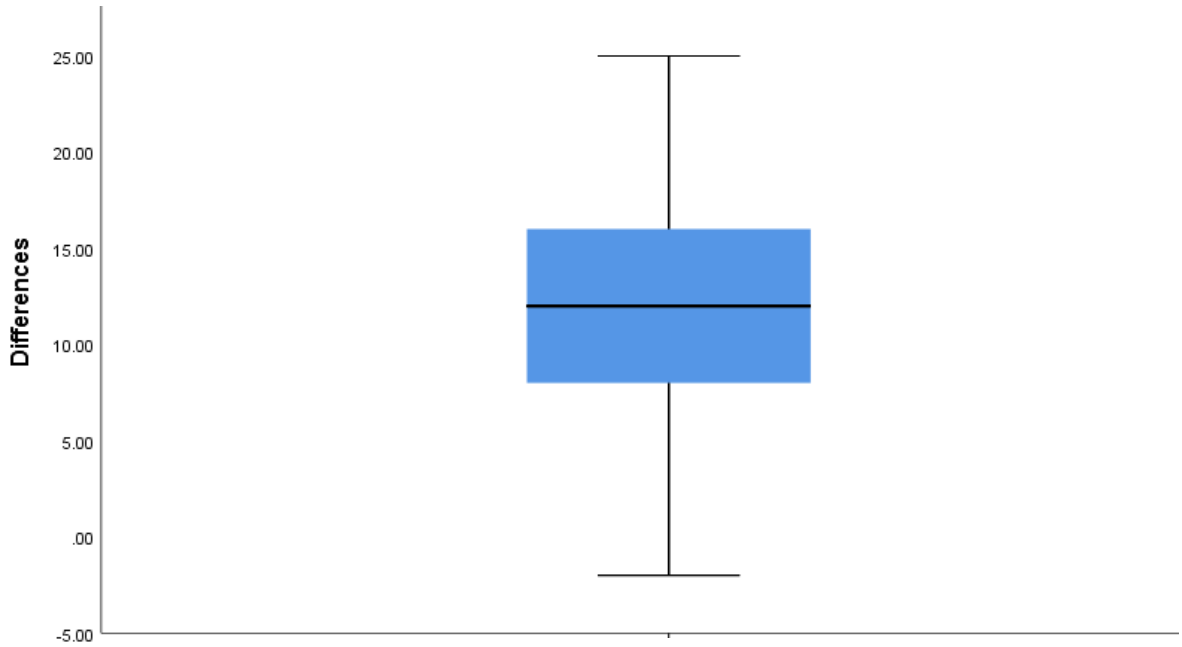


Figure V.8. Boxplot showing no outliers in the differences between pre- and post-training scores. The box represents the interquartile range which contains the middle 50% of difference values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

VI. Chapter 4: figures for tests of assumptions

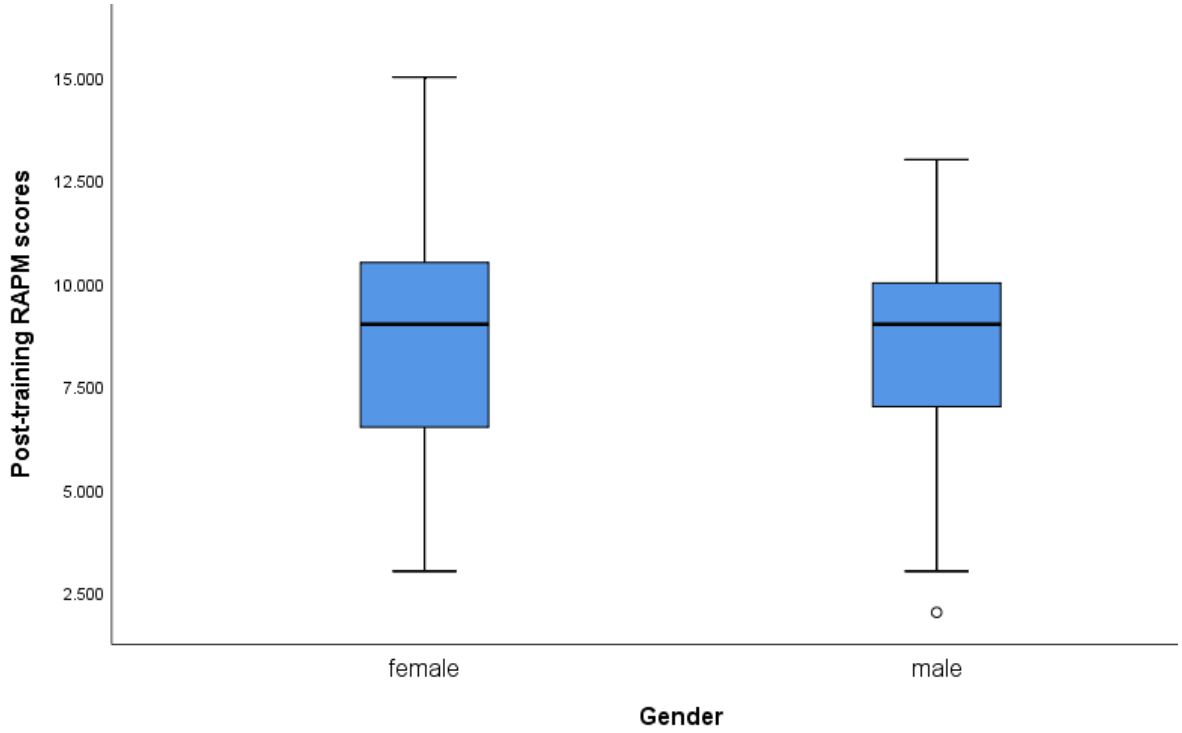


Figure VI.1. Boxplots showing no significant outliers for female and male post-training RAPM scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

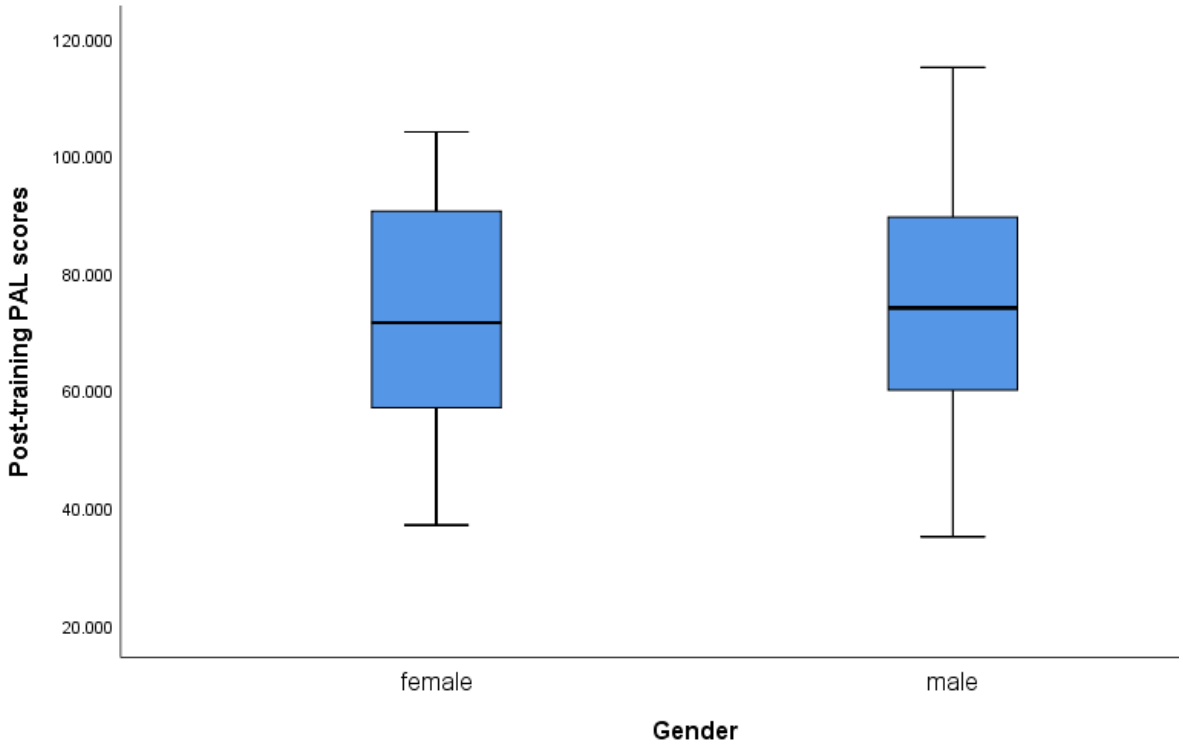


Figure VI.2. Boxplots showing no outliers for female and male post-training PAL scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

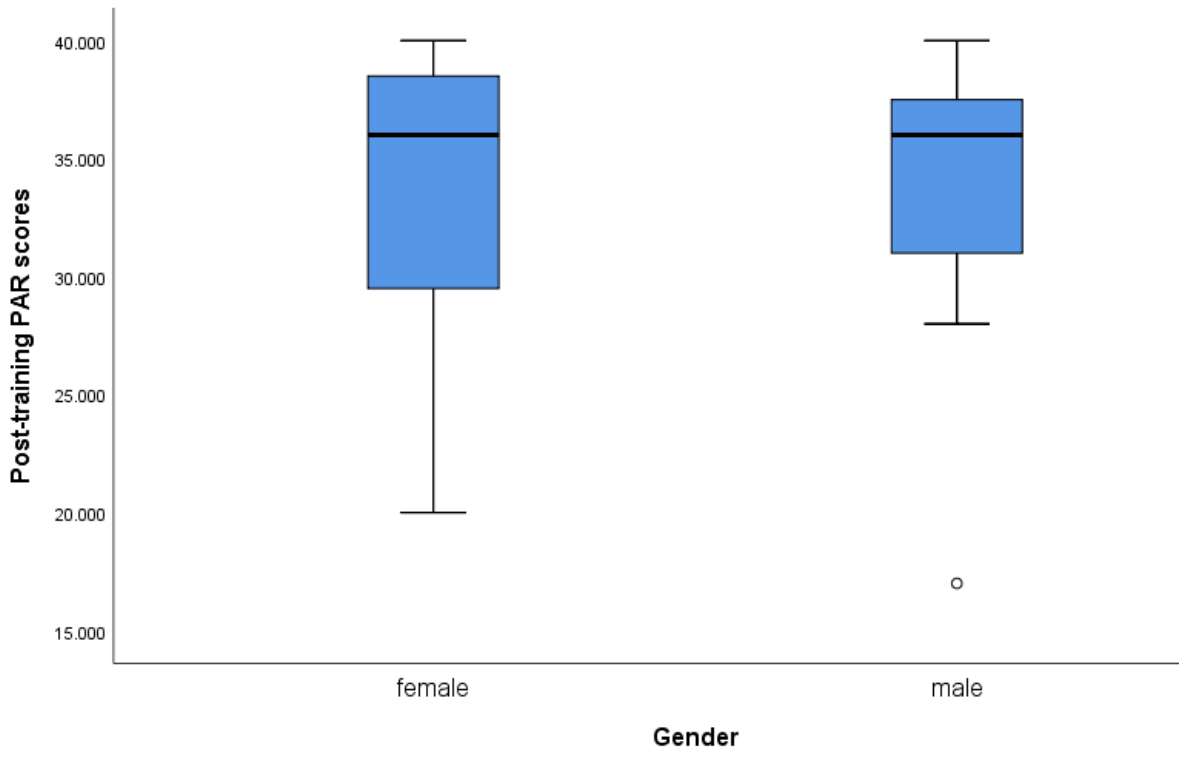


Figure VI.3. Boxplots showing no significant outliers for female and male post-training PAR scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

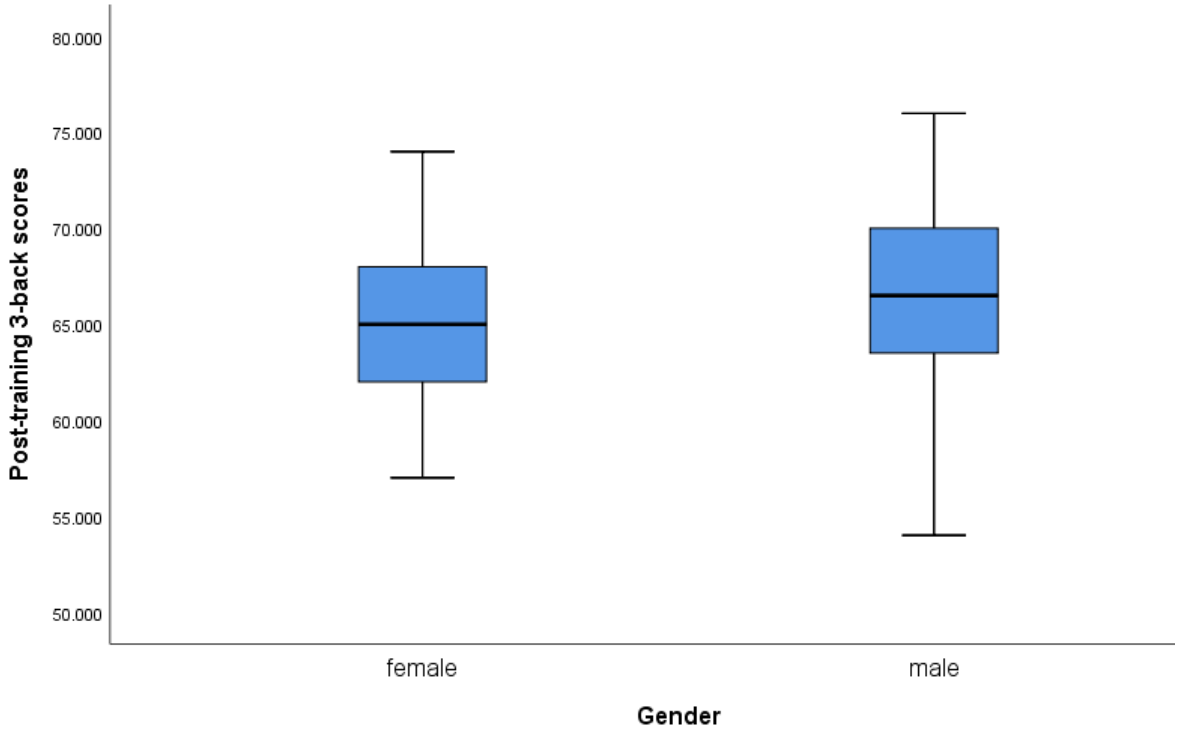


Figure VI.4. Boxplots showing no outliers for female and male post-training 3-back scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

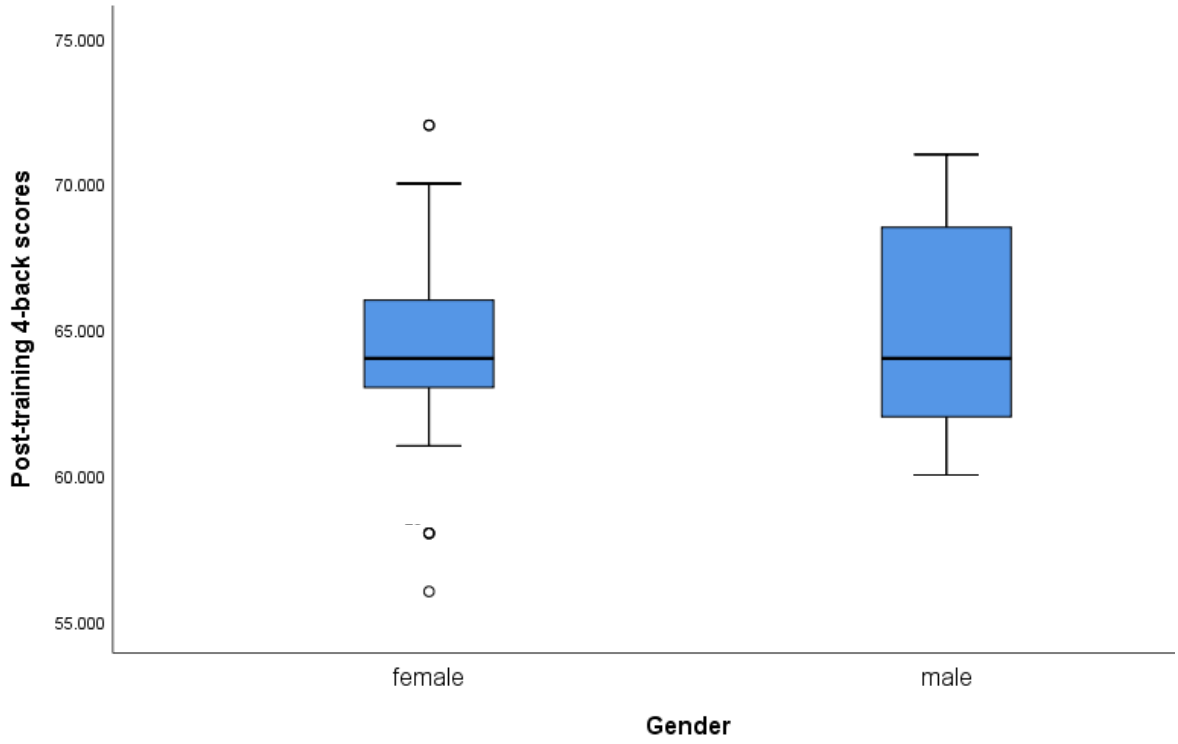


Figure VI.5. Boxplots showing no significant outliers for female and male post-training 4-back scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

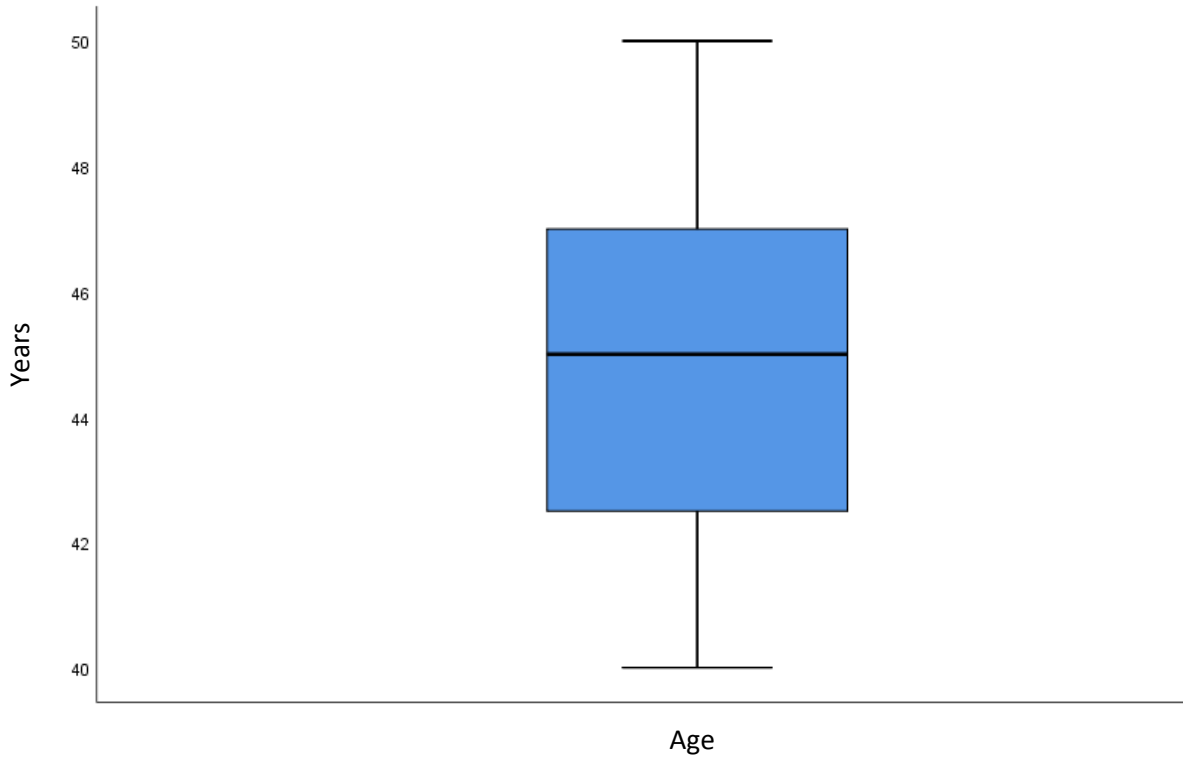


Figure VI.6. Boxplot showing no outliers for age (years). The box represents the interquartile range which contains the middle 50% of ages. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

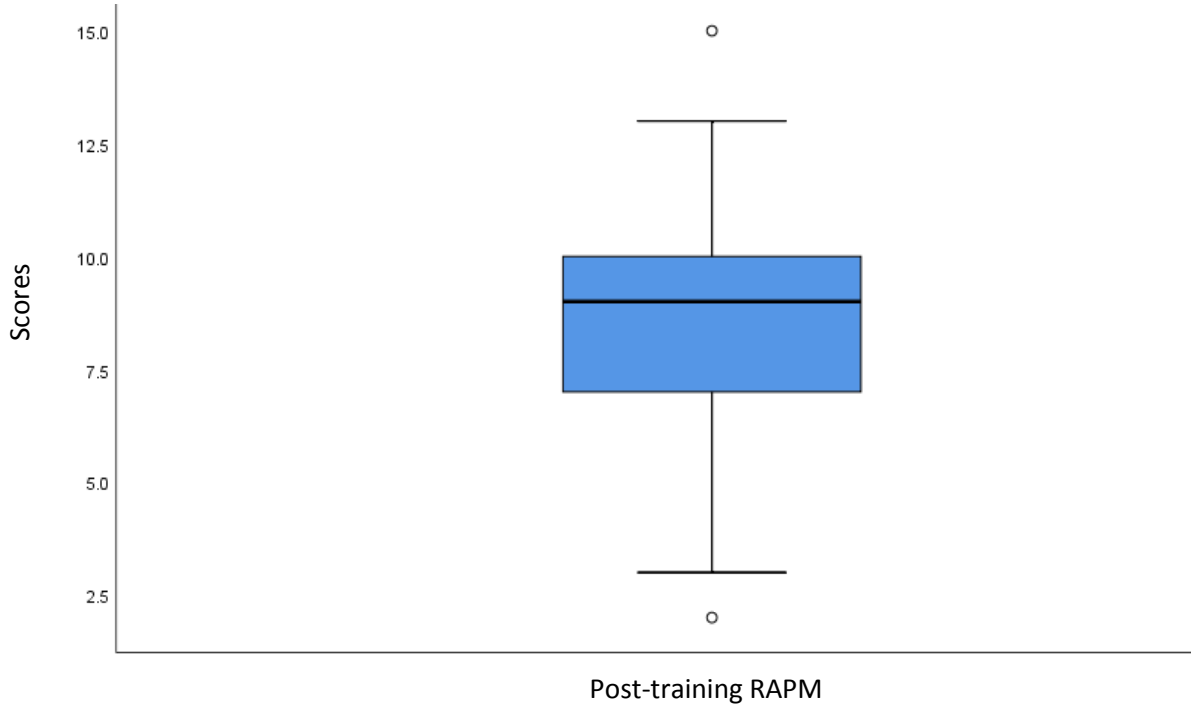


Figure VI.7. Boxplot showing no significant outliers for post-training RAPM scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

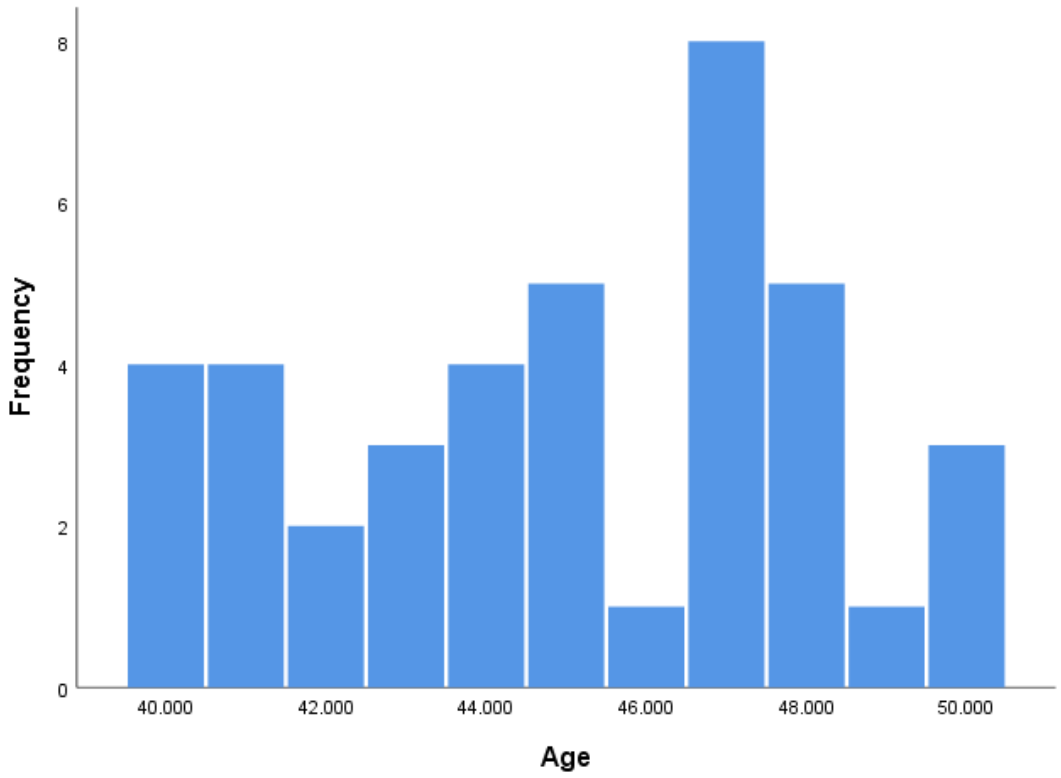


Figure VI.8. Histogram showing the distribution of age (years).

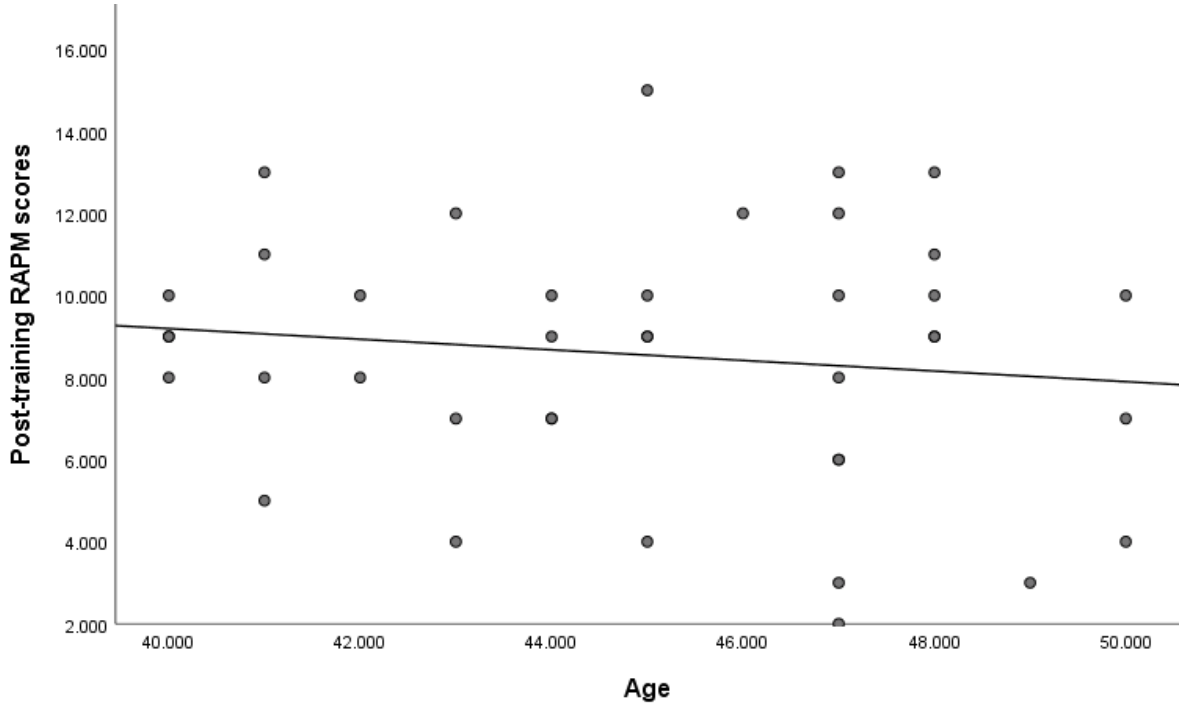


Figure VI.9. Scatterplot of age (years) x post-training RAPM scores. The linear regression line is y = 14.37-0.13*x, R^2 = 0.017.

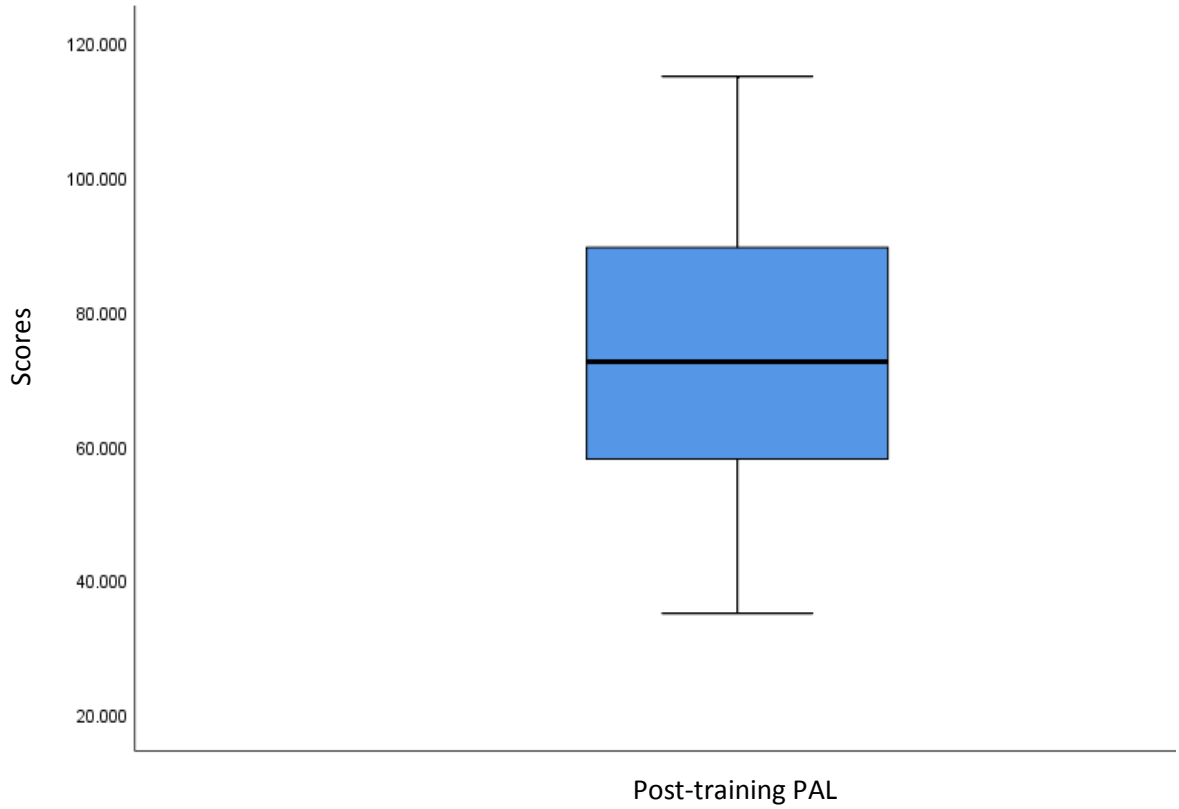


Figure VI.10. Boxplot showing no outliers for post-training PAL scores. The box represents the interquartile range which contains the middle 50% of values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

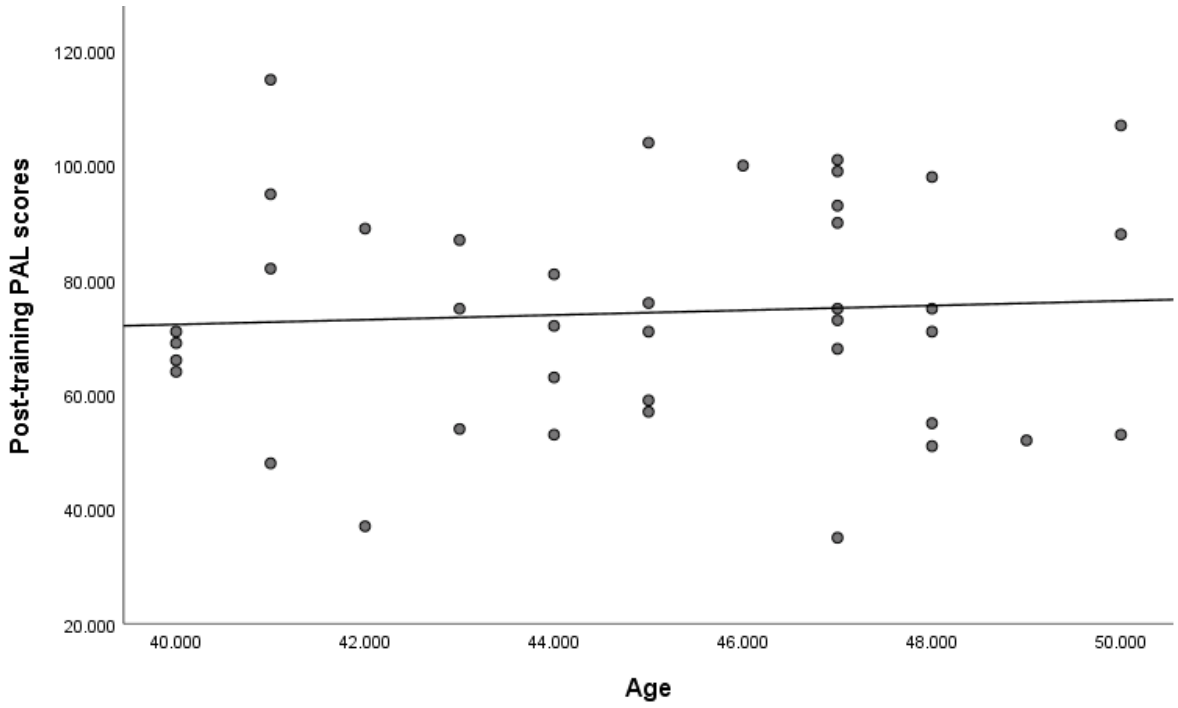


Figure VI.11. Scatterplot of age (years) x post-training PAL scores. The linear regression line is y = 55.76+0.41*x, R^2 = 0.004.

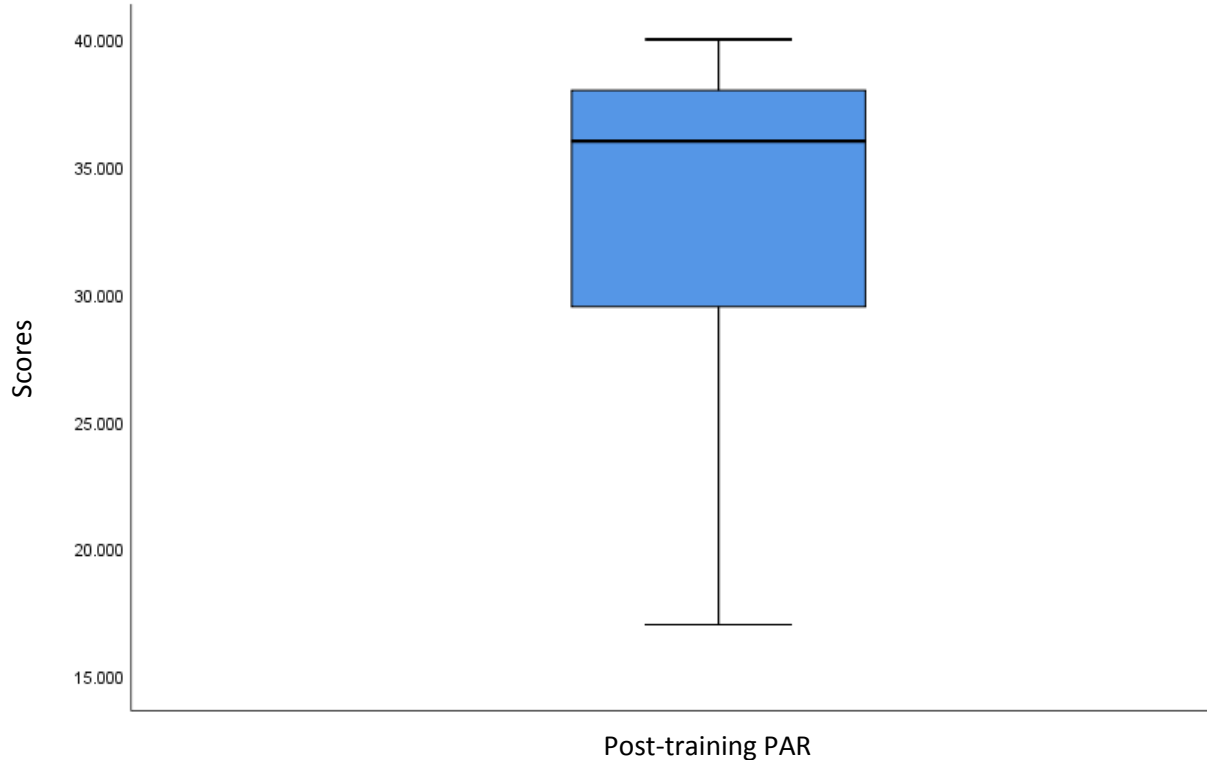


Figure VI.12. Boxplot showing no outliers for post-training PAR scores. The box represents the interquartile range which contains the middle 50% of values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

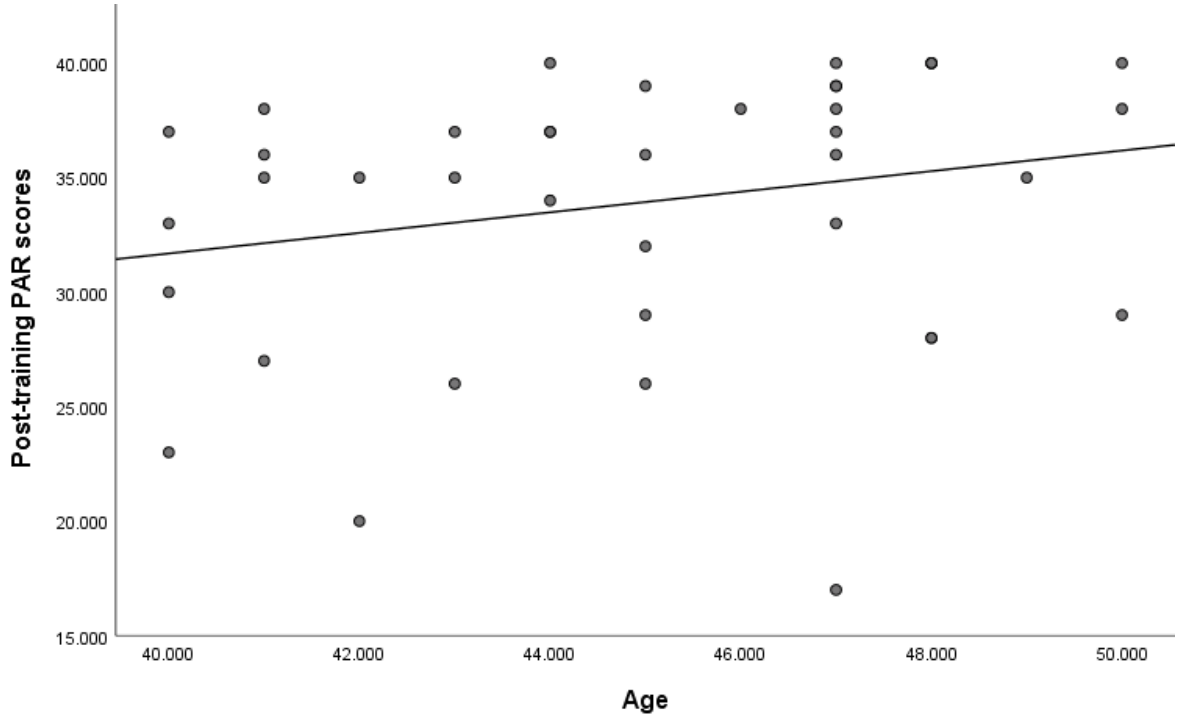


Figure VI.13. Scatterplot of age (years) x post-training PAR scores. The linear regression line is y = 13.71+0.45*x, R^2 = 0.055.

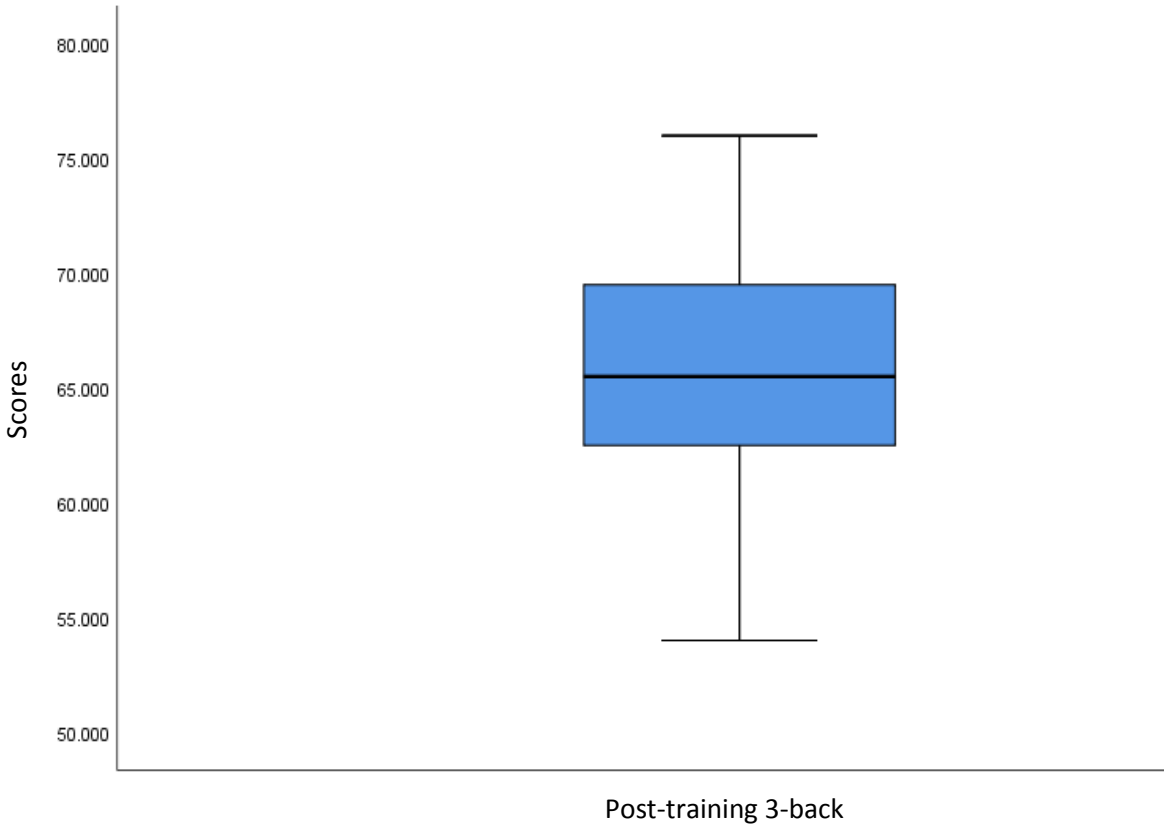


Figure VI.14. Boxplot showing no outliers for post-training 3-back scores. The box represents the interquartile range which contains the middle 50% of values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

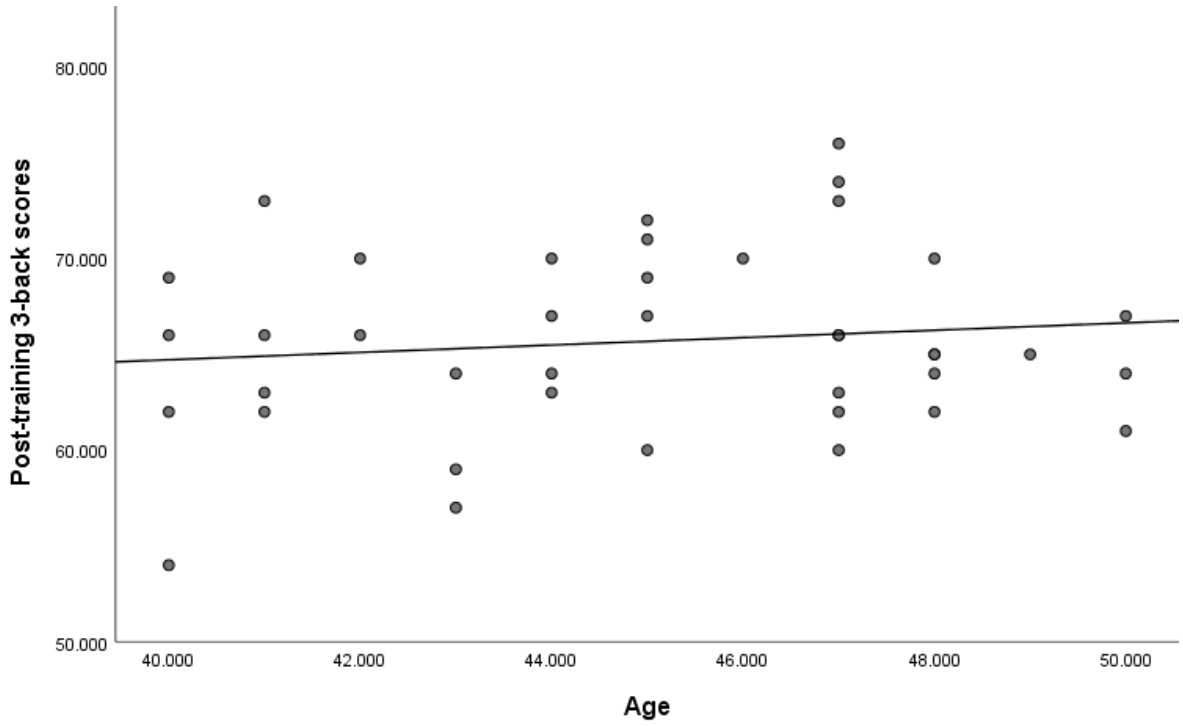


Figure VI.15. Scatterplot of age (years) x post-training 3-back scores. The linear regression line is y = 57.01+0.19*x, R^2 = 0.015.

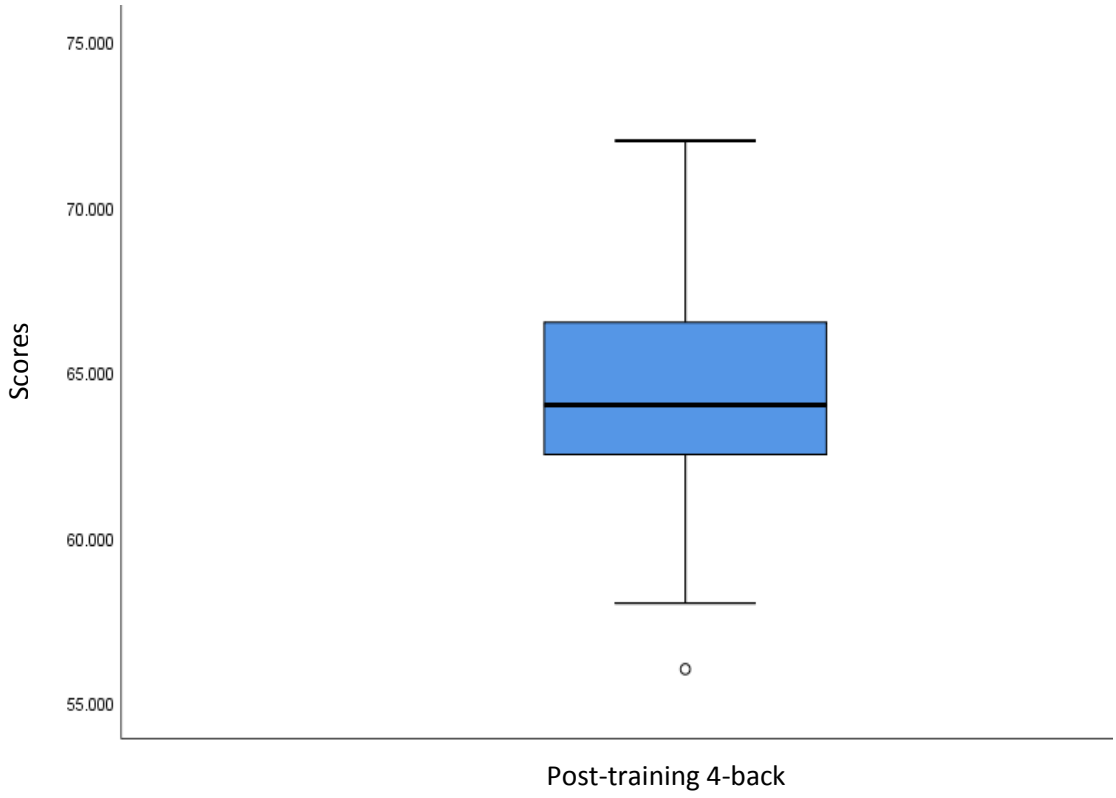


Figure VI.16. Boxplot showing no significant outliers for post-training 4-back scores. The box represents the interquartile range which contains the middle 50% of values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

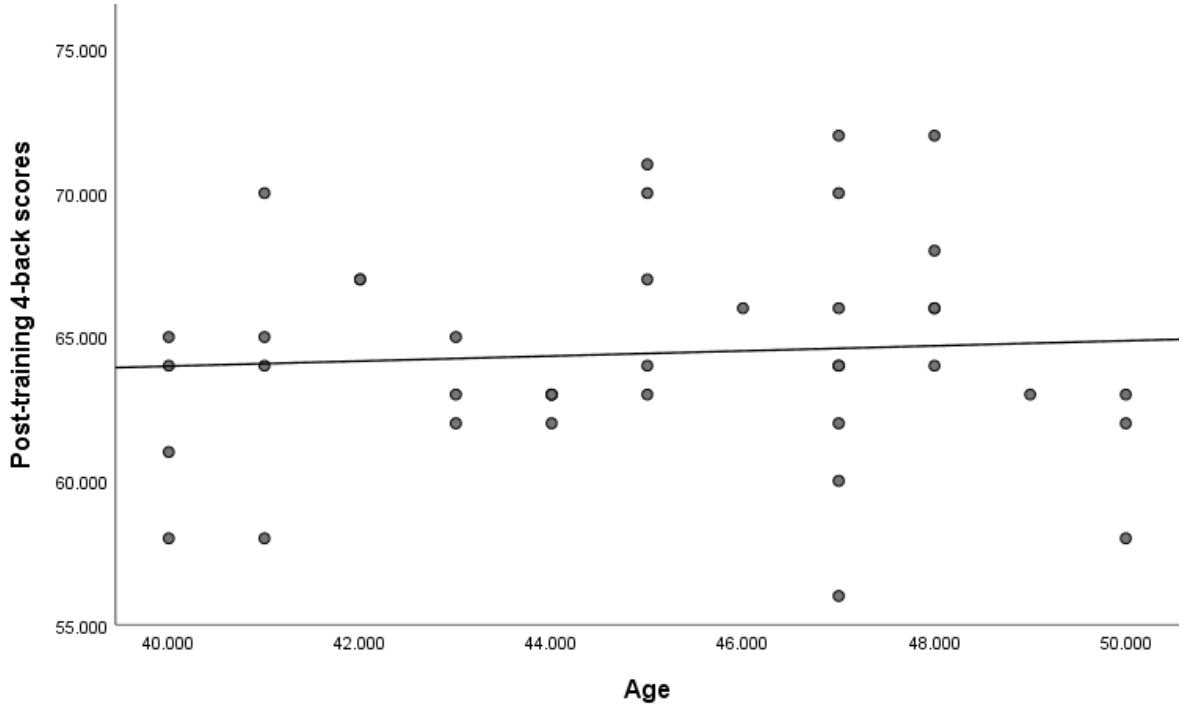


Figure VI.17. Scatterplot of age (years) x post-training 4-back scores. The linear regression line is y = 60.45+0.09*x, R^2 = 0.005.

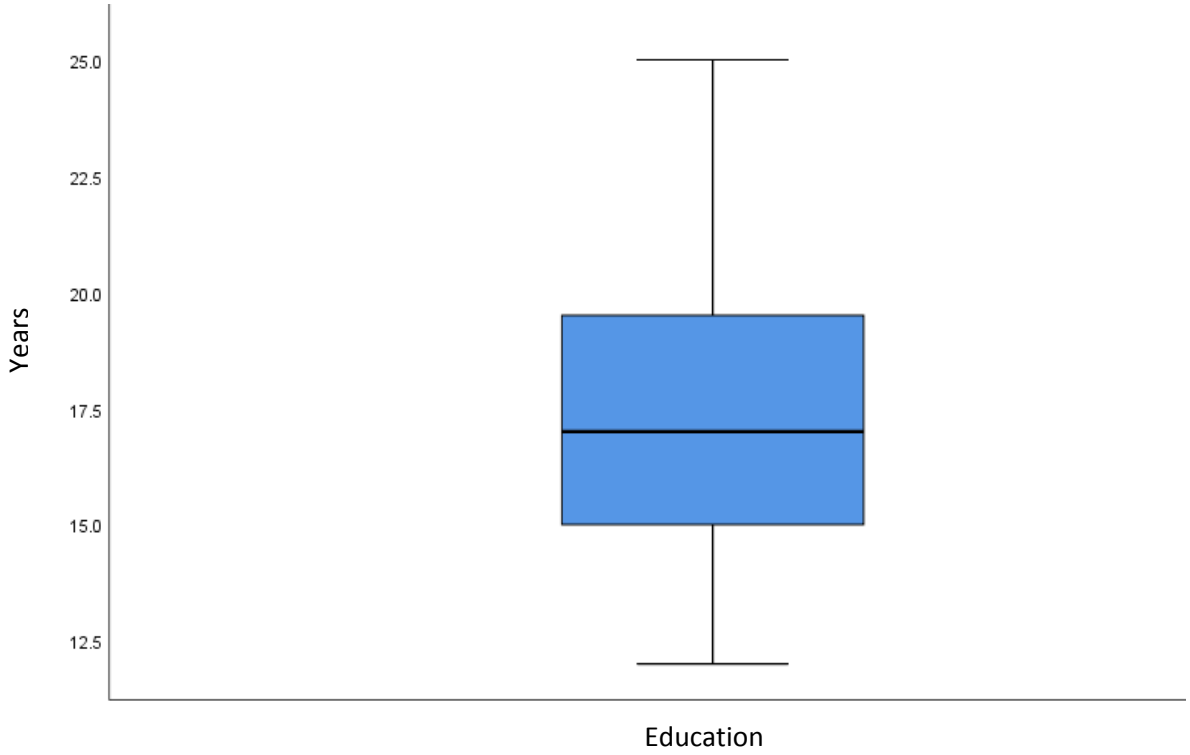


Figure VI.18. Boxplot showing no outliers for education (years). The box represents the interquartile range which contains the middle 50% of values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

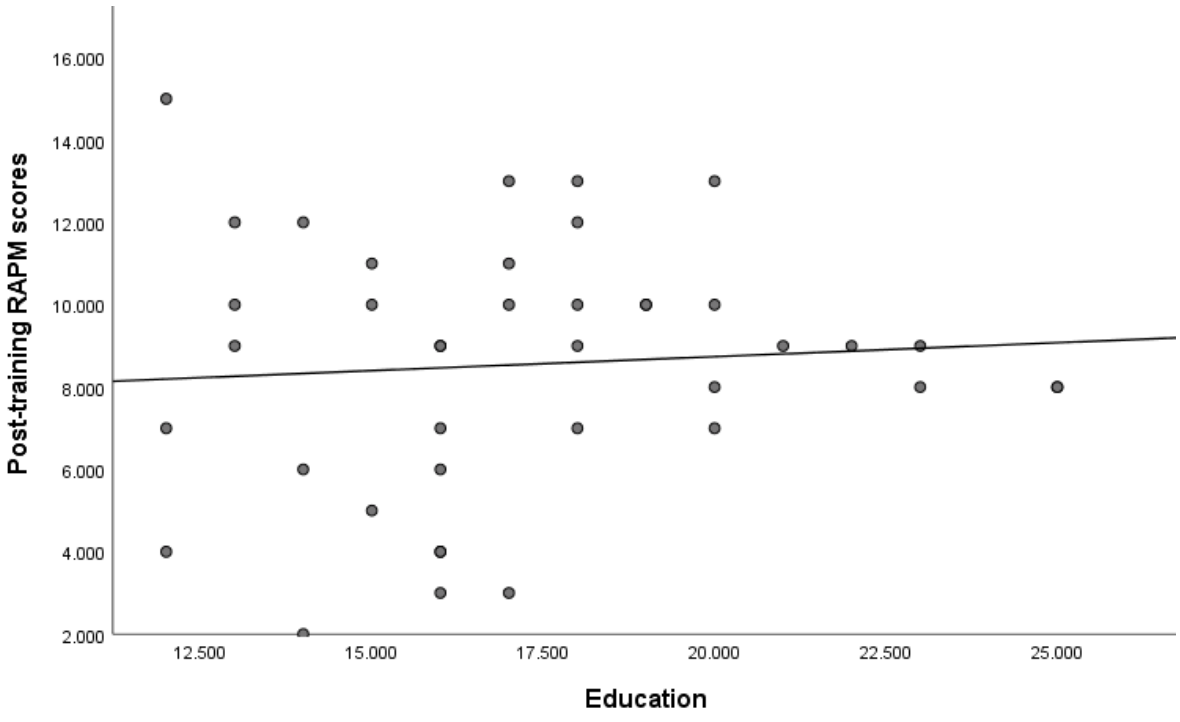


Figure VI.19. Scatterplot of education (years) x post-training RAPM scores. The linear regression line is y = 7.38+0.07*x, R^2 = 0.006.

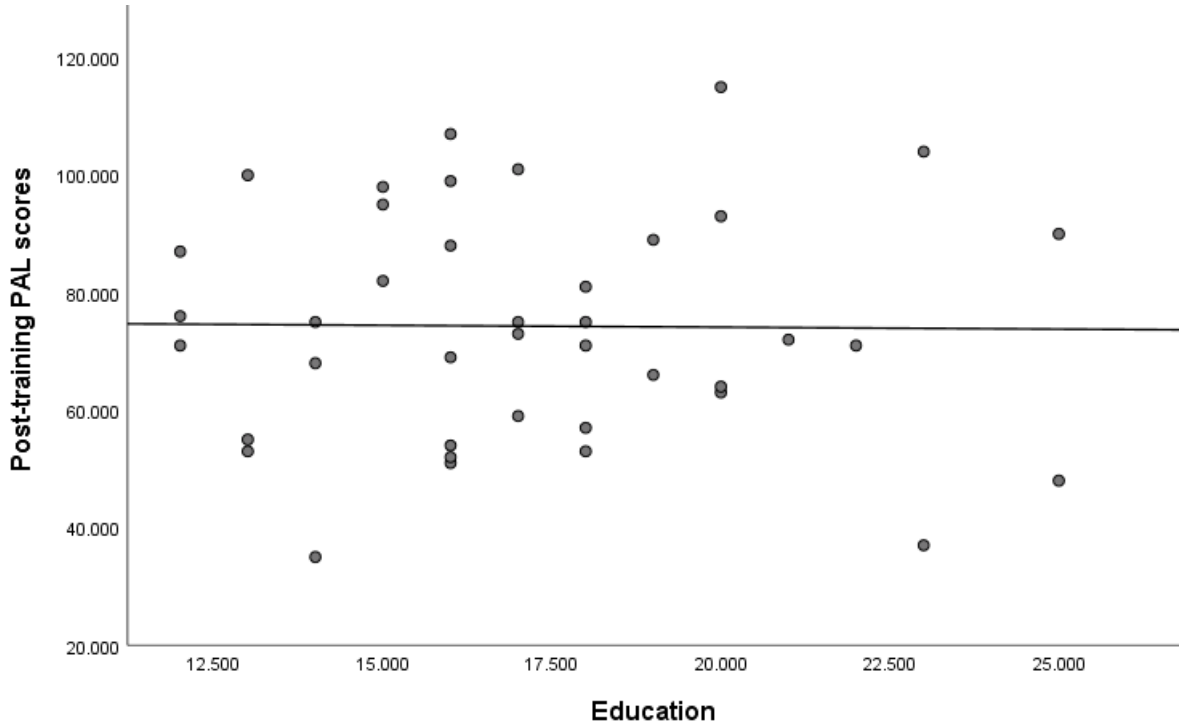


Figure VI.20. Scatterplot of education (years) x post-training PAL scores. The linear regression line is y = 75.42-0.06*x, R^2 = 1.274E-4.

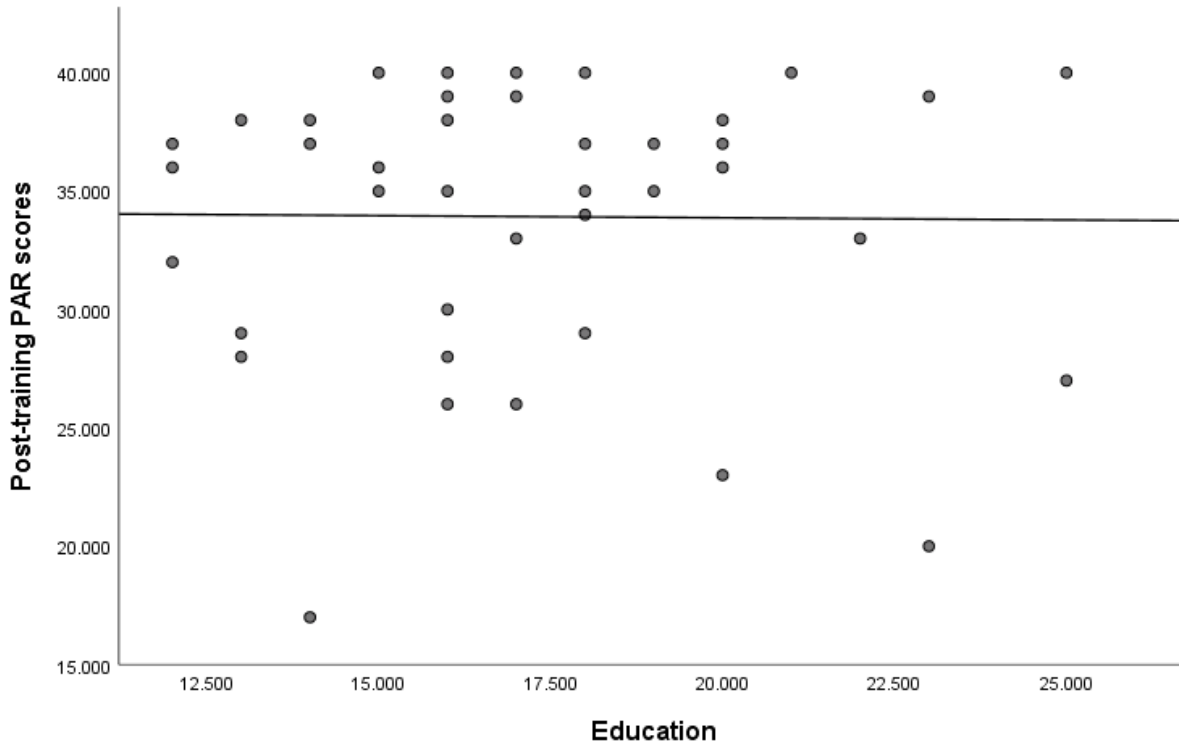


Figure VI.21. Scatterplot of education (years) x post-training PAR scores. The linear regression line is y = 34.24-0.02*x, R^2 = 1.129E-4.

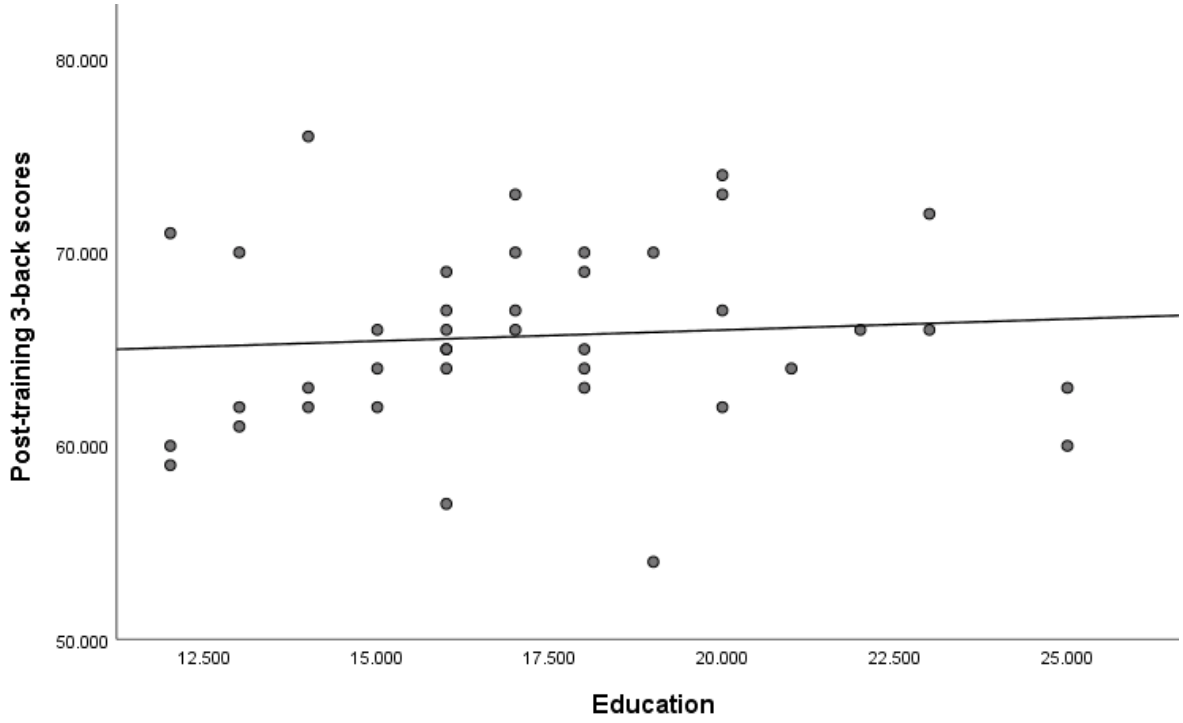


Figure VI.22. Scatterplot of education (years) x post-training 3-back scores. The linear regression line is y = 63.72+0.11*x, R^2 = 0.007.

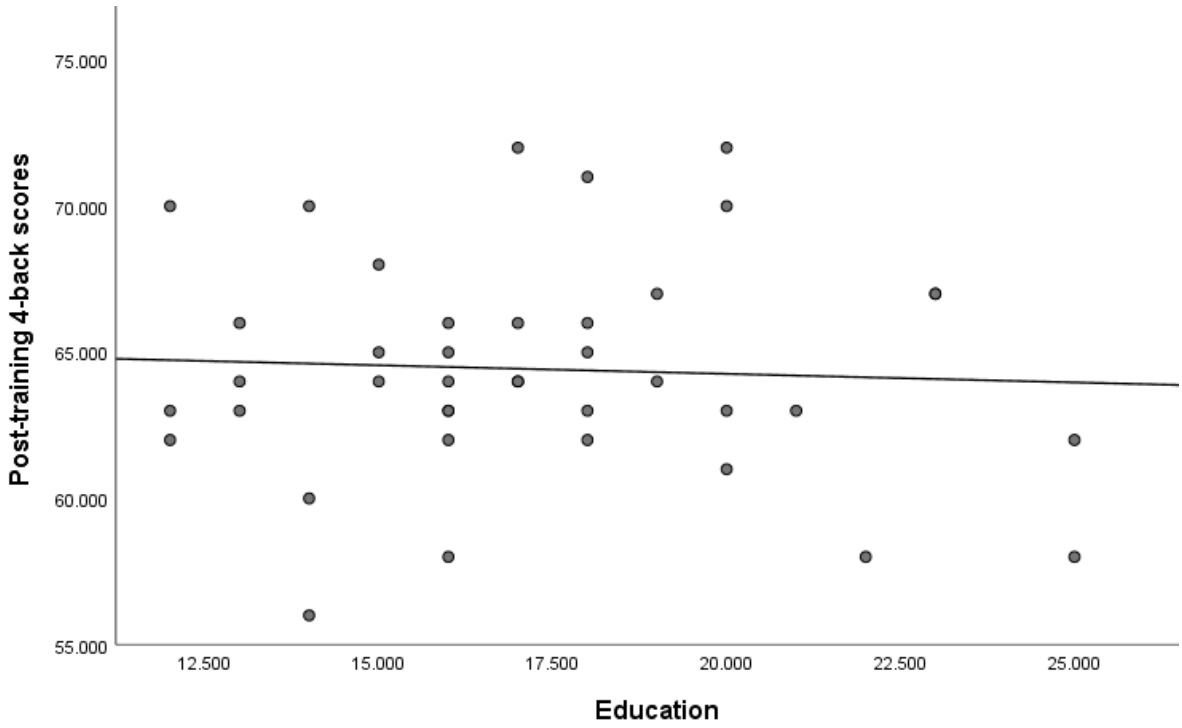


Figure VI.23. Scatterplot of education (years) x post-training 4-back scores. The linear regression line is y = 65.44-0.06*x, R^2 = 0.003.

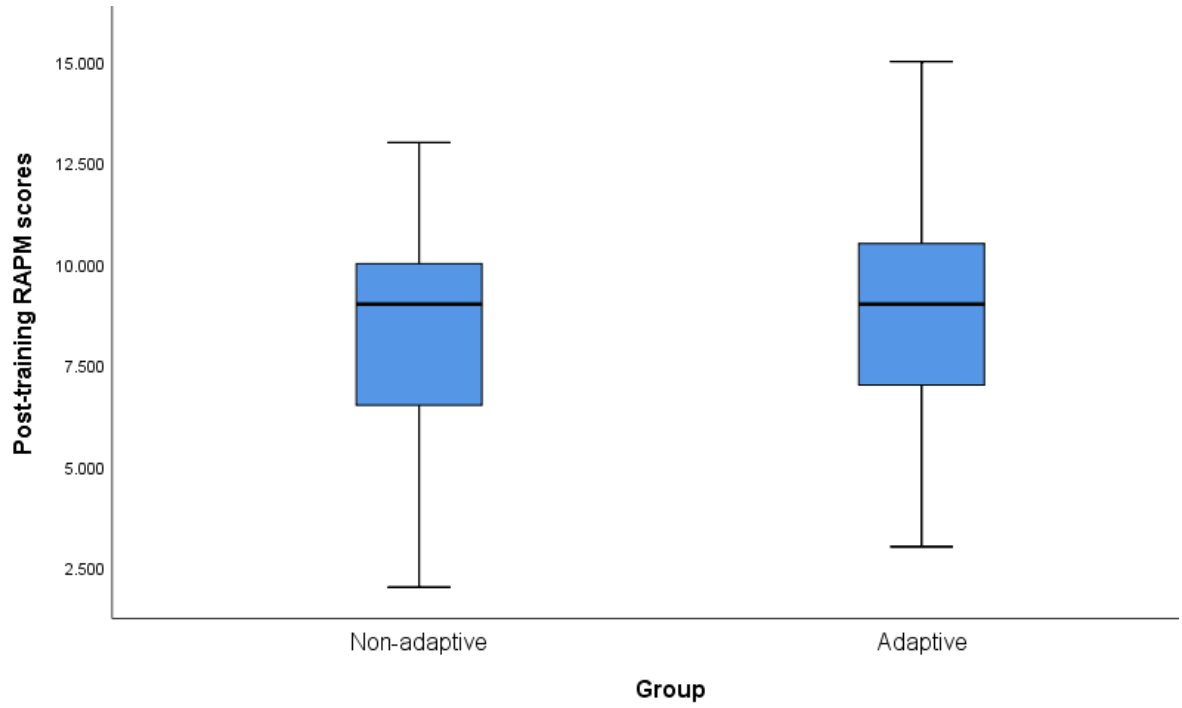


Figure VI.24. Boxplots showing no outliers for non-adaptive and adaptive post-training RAPM scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and

3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

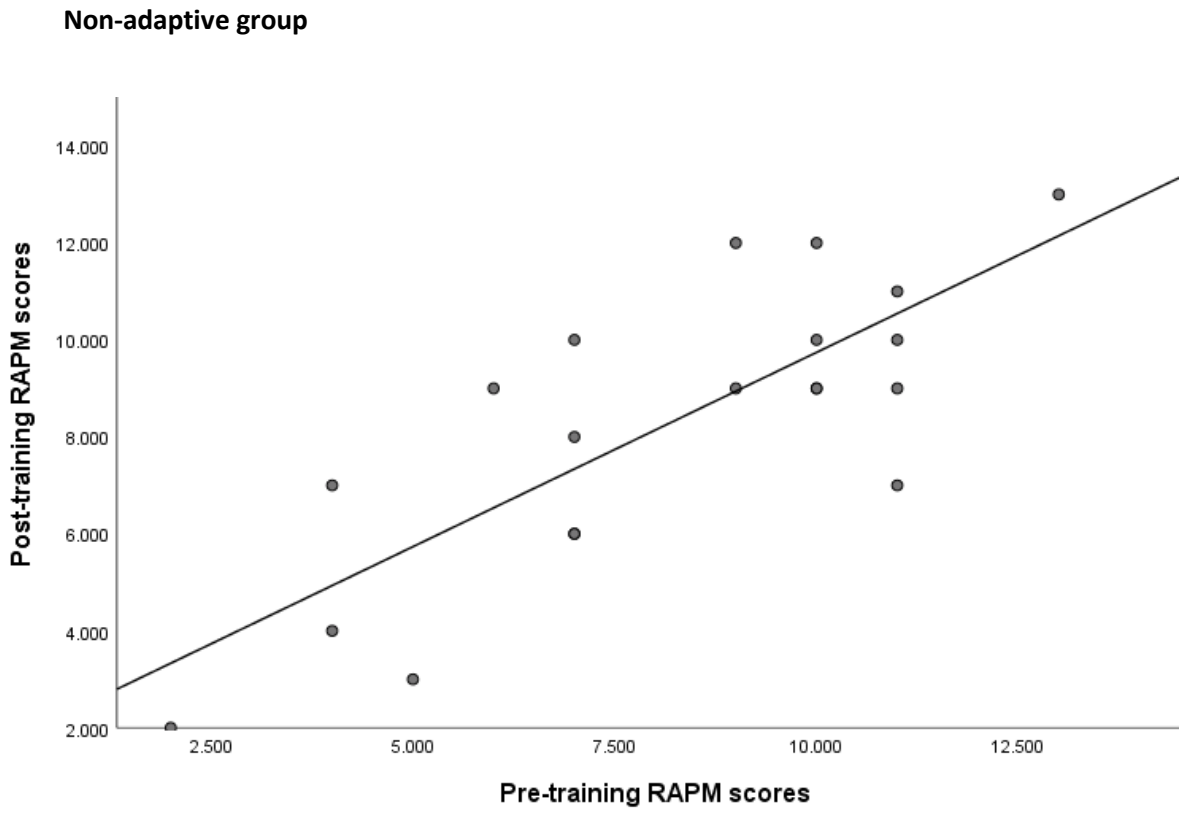


Figure VI.25. Scatterplot of pre-training RAPM scores x post-training RAPM scores for the non-adaptive group. The linear regression line is y = 1.73+0.80*x, R^2 = 0.623.

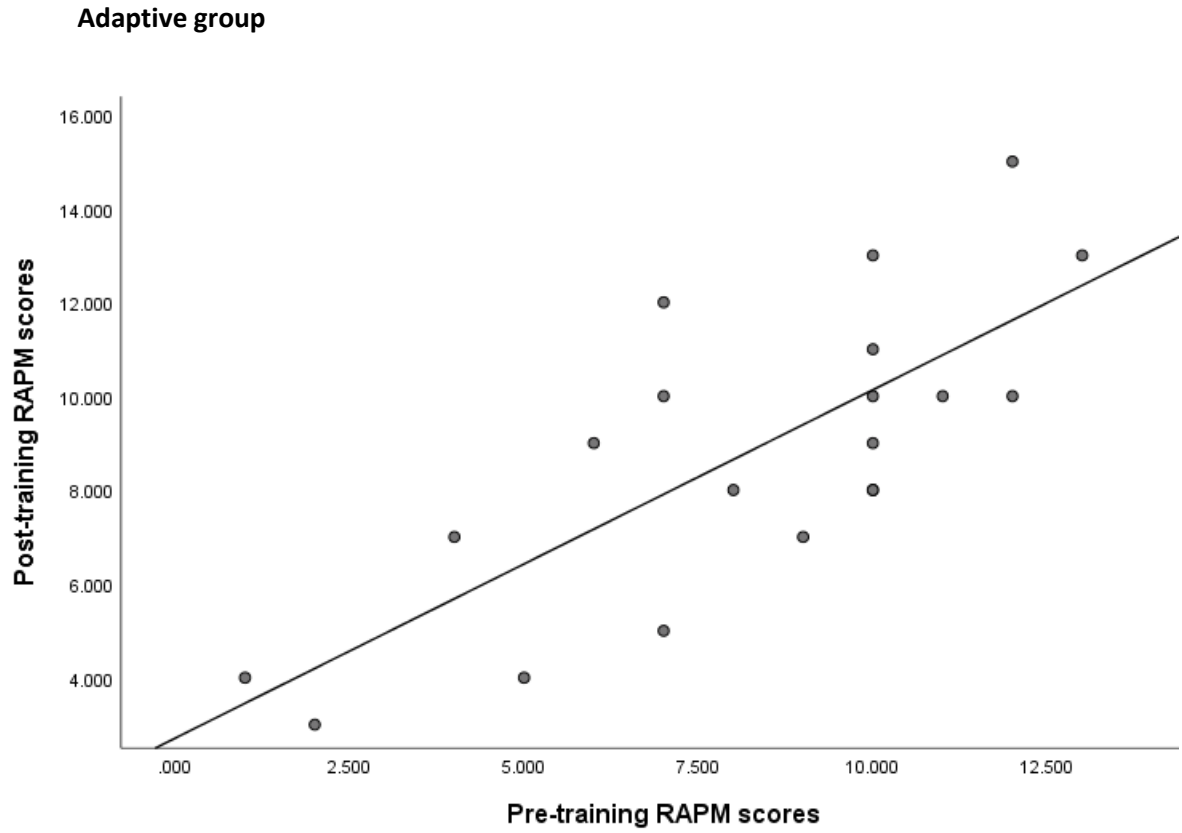


Figure VI.26. Scatterplot of pre-training RAPM scores x post-training RAPM scores for the adaptive group. The linear regression line is y = 2.71+0.74*x, R^2 = 0.579.

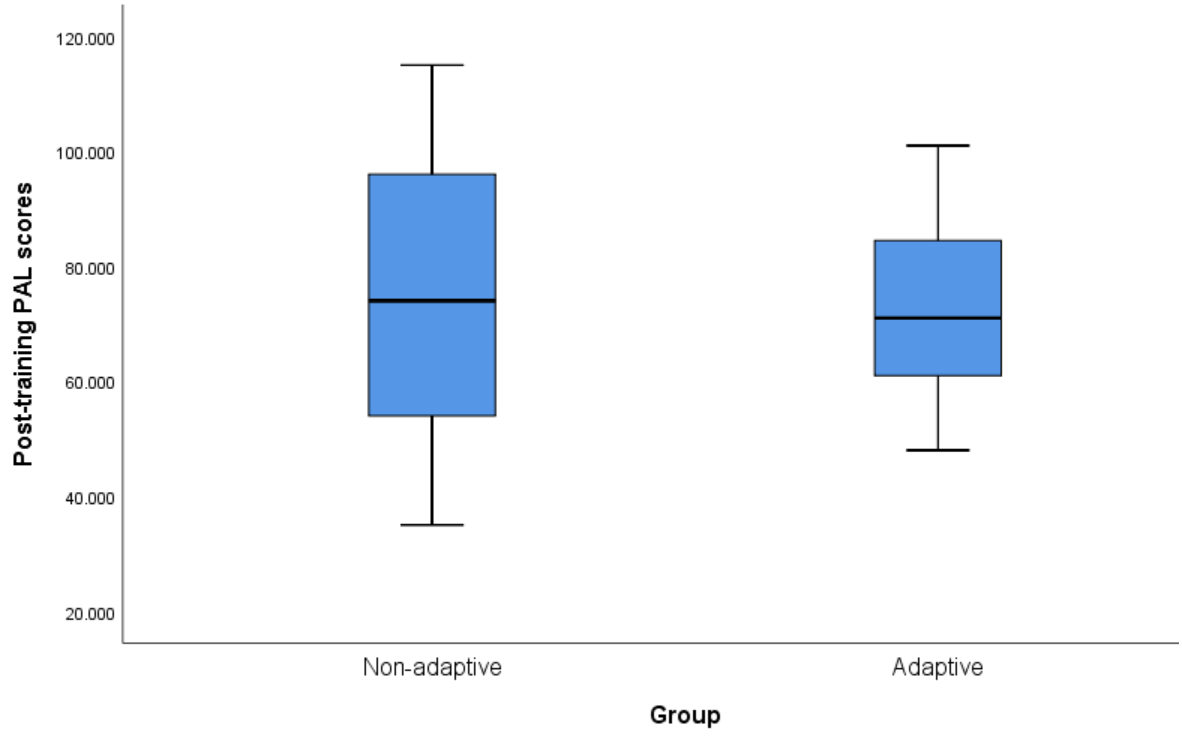


Figure VI.27. Boxplots showing no outliers for non-adaptive and adaptive post-training PAL scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

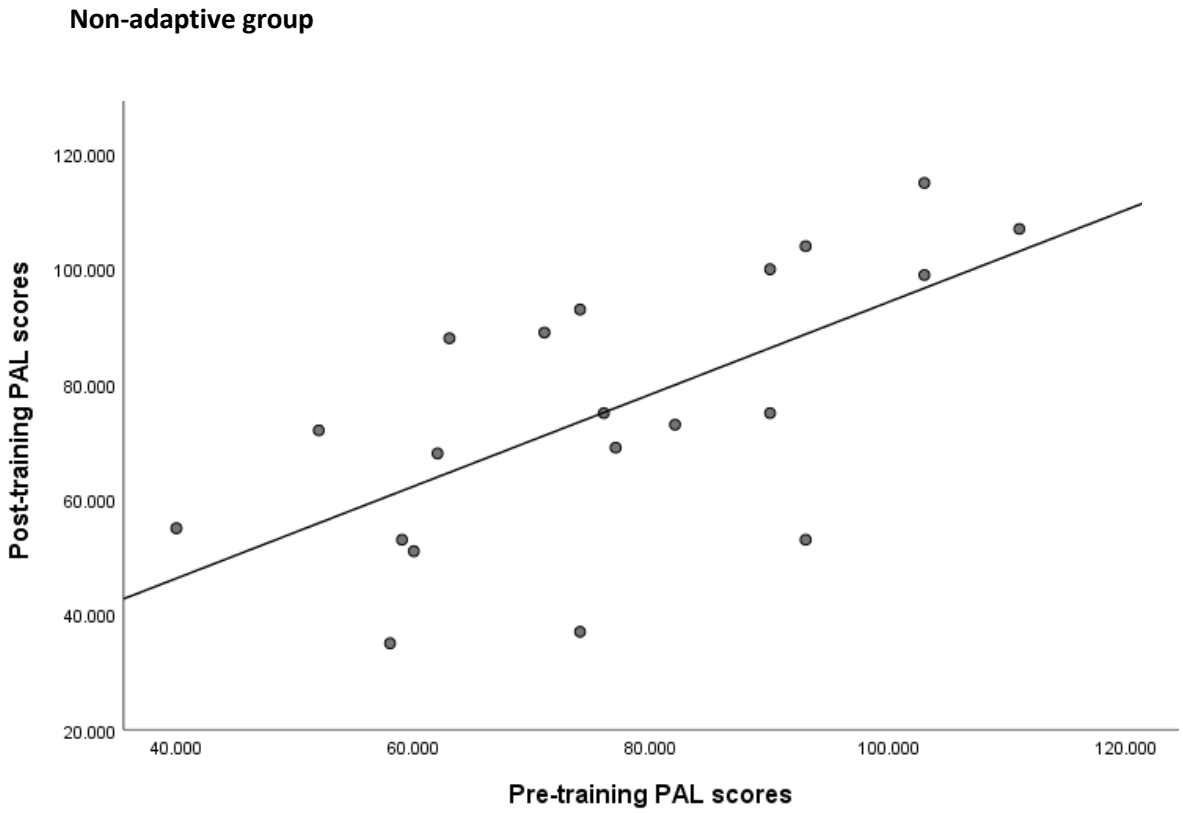


Figure VI.28. Scatterplot of pre-training PAL scores x post-training PAL scores for the non-adaptive group. The linear regression line is y = 14.27+0.80*x, R^2 = 0.419.

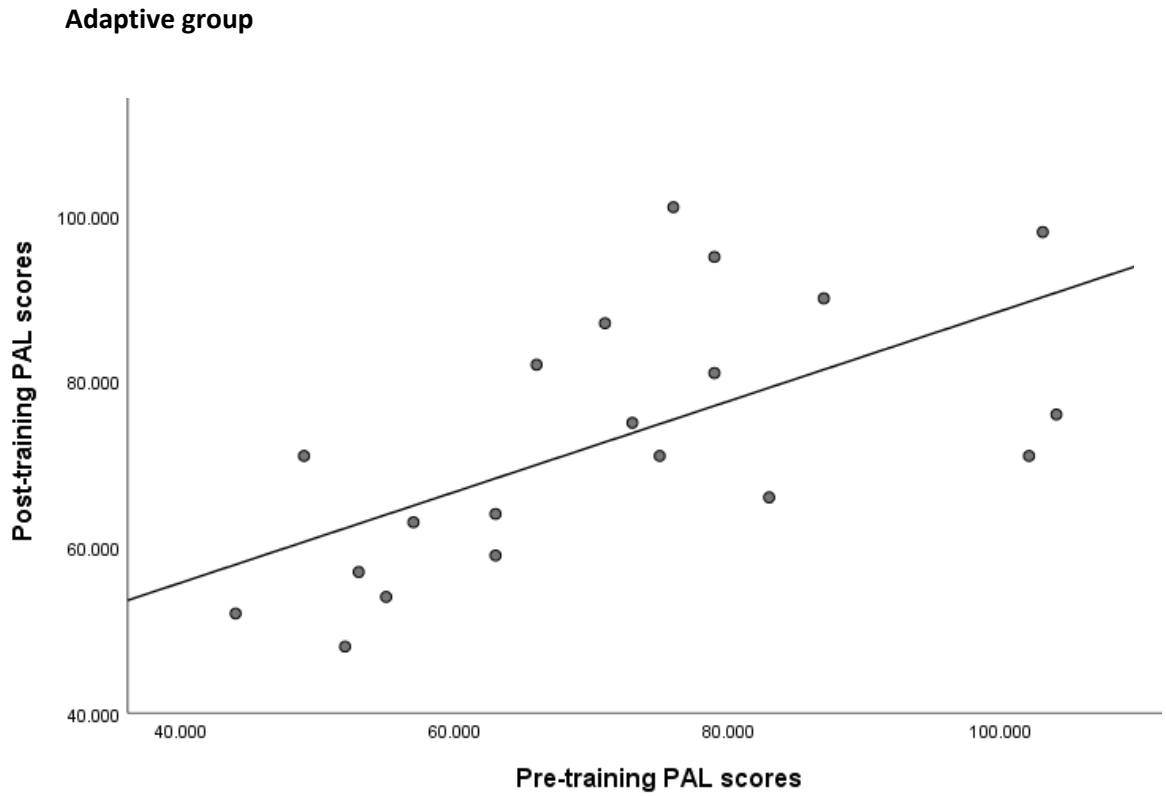


Figure VI.29. Scatterplot of pre-training PAL scores x post-training PAL scores for the adaptive group. The linear regression line is y = 33.85+0.55*x, R^2 = 0.394.

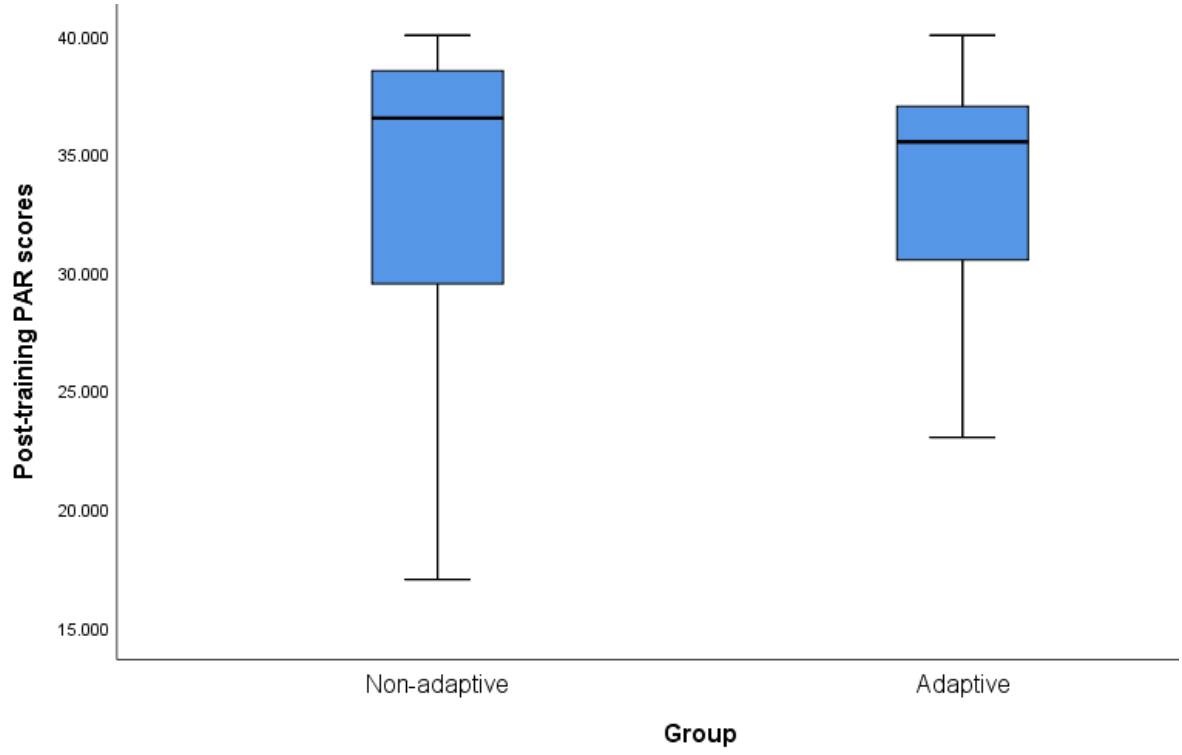


Figure VI.30. Boxplots showing no outliers for non-adaptive and adaptive post-training PAR scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

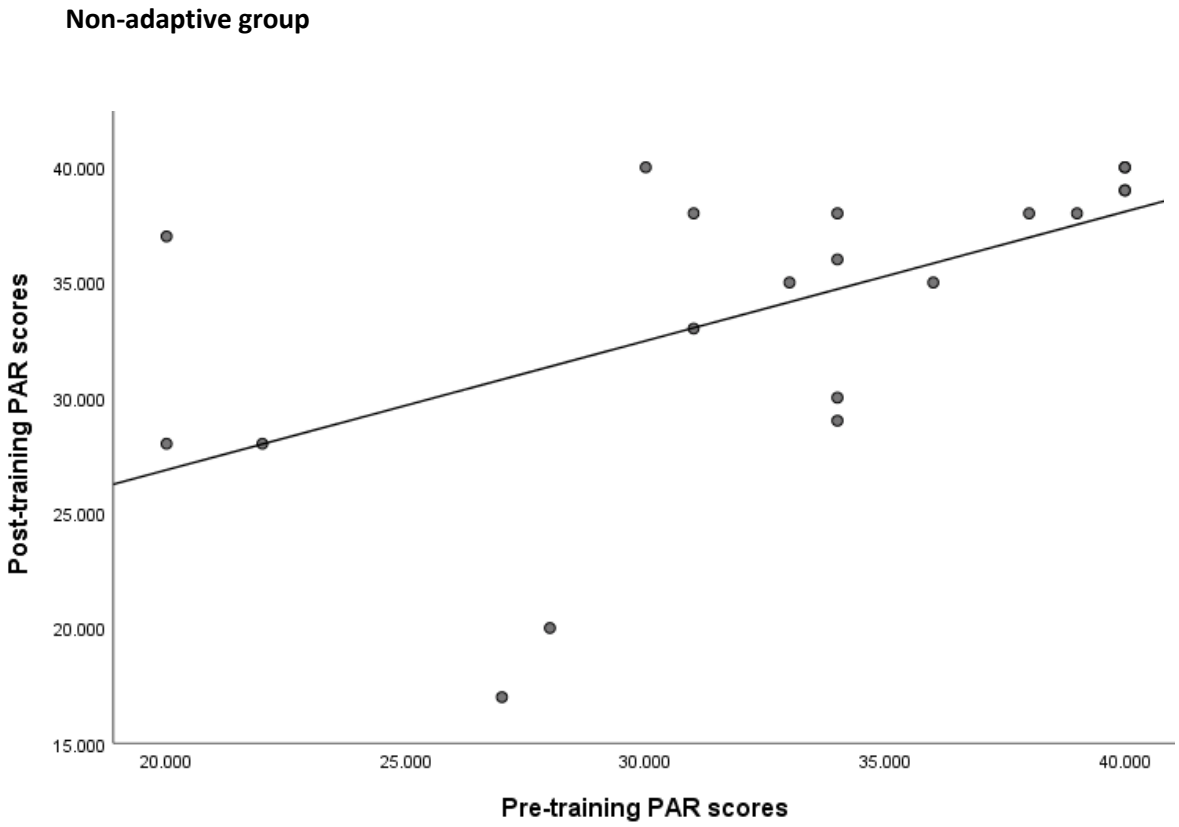


Figure VI.31. Scatterplot of pre-training PAR scores x post-training PAR scores for the non-adaptive group. The linear regression line is y = 15.65+0.56*x, R^2 = 0.302.

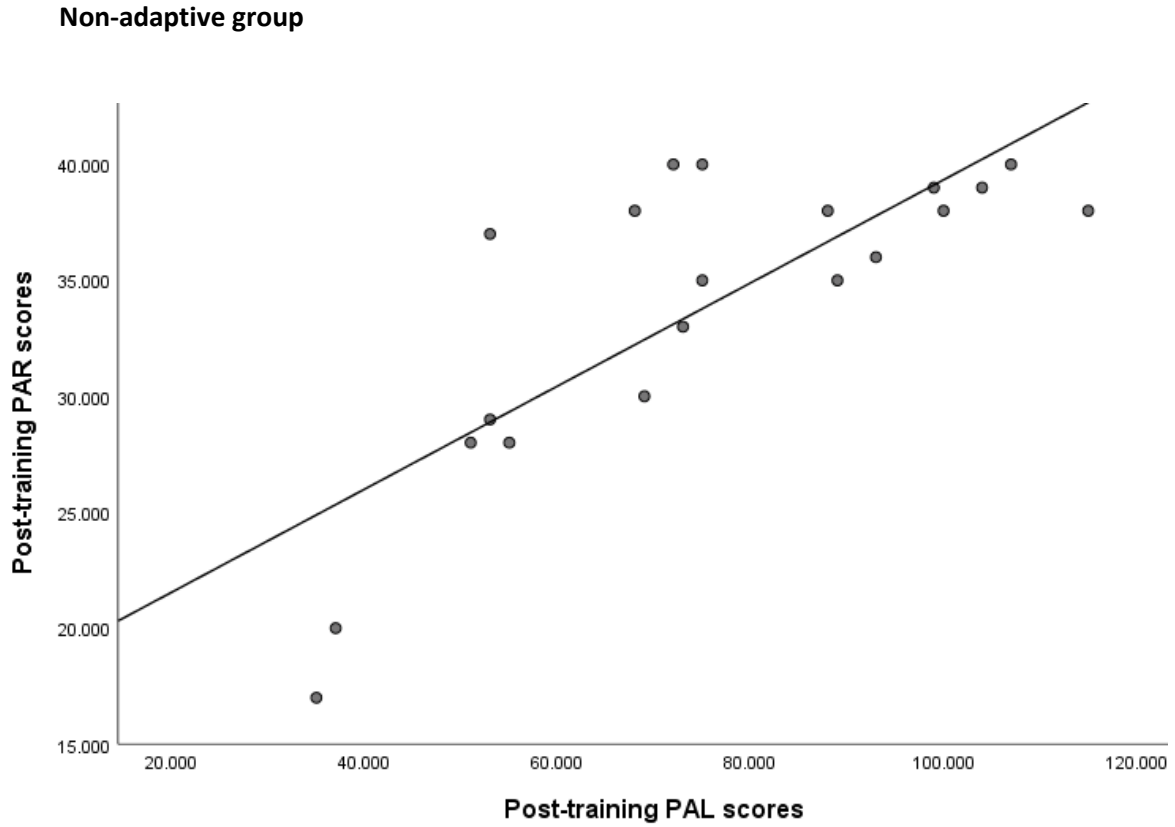


Figure VI.32. Scatterplot of post-training PAL scores x post-training PAR scores for the non-adaptive group. The linear regression line is y = 17.10+0.22*x, R^2 = 0.617.

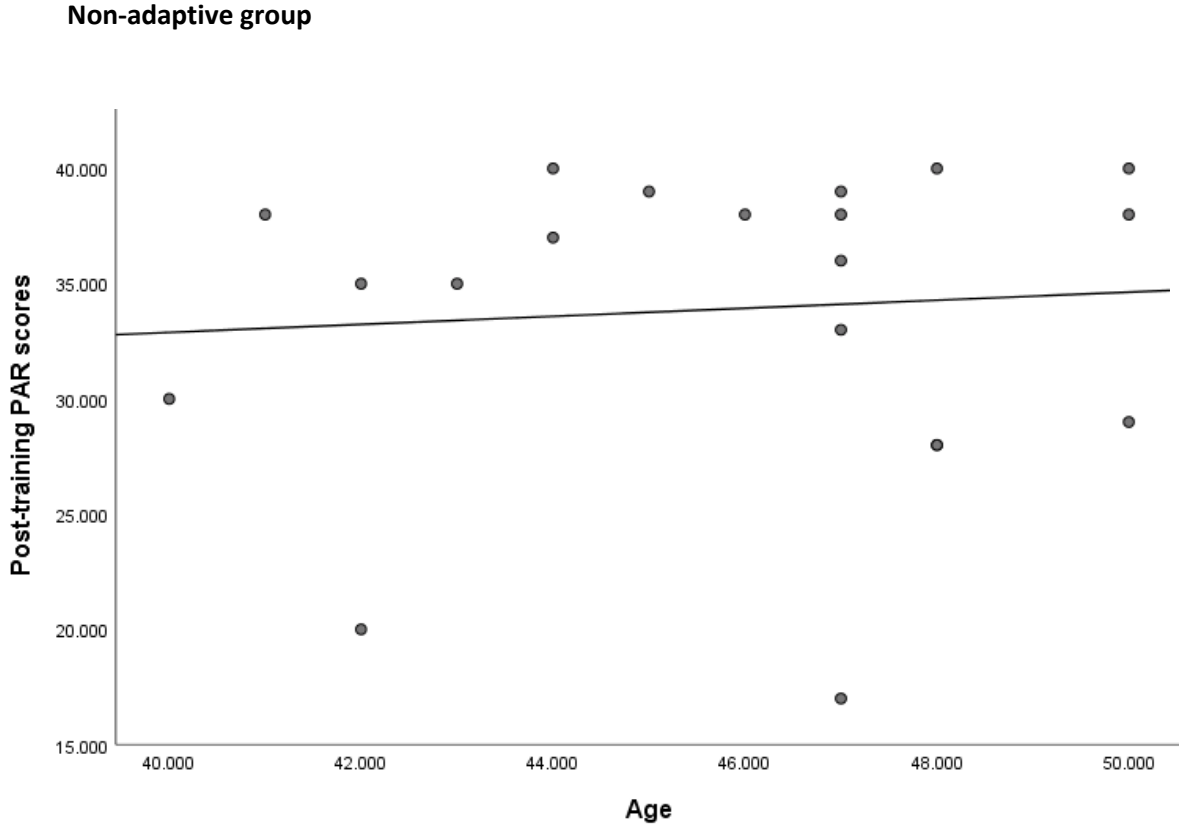


Figure VI.33. Scatterplot of age (years) x post-training PAR scores for the non-adaptive group. The linear regression line is y = 25.90+0.17*x, R^2 = 0.006.

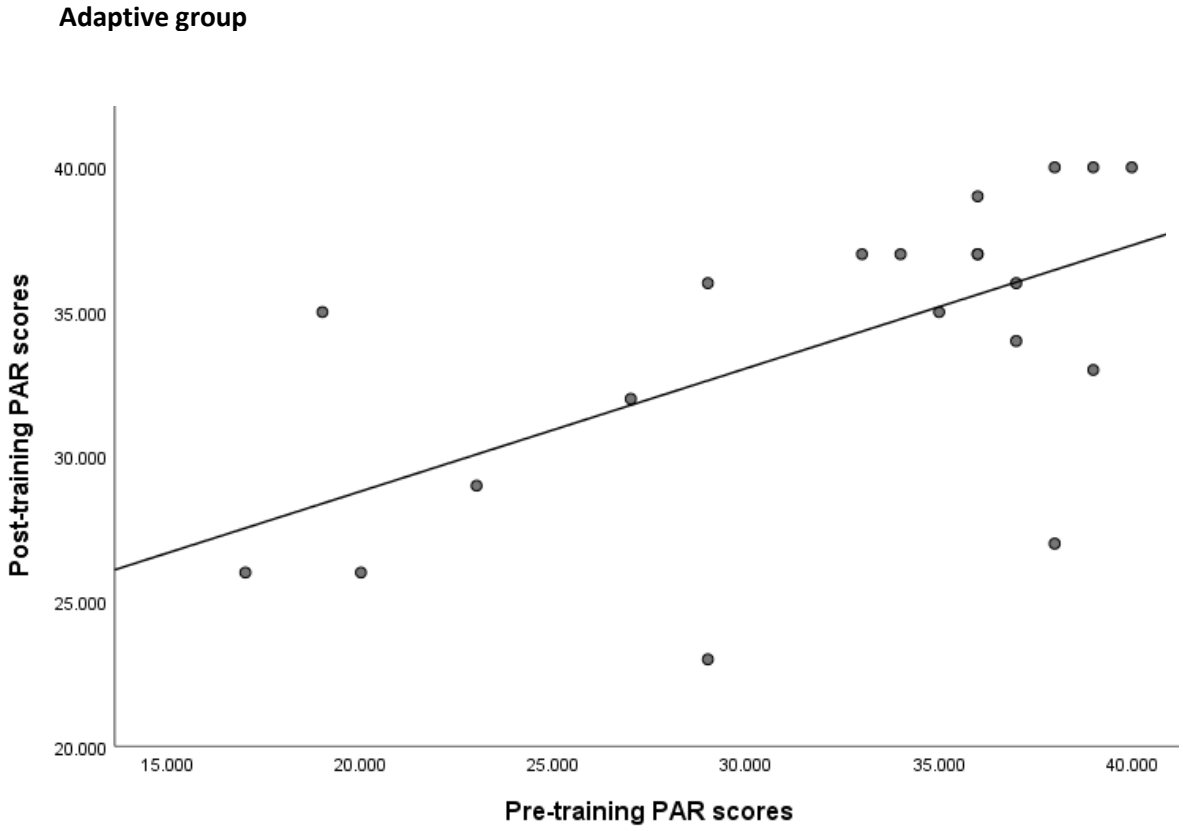


Figure VI.34. Scatterplot of pre-training PAR scores x post-training PAR scores for the adaptive group. The linear regression line is y = 20.31+0.42*x, R^2 = 0.359.

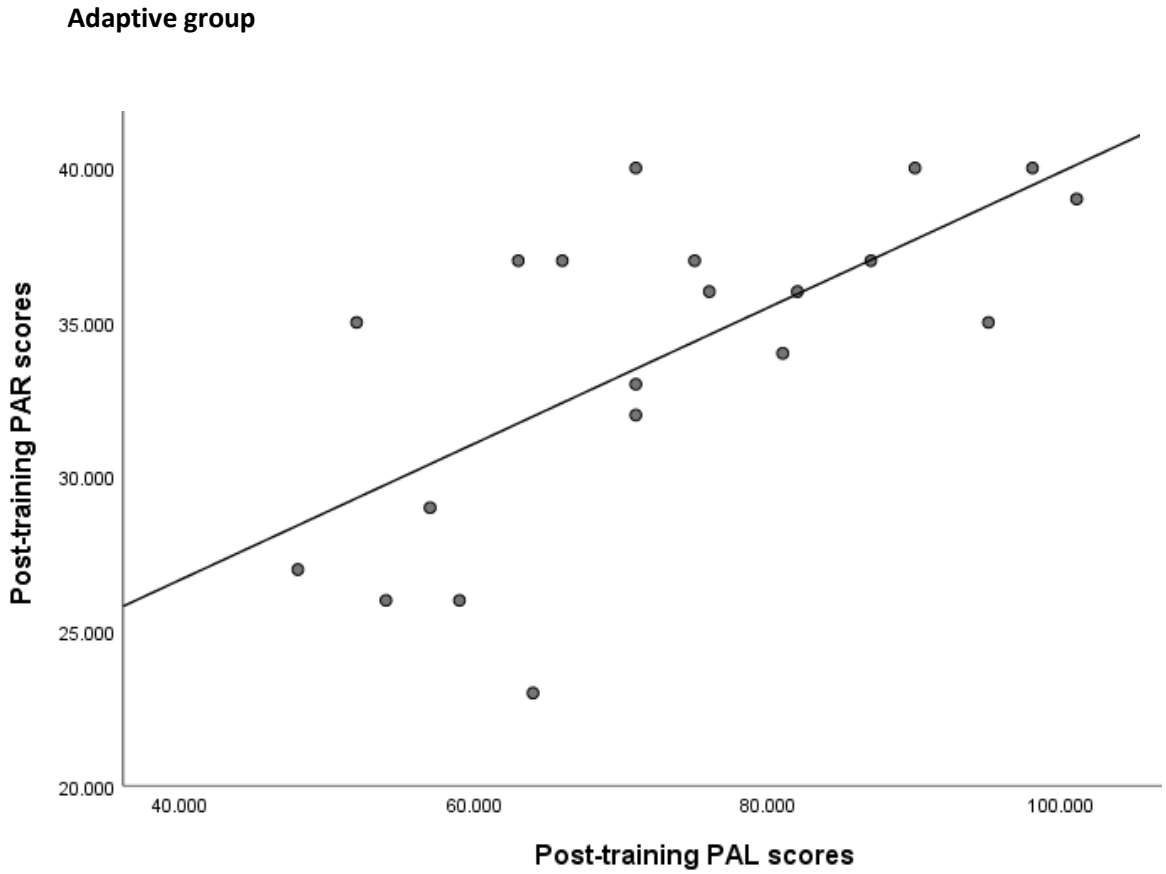


Figure VI.35. Scatterplot of post-training PAL scores x post-training PAR scores for the adaptive group. The linear regression line is y = 17.86+0.22*x, R^2 = 0.446.

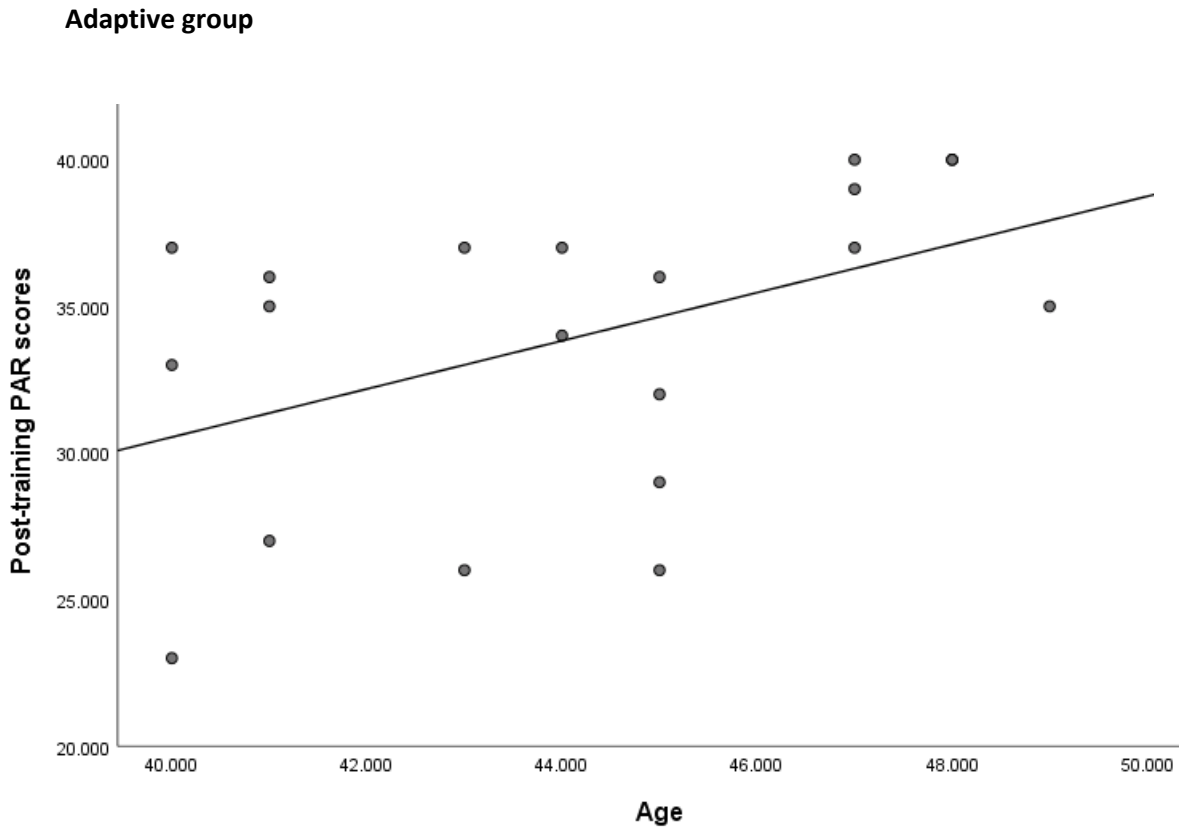


Figure VI.36. Scatterplot of age (years) x post-training PAR scores for the adaptive group. The linear regression line is y = -2.31+0.82*x, R^2 = 0.219.

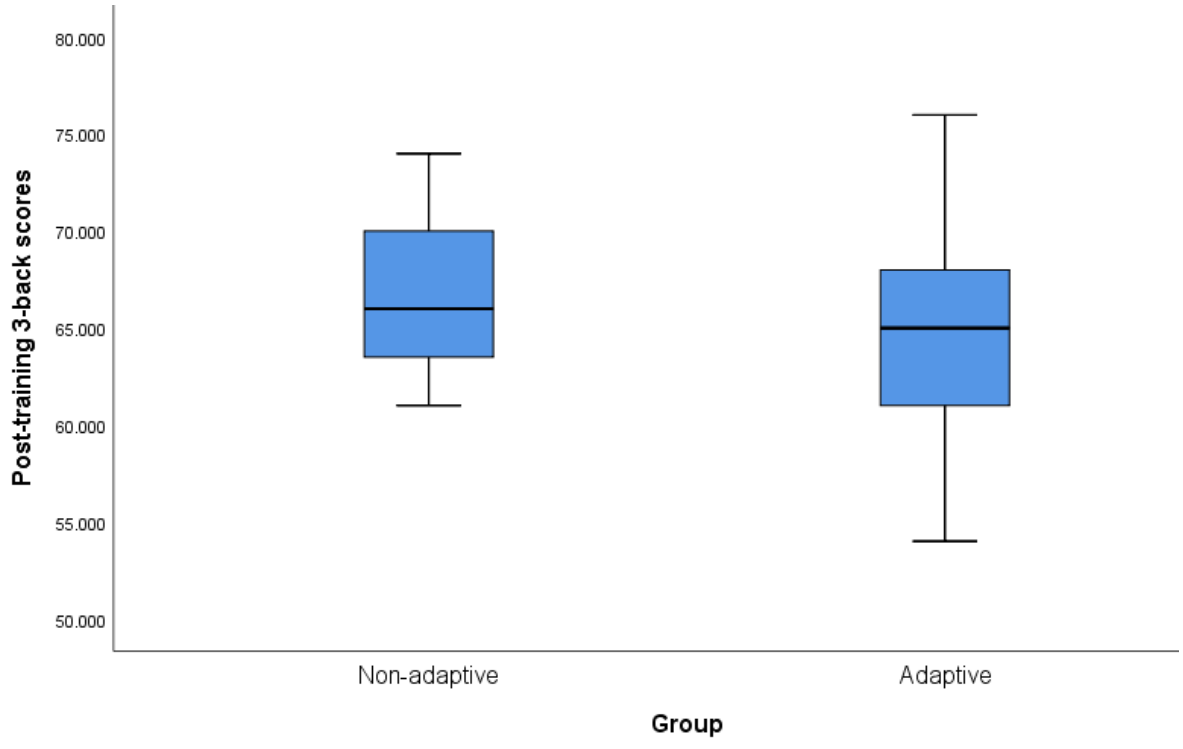


Figure VI.37. Boxplots showing no outliers for non-adaptive and adaptive post-training 3-back scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

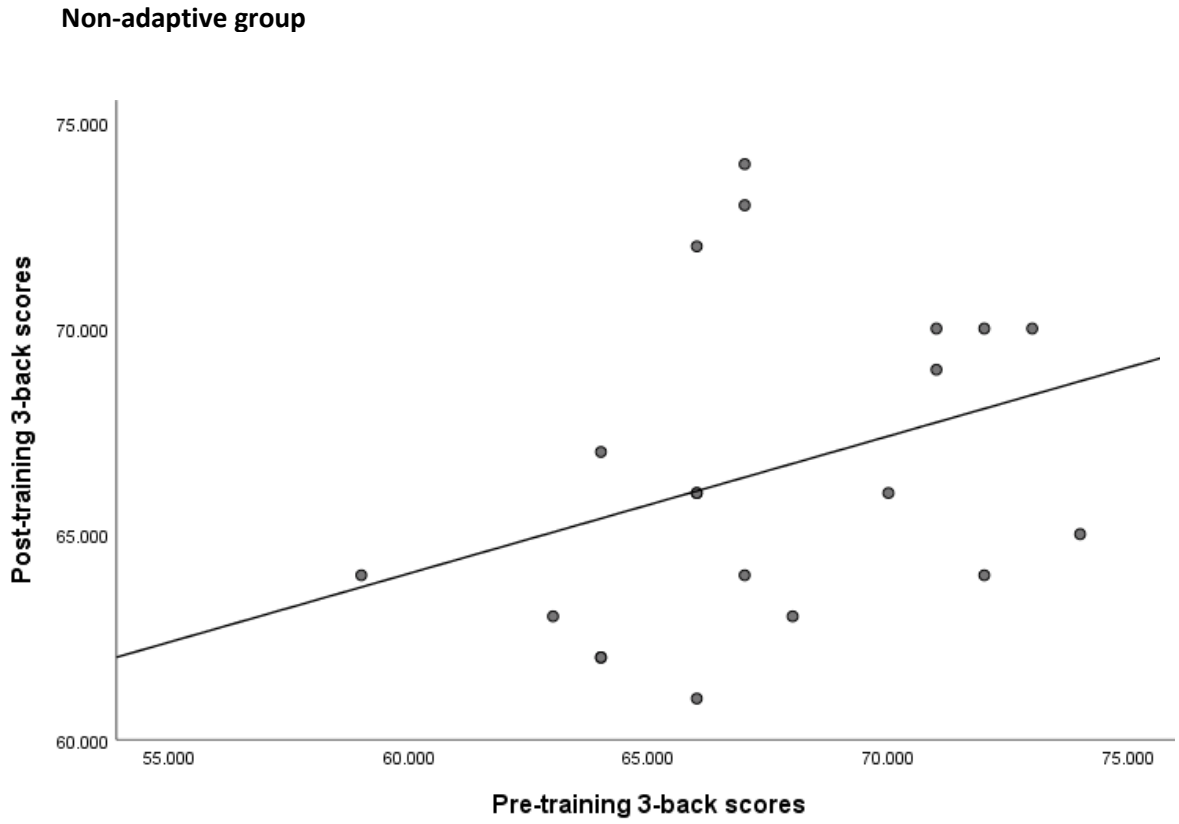


Figure VI.38. Scatterplot of pre-training 3-back scores x post-training 3-back scores for the non-adaptive group. The linear regression line is y = 44.01+0.33*x, R^2 = 0.109.

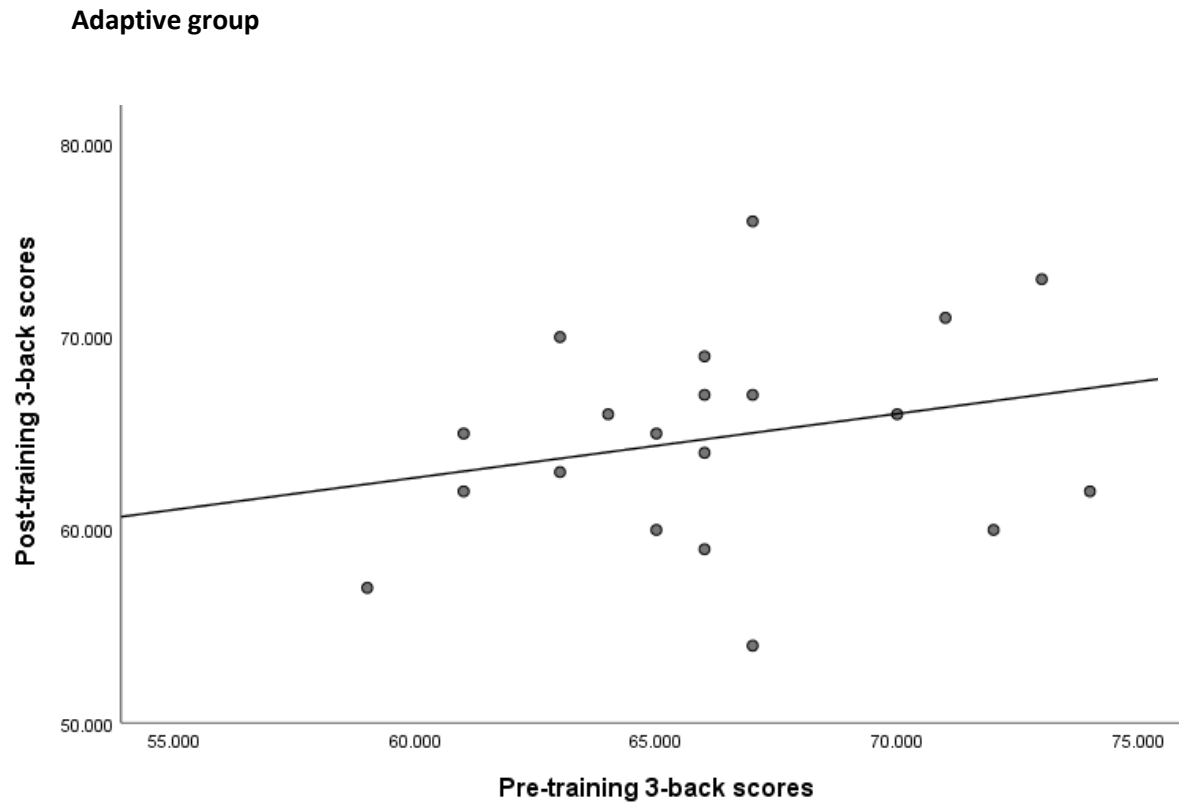


Figure VI.39. Scatterplot of pre-training 3-back scores x post-training 3-back scores for the adaptive group. The linear regression line is y = 42.81+0.33*x, R^2 = 0.061.

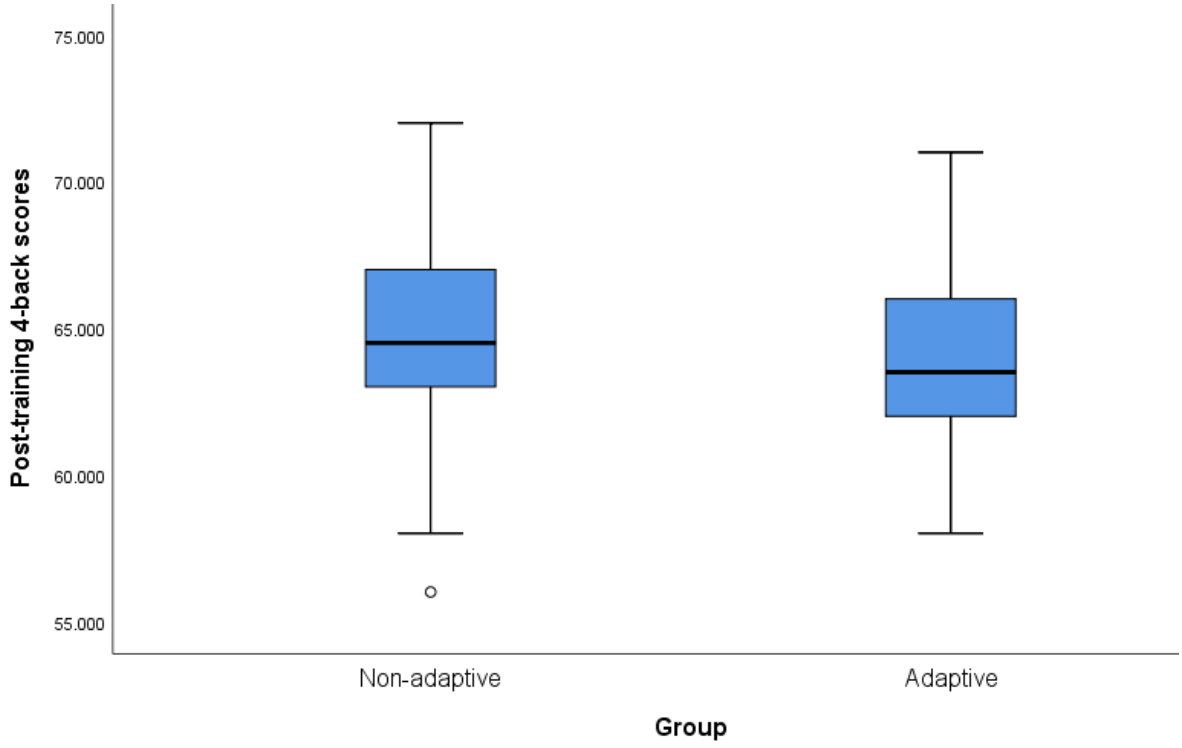


Figure VI.40. Boxplots showing no significant outliers for non-adaptive and adaptive post-training 4-back scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

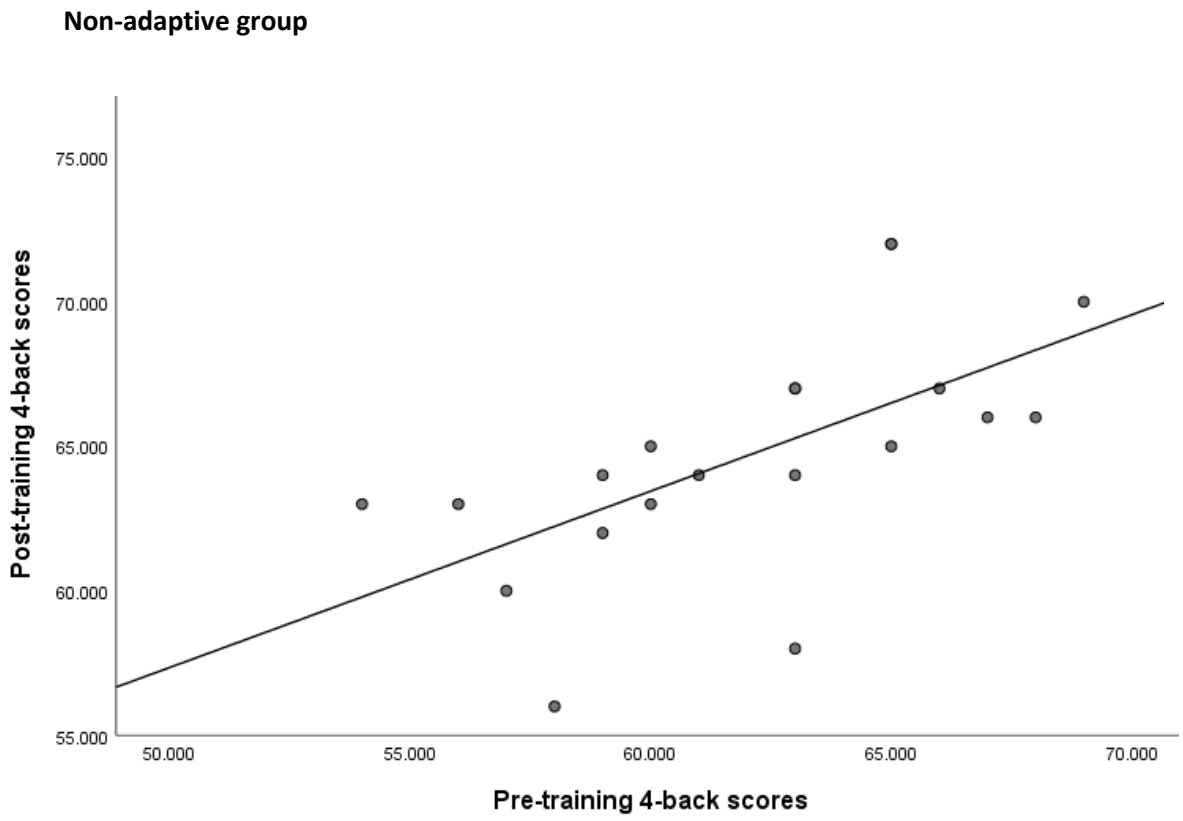


Figure VI.41. Scatterplot of pre-training 4-back scores x post-training 4-back scores for the non-adaptive group. The linear regression line is y = 26.83+0.61*x, R^2 = 0.385.

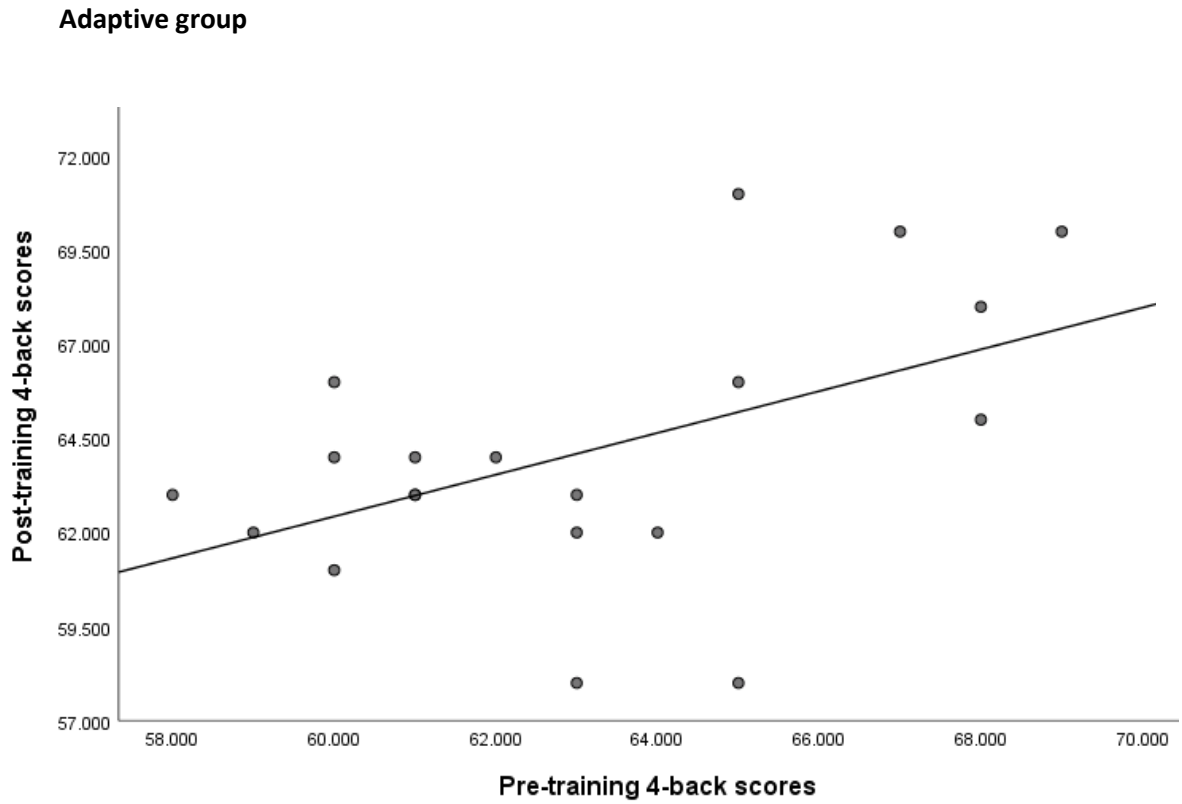


Figure VI.42. Scatterplot of pre-training 4-back scores x post-training 4-back scores for the adaptive group. The linear regression line is y = 29.12+0.56*x, R^2 = 0.249.

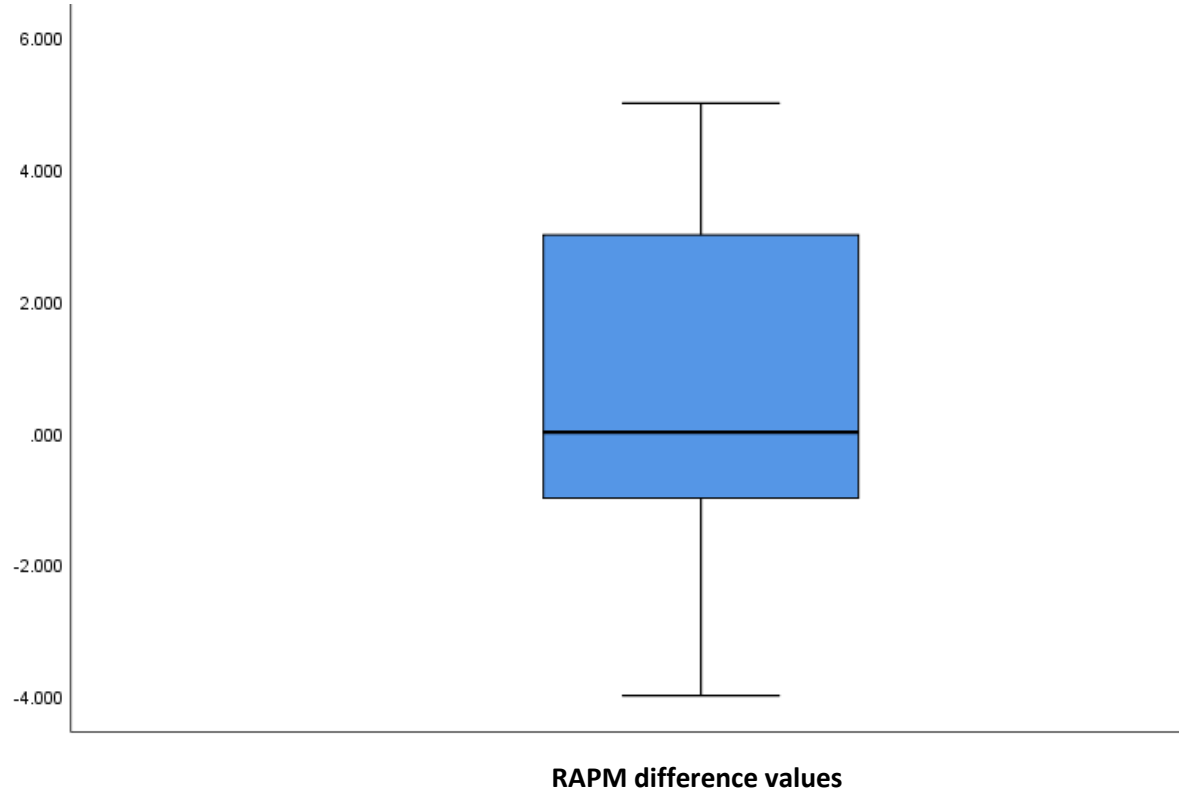


Figure VI.43. Boxplot showing no outliers in the RAPM differences between pre- and post-training scores. The box represents the interquartile range which contains the middle 50% of difference values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

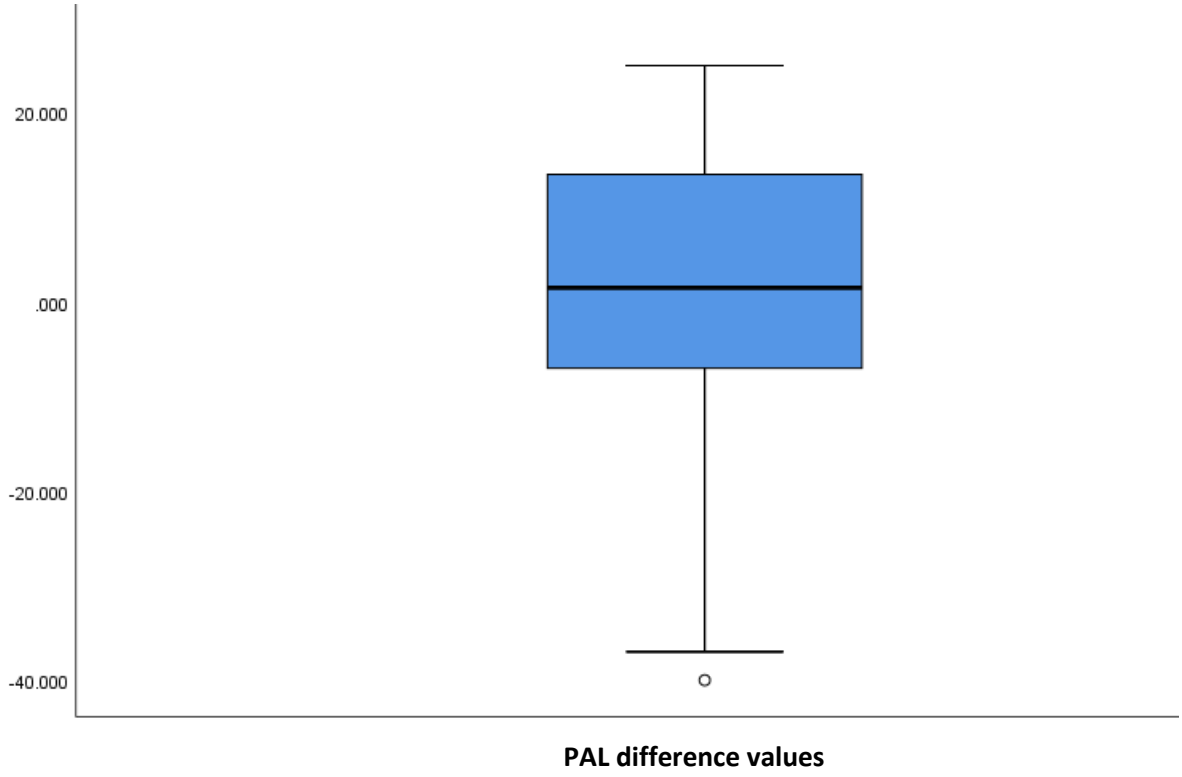


Figure VI.44. Boxplot showing no significant outliers in the PAL differences between pre- and post-training scores. The box represents the interquartile range which contains the middle 50% of difference values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

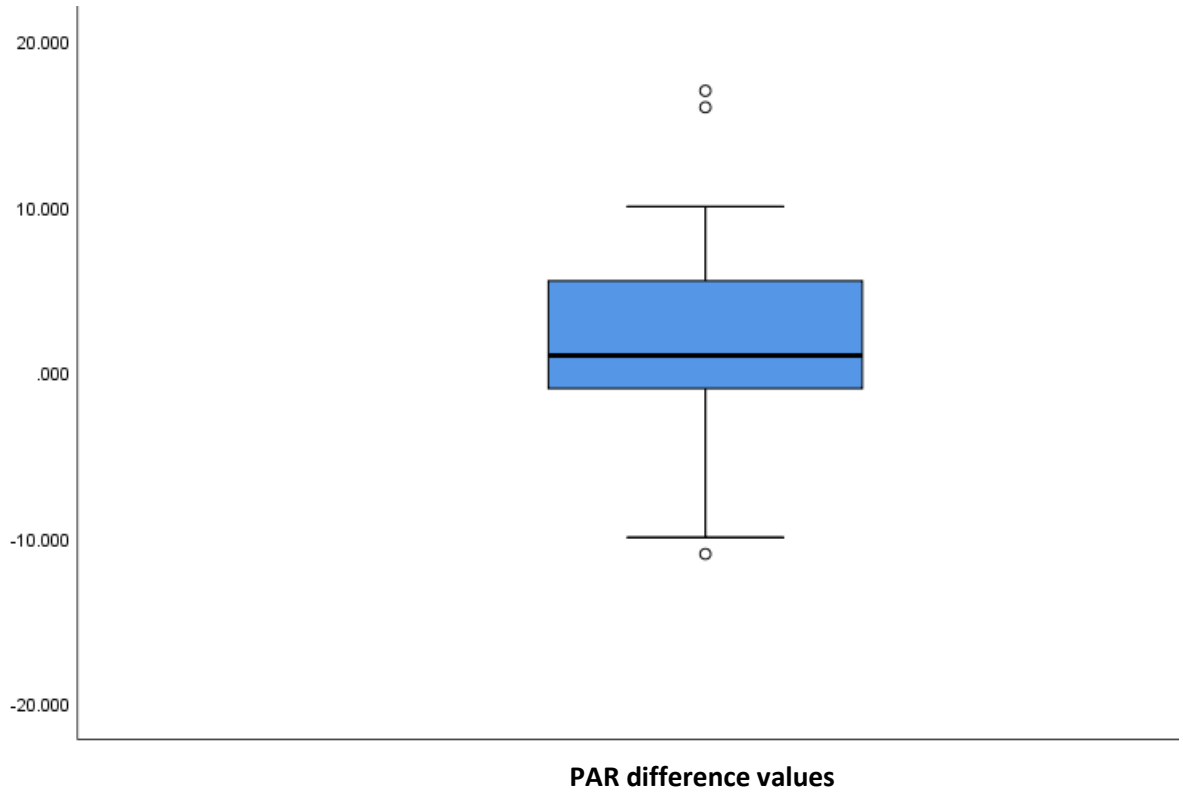


Figure VI.45. Boxplot showing no significant outliers in the PAR differences between pre- and post-training scores. The box represents the interquartile range which contains the middle 50% of difference values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

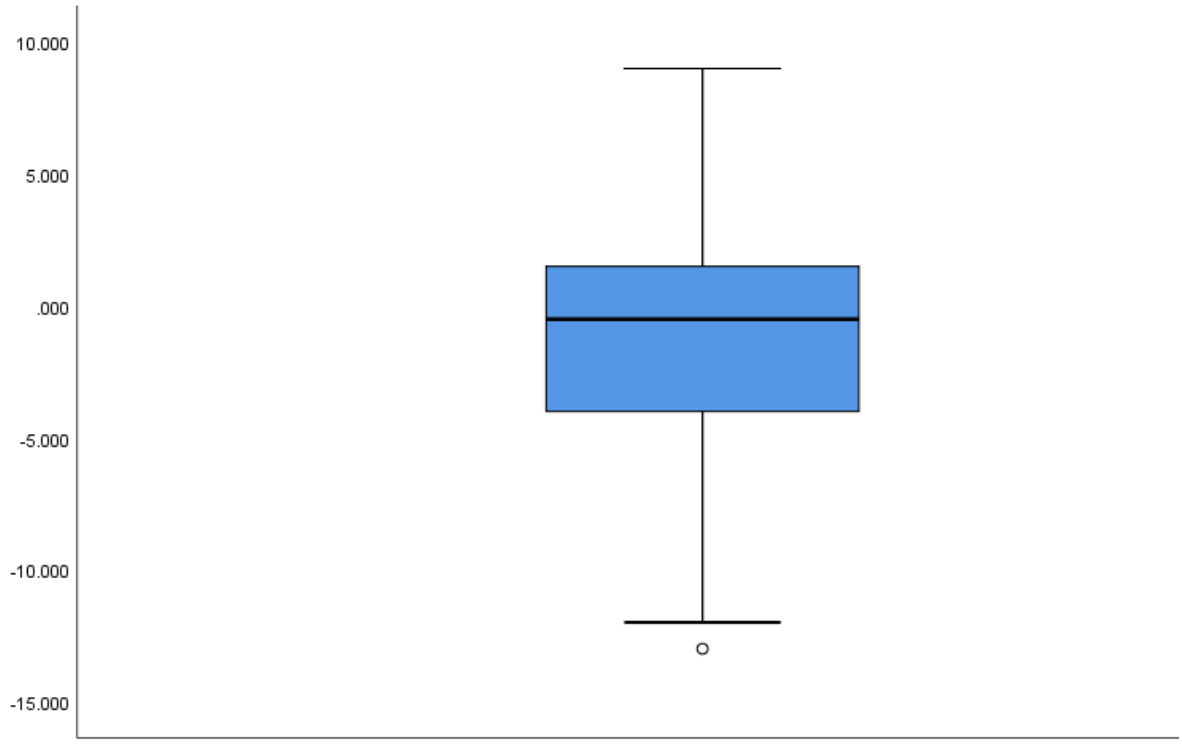


Figure VI.46. Boxplot showing no significant outliers in the 3-back differences between pre- and post-training scores. The box represents the interquartile range which contains the middle 50% of difference values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

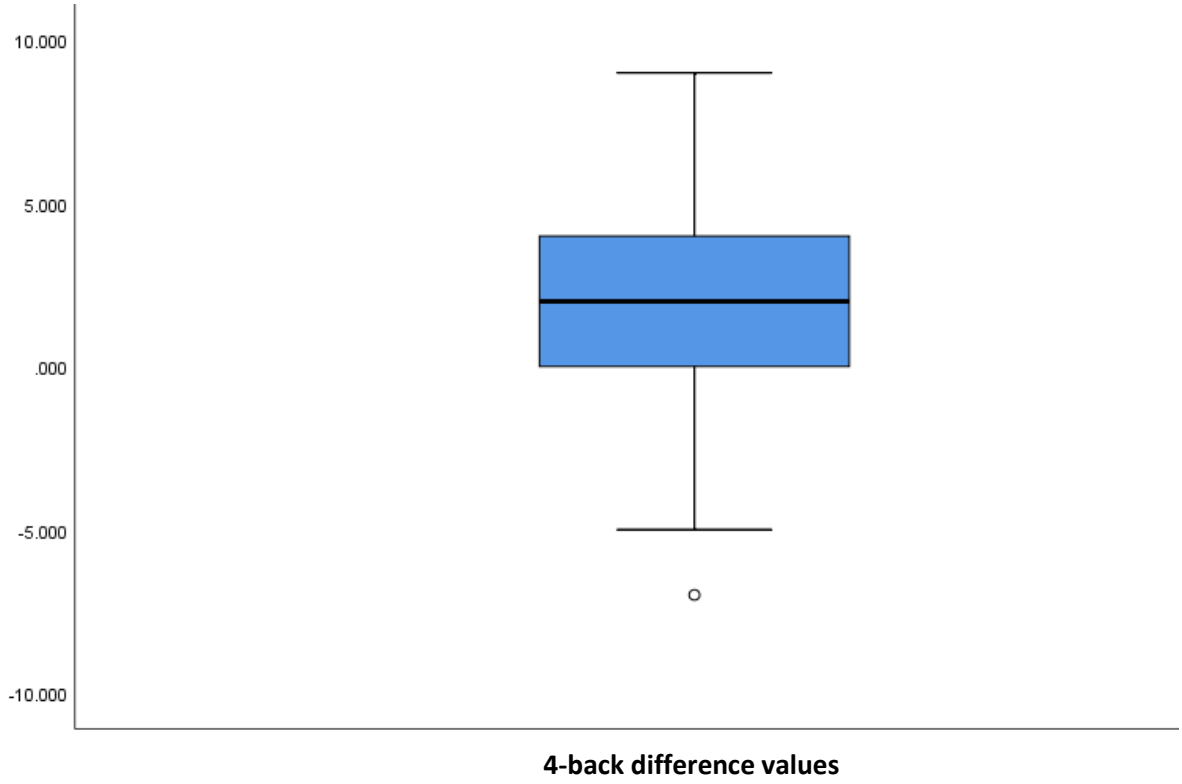


Figure VI.47. Boxplot showing no significant outliers in the 4-back differences between pre- and post-training scores. The box represents the interquartile range which contains the middle 50% of difference values. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

VII. Gender analyses

Independent samples t-tests were conducted to check for any differences in performance between females and males on pre- and post-training transfer tasks. Tests of assumptions for the independent t-tests examining pre-training RAPM, PAL, PAR, 3-back, and 4-back scores indicated no significant outliers for females and none for males (Figures VII.1, VII.2, VII.3, VII.4, and VII.5). Shapiro-Wilks tests for females showed that pre-training RAPM, PAL, 3-back, and 4-back scores are normally distributed, $W(28) = .929$, $p = .059$; $W(28) = .956$, $p = .274$; $W(28) = .954$, $p = .246$; $W(28) = .969$, $p = .554$, respectively. As did Shapiro-Wilks tests for males for pre-training RAPM, PAL, PAR, 3-back, and 4-back scores, $W(12) = .944$, $p = .553$; $W(12) = .939$, $p = .482$; $W(12) = .898$, $p = .148$; $W(12) = .950$, $p = .643$; $W(12) = .977$, $p = .967$, respectively. Levene's tests found that the assumption of homogeneity of variance for female and male pre-training RAPM, PAL, PAR, 3-back, and 4-back scores was met, $F(1,38) = .864$, $p = .359$; $F(1,38) = .039$, $p = .845$; $F(1,38) = .247$, $p = .622$; $F(1,38) = .101$, $p = .752$; $F(1,38) = .520$, $p = .475$, respectively. One of the tests of assumptions was violated in that female pre-training PAR scores were not normally distributed, $W(28) = .890$, $p = .007$. As such, a Mann-Whitney U test was employed to investigate any possible differences in gender with respect to pre-training PAR scores, as this non-parametric test does not require this assumption to be met.

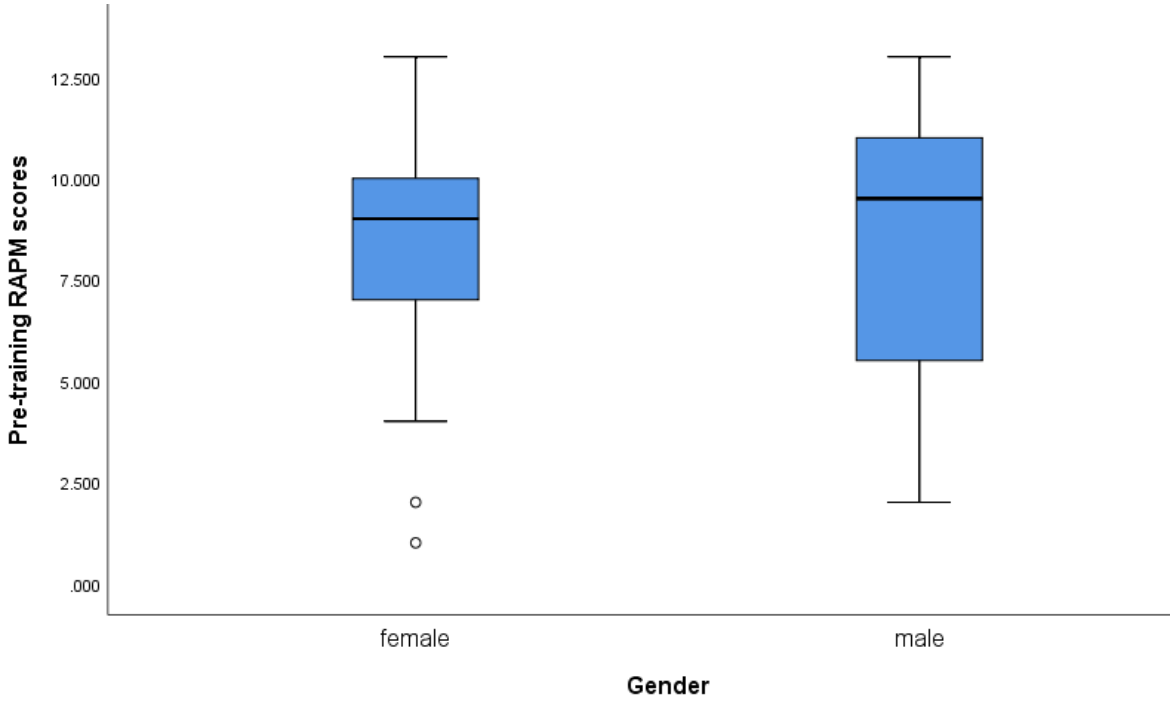


Figure VII.1. Boxplots showing no significant outliers for female and male pre-training RAPM scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

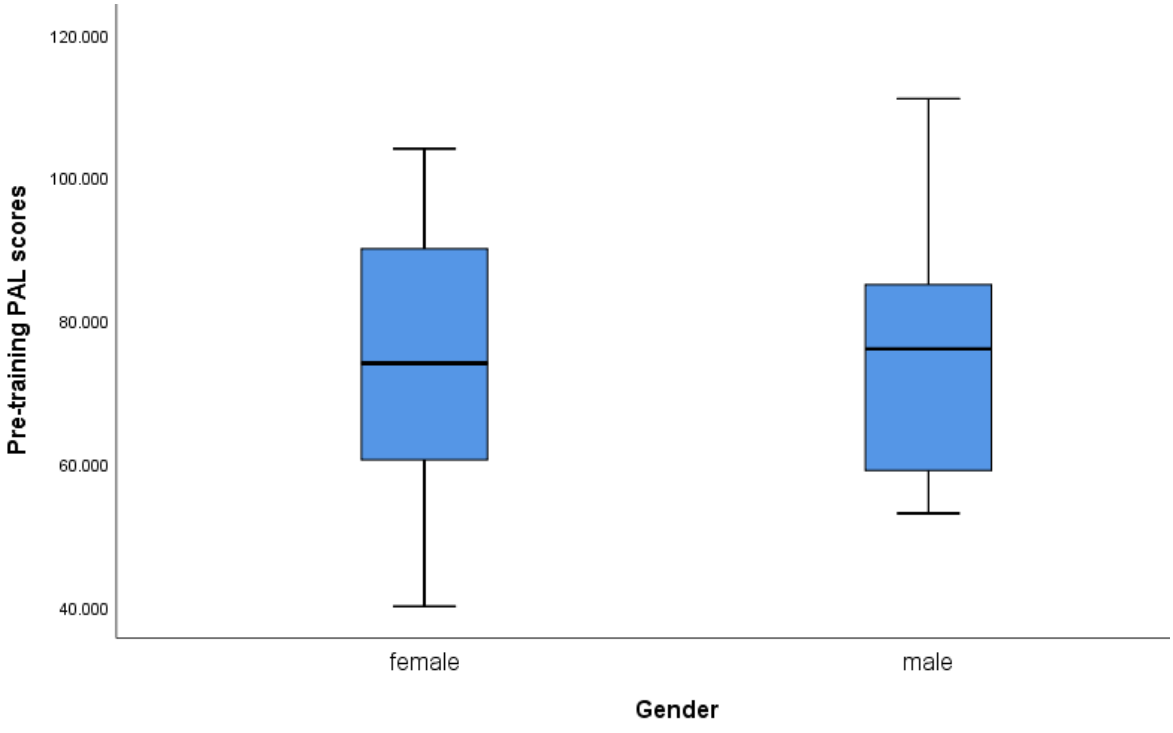


Figure VII.2. Boxplots showing no outliers for female and male pre-training PAL scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

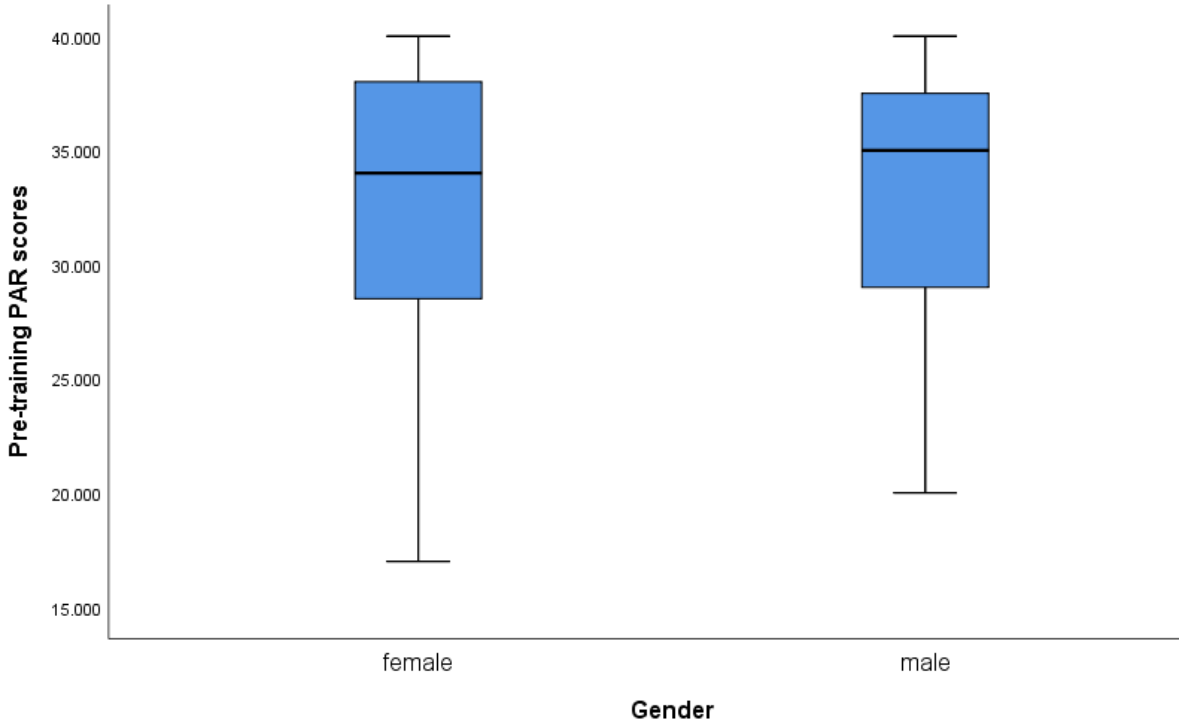


Figure VII.3. Boxplots showing no outliers for female and male pre-training PAR scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

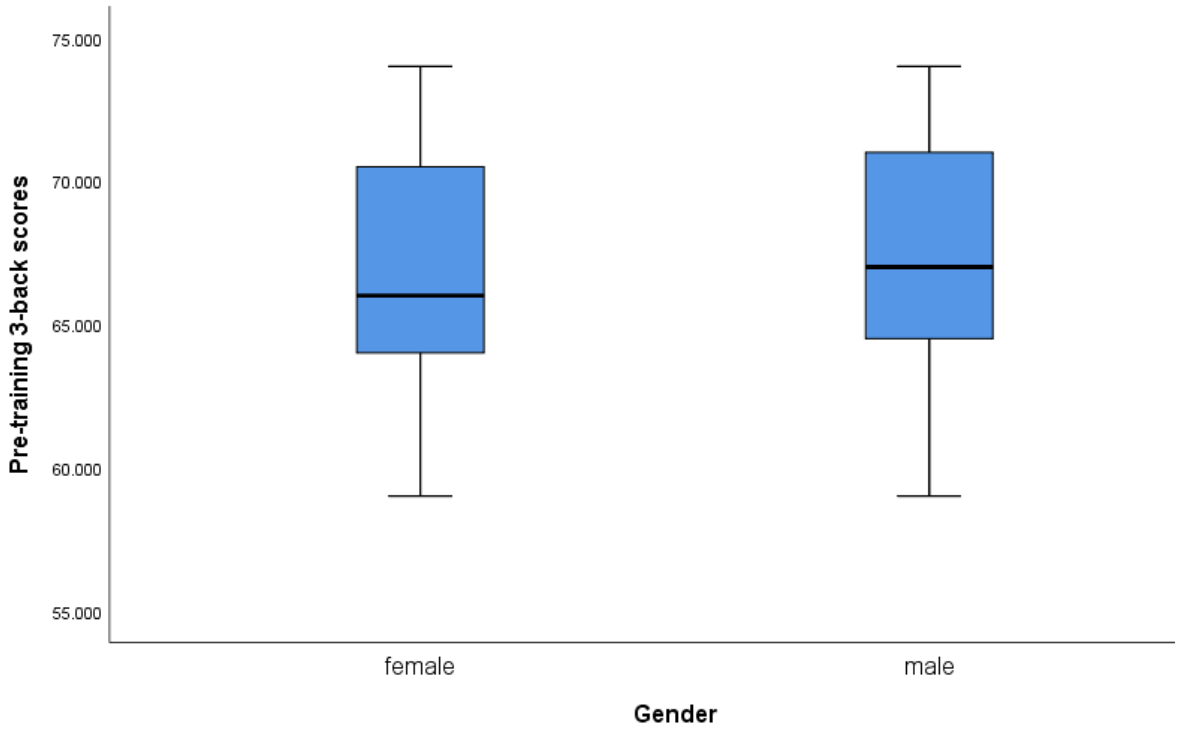


Figure VII.4. Boxplots showing no outliers for female and male pre-training 3-back scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

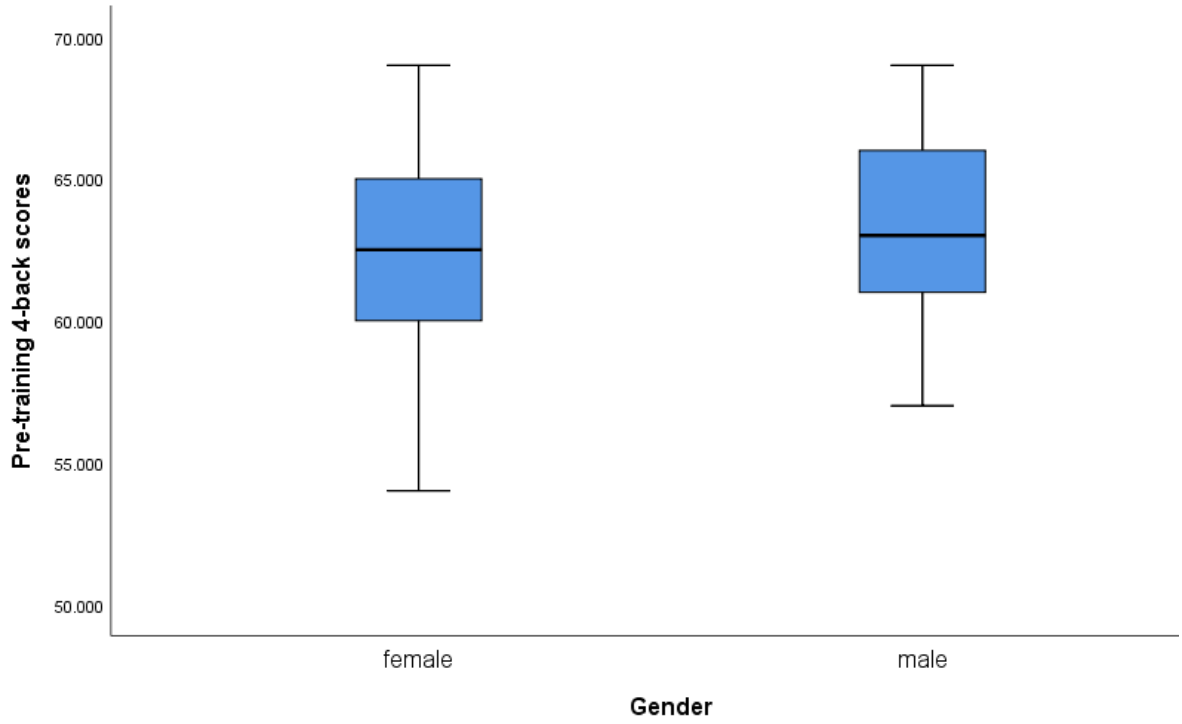


Figure VII.5. Boxplots showing no outliers for female and male pre-training 4-back scores. The box represents the interquartile range which contains the middle 50% of scores. The whiskers are the highest and lowest values which are no greater than 1.5 times the interquartile range. A line across the box indicates the median. Outliers are defined as values between 1.5 and 3 times the interquartile range. Significant outliers are defined as values more than 3 times the interquartile range.

The independent t-test for pre-training RAPM scores demonstrated there were no significant differences in performance between females and males, $t(38) = -.177$, $p = .861$. The independent t-test for pre-training PAL scores demonstrated there were no significant differences in performance between females and males, $t(38) = -.511$, $p = .612$. The independent t-test for pre-training 3-back scores showed there were no significant differences in performance between females and males, $t(38) = -.448$, $p = .656$. The independent t-test for pre-training 4-back scores indicated there were no significant differences in performance between females and males, $t(38) = -.753$, $p = .456$. The Mann-Whitney U test for pre-training PAR scores demonstrated there were no significant differences in performance between females and males, $U = 157.00$, $p = .745$.

Tests of assumptions for the independent t-tests examining post-training RAPM, PAL, PAR, 3-back, and 4-back scores were not violated and are reported in Chapter 4 (4.3

Results, pg. 143), with the exception that female post-training PAR scores were not normally distributed, $W(28) = .882$, $p = .004$. As such, a Mann-Whitney U test was employed to investigate any possible differences in gender with respect to post-training PAR scores.

The independent t-test for post-training RAPM scores demonstrated there were no significant differences in performance between females and males, $t(38) = .289$, $p = .774$. The independent t-test for post-training PAL scores demonstrated there were no significant differences in performance between females and males, $t(38) = -.180$, $p = .858$. The independent t-test for post-training 3-back scores showed there were no significant differences in performance between females and males, $t(38) = -.640$, $p = .526$. The independent t-test for post-training 4-back scores indicated there were no significant differences in performance between females and males, $t(38) = -.715$, $p = .479$. The Mann-Whitney U test for post-training PAR scores demonstrated there were no significant differences in performance between females and males, $U = 165.50$, $p = .941$.

VIII. Whole-brain fMRI analysis for the PCM task

Results of the 2 × 2 repeated measures ANOVA (Testing Phase: Pre-training, Post-training x Trial Performance: Successful, Unsuccessful) yielded a significant main effect of testing phase bilaterally in the cerebellum and pons, in the right thalamus, right subthalamic nucleus, and right lingual gyrus (Table VIII.1). We did not observe a significant main effect of performance or interaction between testing phase and performance.

Table VIII.1. Whole-brain analysis: brain regions with a significant main effect of testing phase for the PCM task.

Brain region	MNI coordinates			*F*-value	Cluster size (voxels)	*P*-value FDR-corrected
	x	y	z			
Cerebellar vermis (10)	3	-46	-34	43.09	251	.003
Left pons	-3	-19	-22	26.69		
Right thalamus	6	-22	-1	20.56		
Right pons	3	-28	-37	15.34		
Right subthalamic nucleus	9	-13	-10	12.43		
Left cerebellum (Crus 2)	-3	-85	-22	45.77	132	.047
Right cerebellum (Crus 1)	6	-85	-19	38.90		
Right lingual gyrus	21	-94	-7	27.58		
Right cerebellum (Crus 2)	6	-85	-25	17.20		

A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, after clusters were formed with an uncorrected $p < .001$. P values are reported at the cluster level. The MNI coordinates refer to the peak F-value. Local maxima that are more than 8 mm apart are shown for each cluster.

We examined the differences in testing phase more closely using the contrasts Pre-training > Post-training and Post-training > Pre-training. We found a significant effect for the two contrasts. Specifically, there was greater activity bilaterally in cerebellum and in right lingual gyrus in the pre-training phase compared to the post-training phase (Table VIII.2). In the post-training phase relative to the pre-training phase, there was increased

activation in cerebellum, bilaterally in pons, right thalamus, right subthalamic nucleus, right precuneus, right mid cingulate cortex, right SMA, and left paracentral lobule (Table VIII.2).

Table VIII.2. Whole-brain analysis: brain regions with increased activity in the pre-training phase compared to the post-training phase (Pre-training > Post-training) of the PCM task. Followed by brain regions with increased activity in the post-training phase relative to the pre-training phase (Post-training > Pre-training).

Brain region	MNI coordinates			*t*-value	Cluster size (voxels)	*P*-value FDR-corrected
	x	y	z			
Pre-training > Post-training						
Left cerebellum (Crus 2)	-3	-85	-22	6.77	159	.014
Right cerebellum (Crus 1)	6	-85	-19	6.24		
Right lingual gyrus	21	-94	-7	5.25		
Right cerebellum (Crus 2)	6	-85	-25	4.15		
Post-training > Pre-training						
Cerebellar vermis (10)	3	-46	-34	6.56	317	.002
Left pons	-3	-19	-22	5.17		
Right thalamus	6	-22	-1	4.53		
Right pons	3	-28	-37	3.92		
Right subthalamic nucleus	9	-13	-10	3.53		
Right precuneus	12	-43	53	5.10	185	.019
Right mid cingulate cortex	9	-1	41	4.56		
Right SMA	3	-22	65	4.05		
Left paracentral lobule	-3	-16	68	4.04		

The results are shown using a statistical significance of $p < .05$ after FDR-correction at the cluster level, clusters formed using $p < .001$. P values are reported at the cluster level. The MNI coordinates refer to the peak t-value. Local maxima that are more than 8 mm apart are shown for each cluster.

IX. Whole-brain fMRI analysis for the PAR task

Results of the 2 (group: adaptive, non-adaptive) × 2 (session: pre-training, post-training) x 3 (period: cue, delay, target) mixed ANOVA yielded a significant interaction between session and task period in right fusiform gyrus, right lingual gyrus, right parahippocampal gyrus, right inferior occipital gyrus, right calcarine sulcus, right cuneus, and right precuneus (Table IX.1). We did not observe a main effect of group, nor a main effect of session, and no main effect of task period. Interactions between group and session, group and period, and group x session x period, were also not significant.

Table IX.1. Whole-brain analysis for the PAR task: brain regions with a significant interaction between session and task period.

Brain region	MNI coordinates			*F*-value	Cluster size (voxels)	*P*-value FDR-corrected
	x	y	z			
Right fusiform gyrus	22	-44	-12	16.39	376	< .001
Right lingual gyrus	28	-62	0	10.39		
Right parahippocampal gyrus	20	-34	-12	9.22		
Right inferior occipital gyrus	42	-78	-16	8.59		
Right calcarine sulcus	24	-54	12	11.69	116	.039
Right cuneus	18	-66	36	11.57	103	.044
Right precuneus	16	-60	28	9.16		

A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, after clusters were formed with an uncorrected $p < .001$. P values are reported at the cluster level. The MNI coordinates refer to the peak F-value. Local maxima that are more than 8 mm apart are shown for each cluster.

We examined the interaction between session and task period more closely using the contrasts pre-training_cue > post-training_cue, post-training_cue > pre-training_cue, pre-training_delay > post-training_delay, post-training_delay > pre-training_delay, pre-training_target > post-training_target, and post-training_target > pre-training_target. We found a significant effect for the contrasts post-training_cue > pre-training_cue and post-

training_target > pre-training_target. Specifically, there was greater activity in right fusiform gyrus and right parahippocampal gyrus during the cue in the post-training session compared to the pre-training session (Figure IX.1). In the target post-training session relative to the pre-training session, there was increased activation bilaterally in fusiform gyrus, parahippocampal gyrus, cuneus, precuneus, and in left lingual gyrus, right calcarine sulcus, right angular gyrus, and right middle occipital gyrus (Figure IX.2). No other contrasts showed significant effects.

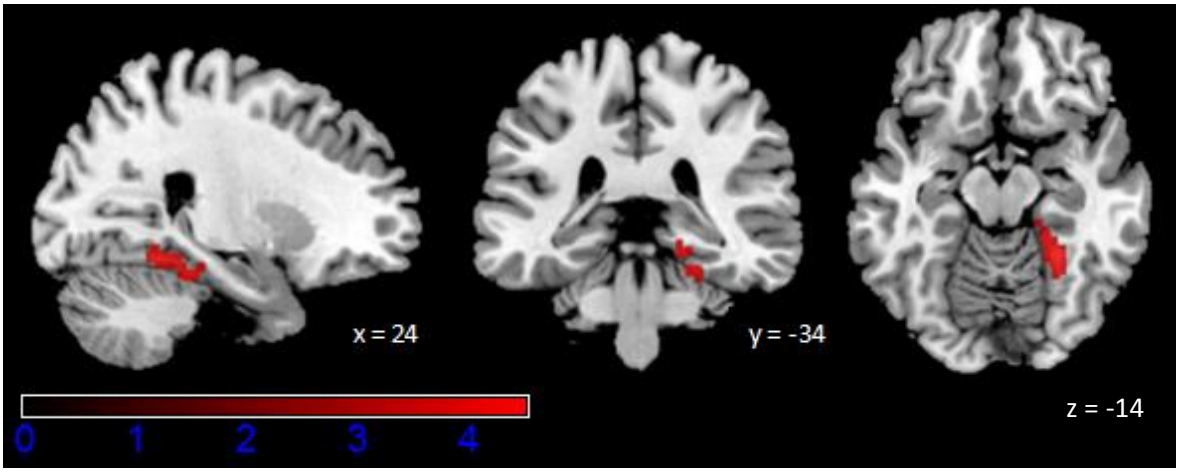


Figure IX.1. Whole-brain analysis for the PAR task: increased activity during the post-training cue period in right fusiform gyrus and right parahippocampal gyrus. A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, after clusters were formed with an uncorrected $p < .001$.

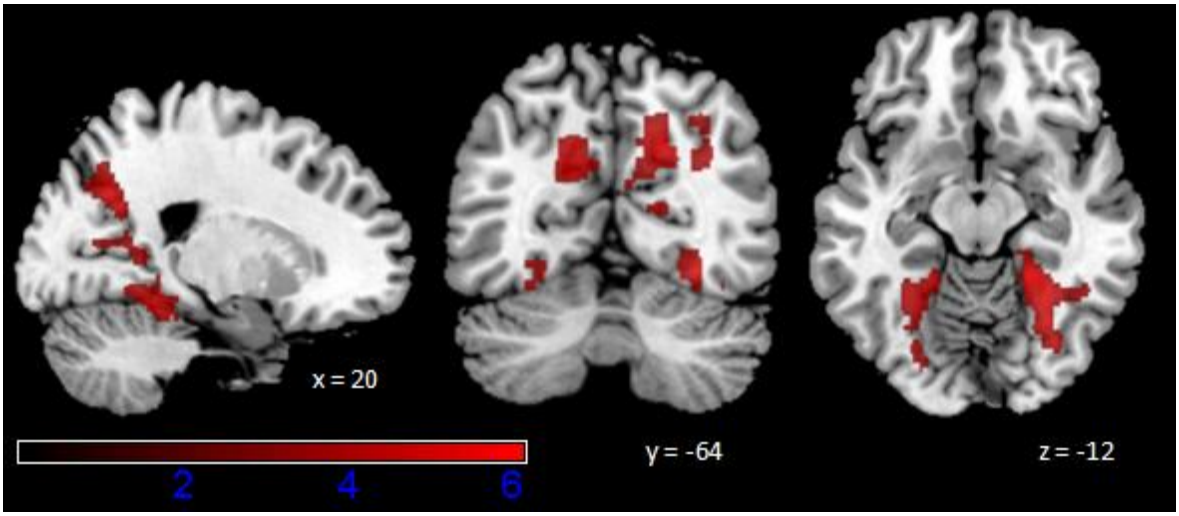


Figure IX.2. Whole-brain analysis for the PAR task: increased activation during the post-training target period bilaterally in fusiform gyrus, parahippocampal gyrus, cuneus, precuneus, and in left lingual gyrus, right calcarine sulcus, right angular gyrus (not shown), and right middle occipital gyrus. A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, after clusters were formed with an uncorrected $p < .001$.

X. Whole-brain fMRI analysis for the N-back task

Results of the 2 × 2 x 4 mixed ANOVA (group: adaptive, non-adaptive x session: pre-training, post-training x condition: 0-, 1-, 3-, and 4-back) yielded a significant main effect of session in left precentral gyrus, left postcentral gyrus, and right cerebellum (Figure X.1a). There was a significant main effect of N-back condition in left dPFC, left posterior-medial frontal gyrus, left insula, left hippocampus, left fusiform gyrus, left calcarine sulcus, left middle occipital gyrus, left cerebellum, right superior temporal gyrus, right thalamus, bilaterally in precentral gyrus, postcentral gyrus, oPFC, gyrus rectus, and rolandic operculum (Figure X.1b). There was also a significant interaction between session and N-back condition in left vPFC, left oPFC, left posterior-medial frontal gyrus, left superior medial gyrus, left insula, left superior parietal cortex, left inferior parietal cortex, left precuneus, left middle occipital gyrus, right putamen, right thalamus, and bilaterally in dPFC, precentral gyrus, caudate, and cerebellum (Figure X.1c). We did not observe a main effect of group, nor an interaction between group and session, no interaction between group and condition, and no interaction of group x session x condition.

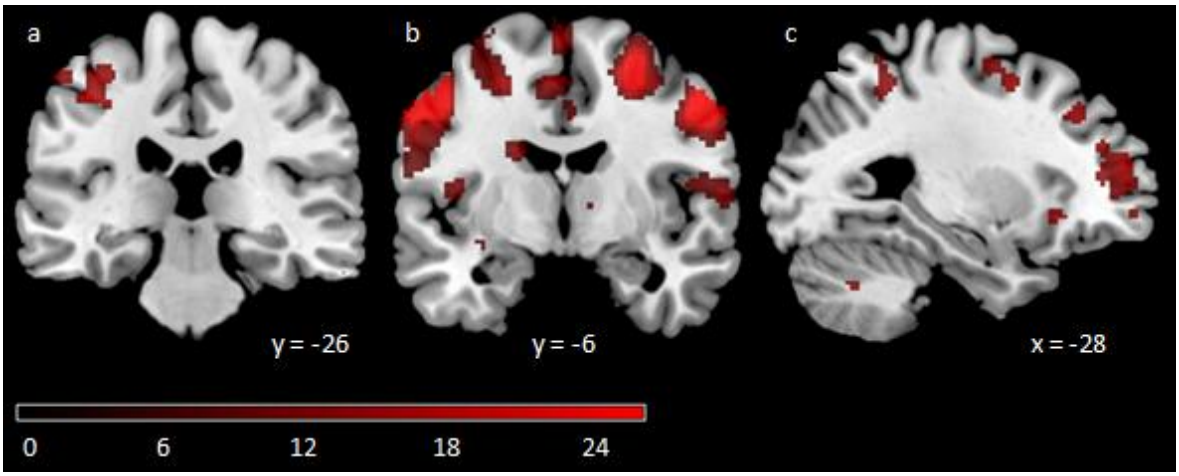


Figure X.1. Whole-brain analysis for the N-back task: a) significant main effect of session in left precentral gyrus, left postcentral gyrus, and right cerebellum (not shown). b) Significant main effect of N-back condition in left dPFC, left posterior-medial frontal gyrus, left insula, left hippocampus (not shown), left fusiform gyrus (not shown), left calcarine sulcus (not shown), left middle occipital gyrus (not shown), left cerebellum (not shown), right superior temporal gyrus, right thalamus, bilaterally in precentral gyrus, postcentral gyrus, oPFC (not shown), gyrus rectus

(not shown), and rolandic operculum. c) Significant interaction between session and N-back condition in left vPFC (not shown), left oPFC, left posterior-medial frontal gyrus, left superior medial gyrus, left insula, left superior parietal cortex (not shown), left inferior parietal cortex (not shown), left precuneus, left middle occipital gyrus (not shown), right putamen (not shown), right thalamus (not shown), and bilaterally in dPFC, precentral gyrus, caudate (not shown), and cerebellum. A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, clusters were formed with an uncorrected $p < .001$.

We examined the differences in session and N-back working memory load more closely using the contrasts pre-training_1-back > post-training_1-back, post-training_1-back > pre-training_1-back, pre-training_3-back > post-training_3-back, post-training_3-back > pre-training_3-back, pre-training_4-back > post-training_4-back, and post-training_4-back > pre-training_4-back (N.B., 0-back baseline activity was subtracted from the 1-, 3-, and 4-back conditions). We found a significant effect for two of the contrasts. Specifically, there was greater activity in left precentral gyrus and left postcentral gyrus for the pre-training 1-back condition compared to the post-training session (Figure X.2). For the 4-back working memory load, there was increased activation in the post-training session relative to the pre-training session in left vPFC, left posterior-medial frontal gyrus, left superior medial gyrus, left middle occipital gyrus, right superior parietal cortex, right angular gyrus, right cerebellum, and bilaterally in dPFC, precentral gyrus, and inferior parietal cortex (Figure X.3).

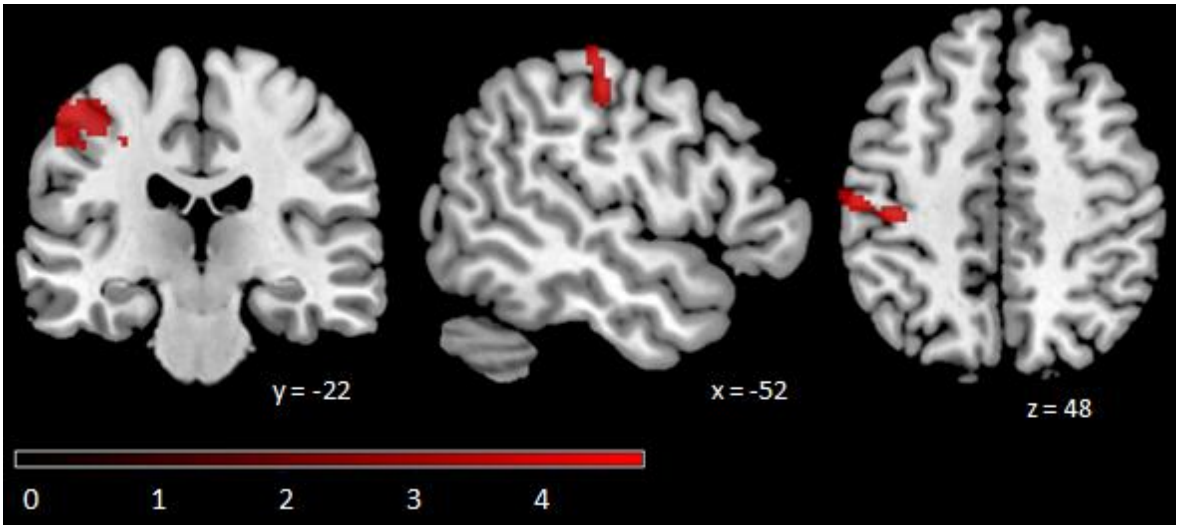


Figure X.2. Whole-brain analysis for the N-back task: significantly increased activity for the pre-training 1-back working memory load in left precentral gyrus and left postcentral gyrus. A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, clusters were formed with an uncorrected $p < .001$.

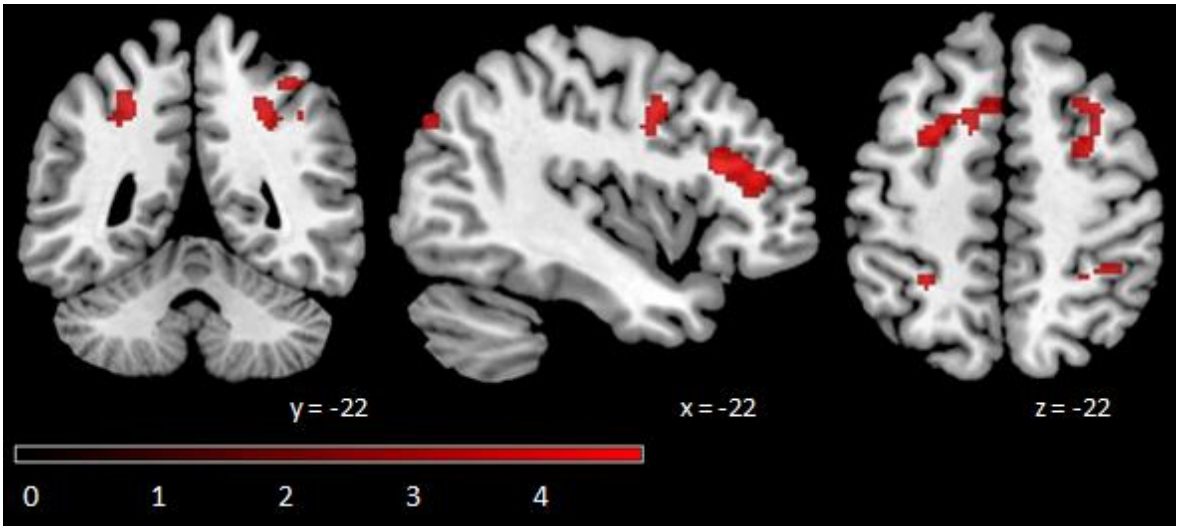


Figure X.3. Whole-brain analysis for the N-back task: significantly increased activity for the post-training 4-back working memory load in left vPFC (not shown), left posterior-medial frontal gyrus, left superior medial gyrus, left middle occipital gyrus (not shown), right superior parietal cortex, right angular gyrus (not shown), right cerebellum (not shown), and bilaterally in dPFC, precentral gyrus, and inferior parietal cortex (not shown). A statistical significance threshold of $p < .05$ FDR-correction at the cluster level was used, clusters were formed with an uncorrected $p < .001$.