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Physical exercise training as treatment for working memory impairment in major depressive disorder

Understanding of the underlying mechanisms

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M.Sc. – Psych. Melanie Schwefel

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Erstgutachter:
Prof. Dr. Stephan Heinzel

Zweitgutachterin:
Prof. Dr. Katja Wingenfeld

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Table of contents

English Summary

Major Depression Disorder (MDD) is often accompanied by cognitive impairments, including concentration problems and attention deficits. These issues are related to the construct of working memory (WM). Additionally, a reduction in hippocampal volume is frequently observed in Major Depression. There is substantial evidence suggesting that physical exercise training can have positive effects on depressive and cognitive symptoms in MDD. This dissertation aims to integrate these areas of study to investigate the positive effects of physical fitness and exercise on WM in MDD patients, leading to a better understanding of the pathophysiology of the disease and its treatment through physical exercise training.

The dissertation comprises three empirical studies that are part of the SPeED study (Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients). In Study I (Heinzel et al. 2022), we examine whether a prior exercise intervention enhances the success of subsequent cognitive-behavioral therapy (CBT) and whether this effect is associated with specific physiological changes. Study II (Schwefel et al. 2023) analyzes neural activity and physical fitness in depressive patients during a WM task. Study III (Schwefel et al., sub) focuses on functional and structural neural changes following physical exercise training, with particular emphasis on the hippocampus. The n-back paradigm was used to measure WM function during functional magnetic resonance imaging (fMRI). The physical exercise intervention lasted 12 weeks and was supervised by sports therapists.

The results indicate that physical fitness can be improved through training, and surprisingly, depressive symptoms improved in all groups. However, high exercise intensity did not lead to a general *boosting effect* for CBT. Nonetheless, regression analyses revealed that improvement of individual fitness predicted the success of CBT. MDD patients exhibited a specific activation pattern in frontoparietal brain regions, associated with longer reaction times

and poorer performance during high demands in WM tasks compared to healthy controls. Additionally, a parietal fitness correlate was identified in the depressive sample. Improved performance and shorter reaction times were observed after the training intervention, particularly during high demands in the WM tasks. Furthermore, in patients who underwent intensive training, an increased activation of the hippocampus was observed as a result of the training. No structural changes in hippocampal volume were detected.

The findings suggest that physical training holds promise as a treatment option for improving WM function in MDD patients. These insights may serve as a foundation for future research on the effects of physical fitness and exercise on mental health and cognition, offering valuable supplements to optimized physical exercise therapies for the treatment of MDD.

Deutsche Zusammenfassung (German Summary)

Major Depression Disorder (MDD) geht oft mit kognitiven Beeinträchtigungen einher, wie etwa Konzentrationsproblemen und Aufmerksamkeitsstörungen. Diese Probleme stehen im Zusammenhang mit dem Arbeitsgedächtnis. Daneben wird bei MDD oft eine Verringerung des Hippocampusvolumens festgestellt. Es gibt viele Hinweise darauf, dass körperliche Aktivität und Training positive Auswirkungen auf depressive und kognitive Symptome bei MDD haben können. In dieser Dissertation werden diese Bereiche zusammengeführt, um die positiven Effekte von körperlicher Fitness und Training auf das Arbeitsgedächtnis bei MDD-Patienten zu erforschen und ein besseres Verständnis für die Pathophysiologie der Erkrankung und deren Behandlung durch körperliche Aktivität zu entwickeln.

Die Dissertation umfasst drei empirische Studien, die Teil des SPeED-Projekts (Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients) sind. In Studie I (Heinzel et al. 2022) wird untersucht, ob eine vorangehende Trainingsintervention den Erfolg einer nachfolgenden kognitiven Verhaltenstherapie (KVT) steigert und ob dieser Effekt mit spezifischen physiologischen Veränderungen zusammenhängt. In Studie II (Schwefel et al. 2023) werden neuronale Aktivität und körperliche Fitness bei depressiven Patienten während einer Arbeitsgedächtnisaufgabe analysiert. Studie III (Schwefel et al., sub) konzentriert sich auf funktionelle und strukturelle neuronale Veränderungen nach körperlichem Training, insbesondere im Hippocampus. Um die Arbeitsgedächtnisfunktion zu messen, wurde das n-back-Paradigma im Magnetresonanztomographen eingesetzt. Die Trainingsintervention dauerte 12 Wochen an und wurde von Sporttherapeut*innen unter Supervision angeleitet.

Die Ergebnisse zeigen, dass körperliche Fitness durch Training gesteigert werden kann und überraschenderweise die depressive Symptomatik in allen Gruppen verbesserte. Eine hohe Trainingsintensität führte jedoch nicht zu einem generellen *Boosting-Effekt* für die KVT.

Regressionsanalysen zeigten jedoch, dass das Ausmaß der individuellen Fitnessverbesserung den Erfolg der KVT vorhersagte. MDD-Patienten zeigten ein spezifisches Aktivierungsmuster in frontoparietalen Hirnarealen, das mit verlängerten Reaktionszeiten und schlechterer Leistung bei hohen Anforderungen in der Arbeitsgedächtnisaufgabe einherging. Außerdem konnte ein parietales Fitnesskorrelat in der depressiven Stichprobe gefunden werden. Eine verbesserte Leistung und niedrigere Reaktionszeiten bei höheren Anforderungen wurden nach der Trainingsintervention beobachtet. Außerdem wurde bei Patienten, die ein intensives Training absolvierten, eine erhöhte Aktivierung des Hippocampus als Folge des Trainings festgestellt. Strukturelle Veränderungen im Hippocampusvolumen wurden nicht festgestellt.

Die Ergebnisse deuten darauf hin, dass körperliches Training eine vielversprechende Behandlungsoption für MDD-Patienten zur Verbesserung der Arbeitsgedächtnisfunktion darstellt. Diese Erkenntnisse könnten die Grundlage für zukünftige Forschung über die Auswirkungen von körperlicher Fitness und Bewegung auf die psychische Gesundheit und Kognition bilden und als wertvolle Ergänzung zu optimierten Bewegungstherapien für die Behandlung von MDD dienen.

1. Theoretical Background

Major Depressive Disorder (MDD) is one of the most prevalent mental disorders (Wittchen et al., 2011). Many treatment approaches have been tried and described, some have already been scientifically established (psychotherapy and antidepressant medication) and yet there is still no optimal form of treatment, indicated by relatively low remittance rates of 50% and below (Cuijpers et al., 2021). In addition to disrupted mood, cognitive impairment, especially working memory (WM) deficits, has been associated with depression (Rock et al., 2014; Semkovska et al., 2019; Snyder, 2013). MDD severely limits psychosocial functioning and diminishes quality of life (Malhi & Mann, 2018). It has been proven that physical exercise training lead to antidepressive effects (Cooney et al., 2013; Heinzel et al., 2015; Schuch et al., 2018). Improvements in cognitive domains through physical exercise training have also been confirmed in MDD (Contreras-Osorio et al., 2022). To gain a better understanding of how physical activity and exercise training lead to these improvements, it is of fundamental importance to explore the neural underpinnings. The aim of this dissertation project was to investigate the relationship between physical activity/exercise training and brain functioning in MDD. To this end, within a large-scale project, the SPeED study (Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients) (Heinzel et al., 2018), first focused on the relationship between physical exercise training as an add-on treatment to cognitive behavioral therapy (Study I). Using fMRI methods, a cross-sectional analysis was then conducted to investigate whether physical fitness was related to neural activity during WM performance in MDD (Study II). A longitudinal analysis was then conducted to investigate the effects of physical exercise training on neural activity during WM performance in MDD (Study III). Throughout the work, I use the term *physical activity* for simple physical activity and *physical exercise training* for targeted physical interventions. *Physical fitness* refers to the overall health, strength, flexibility, and endurance of the body, achieved through regular exercise or/and a balanced lifestyle.

In section 1.1. there will be an overview of MDD and its clinical, cognitive, and neurobiological characteristics. Then, in 1.2., the concept of WM in the context of depression will be presented. In 1.3. an overview of the current state of research on physical activity/exercise training and depression will be described. Finally, section 1.4. summarises the current state of research on physical exercise in WM processes in MDD.

1.1. Major depressive Disorder

With an estimated 322 million people affected, MDD are among the most common mental disorders worldwide (World Health Organization, 2017). It is a neuropsychiatric illness characterized by persistent low mood and loss of interest in pleasurable (American Psychiatric Association, 2013). Woman (prevalence: 4.5%) are more affected than men (prevalence: 3%) (World Health Organization, 2022).

1.1.1. Clinical characteristics

MDD is characterized by a persistent and pervasive low mood or a loss of interest or pleasure in almost all activities. The clinical features encompass a range of emotional, cognitive, physical, and behavioral symptoms. This typically manifests itself in dejection, joylessness, emotional emptiness, listlessness, loss of interest and physical complaints (Hautzinger, 1998). They are classified into mild, moderate and severe severity (Dilling & Freyberger, 2019).

According to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM – 5, Falkai et al., 2018), to meet criteria for MDD, depressed mood, loss of interest or pleasure in daily activities must have been present for at least two weeks. This mood must limit the person's ability to function in social, occupational, or educational settings and cause distress. In addition, there must be at least five of nine symptoms that occurred almost every day for most of the day during this episode. These symptoms include: (1) depressed mood, (2) loss of interest, (3) significant weight loss/gain or increase/decrease in appetite, (4) insomnia or hypersomnia, (5)

psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of one's own worthlessness or excessive or inappropriate guilt, (8) impaired thinking ability, difficulty concentrating, or indecision, and (9) recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt (Gruenberg et al., 2005).

1.1.2. Cognitive characteristics

Cognitive impairment represents a core feature of depression (Rock et al., 2014; Semkovska et al., 2019). These primarily affect information processing speed, visual selective attention, verbal learning, long-term memory, and executive functioning (Henry & Crawford, 2005; Kriesche et al., 2023; Smith, 2014). Cognitive flexibility, problem-solving and decision-making and negative cognitive bias are additional affected areas, which could be impaired. Rock et al. (2014) report that approximately two-thirds of all MDD patients show cognitive deficits and in at least one-third they persist even after depressive disorder. Similarly, Semkovska et al. (2019) have also argued that impairments in selective perception, working memory, and long-term memory persist even after remission of a depressive episode and worsen with repeated episodes.

Cognitive processing in individuals with depression is influenced by cognitive biases, as highlighted in Beck's cognitive model of depression (Beck, 2008). These biases involve a tendency to prioritize negative emotional material in memory processing that is congruent with one's mood. This plays a crucial role in the development and persistence of depression. Excessive attention and processing of negative information can lead individuals to form negative perceptions about themselves and their social interactions (Judd et al., 2000), increasing the risk of future major depression (Cuijpers & Smit, 2004). Attention bias, interpretation bias, and memory bias are associated with deficits in the processing of negative emotional stimuli within WM (Joormann & Tanovic, 2015). Individuals with depression may exhibit biases against actively maintaining positive information and a tendency to hold onto negative content in WM, contributing to the maintenance of negative mood states (Levens &

Gotlib, 2010). Studies have consistently shown that impaired functioning in WM is a core cognitive deficit in depression (Baddeley, 2013; Beblo et al., 2020; Hammar et al., 2022). Moreover, the neural oscillatory activity in individuals with depression during WM encoding and maintenance is different from that observed in healthy individuals (Murphy et al., 2019). Furthermore, a systematic review has found significant WM impairment in individuals with depression who have a history of suicide attempts (Lalovic et al., 2022). The cognitive deficits observed in depressive disorders can occur independently of other symptoms, but they interact with emotional and social factors to impact the individual's social functioning (Baune et al., 2010; Bortolato et al., 2014; Knight et al., 2018).

In summary, cognitive biases and deficits in WM processing play a crucial role in the cognitive impairments observed in individuals with depression. These impairments contribute to the development, maintenance, and severity of depressive symptoms.

1.1.3. neurobiological characteristics

MDD is a complex psychiatric disorder that has neurobiological features in addition to clinical and cognitive features. While the exact causes of MDD are not fully understood, several neurobiological factors have been identified as playing a role in the development and manifestation of the disorder (Dean & Keshavan, 2017; Lima-Ojeda et al., 2018; Malhi & Mann, 2018). Without claiming to be exhaustive, given the wealth of current research, some key features are briefly mentioned here: monoamine neurotransmission, neuroendocrine dysregulation, neurogenesis and neuroplasticity, structural and functional brain changes, genetics and family history, inflammatory processes, epigenetic factors. In the following, I will further focus these mechanisms that are relevant to my research question here.

Neurogenesis and Neuroplasticity:

Brain plasticity, the brain's ability to change and adapt, relies on various molecular factors, including brain-derived neurotrophic factor (BDNF). BDNF promotes the survival of neurons, facilitates the growth of new neurons and synapses, and supports neuroplasticity (Allen & Dawbarn, 2006). Neuroplasticity, particularly through neurogenesis (the generation of new neurons), is a key discovery in understanding cellular adaptability in the adult brain. Inflammation and dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, often triggered by environmental stress, can alter neuroplasticity (Egeland et al., 2015). Evidence suggests that BDNF is expressed early in the development of brain areas associated with depression, such as the hippocampus (Huang & Reichardt, 2001). Several meta-analysis have found reduced levels of BDNF in individuals diagnosed MDD, suggesting a potential involvement of BDNF in the underlying mechanisms of depression (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Sen et al., 2008). Importantly, antidepressant therapies have been shown to restore reduced BDNF levels and promote neurogenesis, contributing to their clinical effects (Molendijk et al., 2014). Limiting neurogenesis in animal studies prevents antidepressant action and induces depression-like symptoms, highlighting neurogenesis's role in resilience against stress and its relevance to antidepressant effects (Kraus et al., 2017). Post-mortem studies in depressed patients reveal deficits in granule neurons in the dentate gyrus (an integral region of the hippocampal formation), while treated individuals exhibit increased neuronal progenitor cells (Gururajan et al., 2016). These findings align with mouse studies suggesting that antidepressants work by enhancing neurogenesis in the adult brain (Malhi & Mann, 2018).

Structural and functional brain changes

Neuroimaging studies have revealed structural and functional alterations in the brains of individuals with MDD. Reduced volume and abnormal activity have been observed in

regions such as the prefrontal cortex, hippocampus, amygdala, and anterior cingulate cortex (ACC) (Bora et al., 2012; Gray et al., 2020; Lorenzetti et al., 2009; Schmaal et al., 2016). These brain regions are involved in emotional regulation, cognitive control, reward processing, and the formation of memories. Functional neuroimaging studies consistently indicate that memory processes in the hippocampus are impaired in MDD (Fairhall et al., 2010; Milne et al., 2012; Schmaal et al., 2016; Shunkai et al., 2023; Toki et al., 2014). In particular, the finding that hippocampal volume is reduced was consistently confirmed (Arnone et al., 2012; Schmaal et al., 2016). Some studies suggest a correlation between the extent of volume loss and the duration of untreated lifetime depression (Cole et al., 2011; Kempton et al., 2011). Post-mortem investigations reveal that the volume of the dentate gyrus in untreated depressed patients is approximately half that of both non-depressed individuals and treated depressed patients (Boldrini et al., 2018; Boldrini et al., 2013). The question of whether the diminished hippocampal size can be reversed through treatment and if it is essential for an antidepressant response remains unanswered in clinical research.

Monoamine Neurotransmission:

One of the most widely studied biological factors in MDD is the dysregulation of neurotransmitters, such as serotonin, norepinephrine, and dopamine. These neurotransmitters are involved in regulating mood, emotions, and motivation. Imbalances or abnormalities in their functioning have been associated with depressive symptoms. For a long time, the serotonin *chemical imbalance* theory of depression was postulated, stating that serotonin metabolism is reduced in MDD, which was primarily based on the efficacy of antidepressant medications (for review, see Dean & Keshavan, 2017). A recent umbrella study (Moncrieff et al., 2022) refuted the serotonin *chemical imbalance* theory, which has since been the subject of much debate in the scientific world (Jauhar et al., 2023).

It's important to note that these characteristics are not exclusive to MDD and can vary among individuals. The interplay between genetic predisposition, environmental factors, and the complex neurobiological mechanisms involved in MDD is still an area of active research.

1.2. Working Memory and Depression

WM is a crucial cognitive system that allows for the temporary storage and processing of goal-relevant information, playing a vital role in cognitive tasks and everyday activities (Wager & Smith, 2003). It is a limited-capacity system that facilitates the retention and manipulation of information over a brief period of time (Baddeley & Logie, 2012; Rottschy et al., 2012), including two types of mechanisms: online maintenance of information and its volitional or executive control (Miller et al., 2018). Baddeley's Multicomponent Theory, with its four components including the central executive (CE), the visuo-spatial sketch pad, phonological loop and episodic buffer, has been influential in understanding WM (Baddeley, 2000; Baddeley & Hitch, 1974). The CE, considered the most complex and core component, is responsible for attentional focus, storage, and decision-making (Baddeley & Logie, 2012). As WM theory and neuroscience have developed, researchers have increasingly focused on the CE. Miyake et al. (2000) examined the separability of WM function and proposed four independent functions, such as shifting attention, updating information, resisting distractions and preventing intrusion of irrelevant memories. Investigating the distinctiveness of sub-functions within the CE system of WM has become a widely adopted method for studying cognitive mechanisms underlying WM on a global scale (Karr et al., 2018). Most researchers use Miyake et al.'s (2000) classification of WM capacity, which is divided into three functional categories: updating, shifting and inhibition (Chen et al., 2023).

In summary, WM is a cognitive system comprising multiple components, with the CE being central and complex. The separability of WM functions, including shifting, updating, resistance to distractions, and intrusion prevention, has been extensively studied. Executive functions,

including WM, inhibition, and cognitive flexibility, are crucial for goal-directed behavior and have a profound impact on the psychosocial adaptation of individuals with depression, regardless of improvements in other symptom domains (Bortolato et al., 2014; Rock et al., 2014).

Over the years, many paradigms have evolved to study WM, including n-back, delayed matching to sample, delayed simple matching, continuous performance test, mental arithmetic, Tower of London tasks and Sternberg (Rottschy et al., 2012). Neuroimaging research with MDD patients completing WM tasks has shown that WM impairments are mediated by abnormalities in prefrontal, temporal, cerebellar, and subcortical regions (Harvey et al., 2005; Vasic et al., 2009). As described in 1.1.3., cortical-limbic/subcortical circuits appear to be involved in the regulation of mood, cognition, and behavior and in the pathophysiology of MDD (Soares & Mann, 1997). In functional brain imaging literature, alterations in brain activation during WM in depression, specifically focusing on the dorsolateral prefrontal cortex (Harvey et al., 2005; Kerestes et al., 2012; Matsuo et al., 2007; Pu et al., 2011) and the involvement of the ACC (Bertocci et al., 2012; Harvey et al., 2005; Hugdahl et al., 2004; Matsuo et al., 2007; Schöning et al., 2009). However, the direction of the activation is still focus of research. Some authors have identified hyperactivations in frontal areas (Harvey et al., 2005; Matsuo et al., 2007; Wagner et al., 2006; Walter et al., 2007), which could potentially compensate for reduced neural efficiency (Barulli & Stern, 2013; Heinzel et al., 2014). In other studies, frontoparietal hypoactivity has been observed in MDD (Garrett et al., 2011; Meusel et al., 2013; Xia et al., 2019; Zhu et al., 2018), indicating that activity levels may be limited by cognitive capacity (Garrett et al., 2011; Meusel et al., 2013), depending on task difficulty and performance. Therefore, the magnitude of WM load appears to be an important factor as an indicator of task demand (Duncan & Owen, 2000; Harvey et al., 2005). A meta-analysis by (Wang et al., 2015) including 13 WM experiments from 11 studies, patients with MDD showed consistent

functional abnormalities in the cortical-limbic-subcortical circuitry during WM processing (Figure 1). Significantly increased activation during WM in the left lateral prefrontal cortex, left precentral gyrus, left insula, right superior temporal area, and right supramarginal area and significantly decreased activity in the right precentral gyrus, right precuneus, and right insula were observed in MDD compared with controls. Wang et al. (2015) postulated, that distinct patterns of neural engagement may reflect compensatory neural strategies to potential dysfunction in MDD.

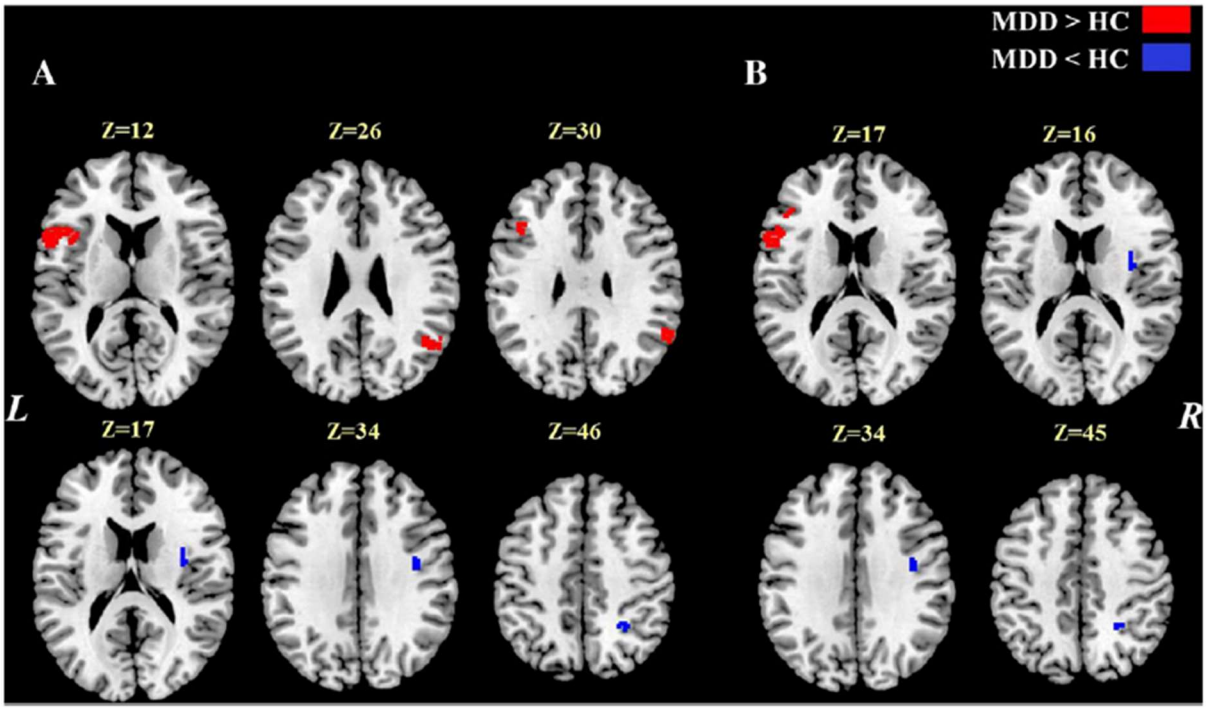

Figure 1. Statistical map of significant clusters in MDD compared with HC. Clusters of relative hyperactivation and hypoactivation are shown in red and blue respectively; numbers represent axial (z) coordinates of each slice in Talairach space. A: In pooled meta-analysis hyperactivation in the left dorsolateral prefrontal cortex, right supramarginal gyrus, left ventrolateral prefrontal cortex (VLPFC), left insula, right superior temporal gyrus, and hypoactivation in the right insula, right precentral gyrus right precuneus. B: In subgroup-analysis hyperactivation in the left middle prefrontal gyrus, left VLPFC, and hypoactivation in the right insula, right precentral gyrus, right precuneus. Results uncorrected at $p < 0.005$ with a minimum cluster size of 10. MDD= Major depressive disorder; HC=healthy controls. Graphic from Wang et al. (2015).

1.2.1. N-back-Paradigm

A commonly used measurement of WM is the n-back task, which allows manipulation of WM load (Nikolin et al., 2021). It involves presenting a series of stimuli, such as letters or numbers, and requires participants to indicate whether the current stimulus matches the one that occurred *n* steps back in the sequence. This task has several advantages: it allows precise measurement of reaction time and accuracy, easy modulation of different levels of loading and it facilitates the simultaneous acquisition of neuroimaging and neurophysiological activity associated with WM processes, e.g., by electroencephalography and fMRI. Besides different load levels, stimuli types (e.g., verbal, visual, spatial, auditory) and presentation modalities (e.g., letters, numbers, faces, objects) can be varied. Since attentional processes are primarily measured and no items in WM need to be updated, the simplest level (0-back) is used as a baseline (Harvey et al., 2004). Higher order WM functions, like updating and manipulation, become necessary as the load factor rises. Accordingly, presumptions regarding potentially compromised cognitive subprocesses in MDD can be formed on the basis of neural brain activity and performance patterns at various n-back stages (Nikolin et al., 2021). Figure 2 shows an example of a numerical n-back task. In a 2-back load, participants must compare the current stimulus with the one presented two steps back in the sequence.

A meta-analysis by (Mencarelli et al., 2019) focusing on the underlying neural substrates of n-back task confirm the known involvement of frontoparietal areas across different types of n-back tasks, as well as the recruitment of subcortical structures, cerebellum and precuneus. Studies using this task in MDD have shown performance degradation in the form of reduced accuracy and slowed reaction times (Harvey et al., 2004; Nikolin et al., 2021; Rose & Ebmeier, 2006; Rottschy et al., 2012).

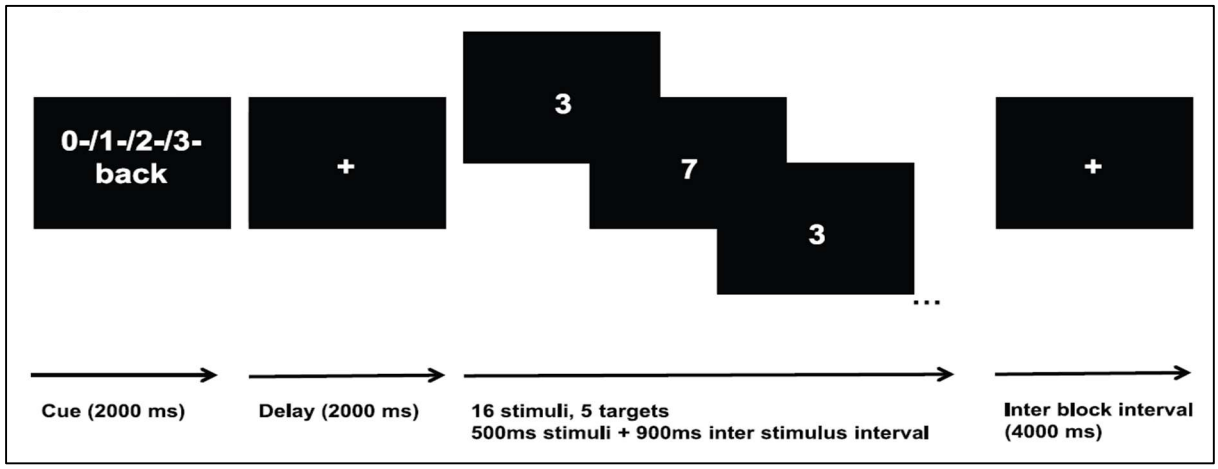

Figure 2. Example of a numeric n-back task. This shows 2-back level. Graphic adapted from (Heinzel et al., 2018).

1.3. Physical Activity/Exercise training and Depression

Regular physical training is associated with a variety of positive physical effects, e.g., improved strength and endurance (Herbsleb, 2021) or a reduction in the risk of coronary heart disease, obesity, and diabetes mellitus (Cleven et al., 2020), as well as an increase in well-being (Brinkmann, 2014). Current activity guidelines recommend at least 150 to 300 minutes of physical activity each week for all adults aged 18 to 65 years (World Health Organization, 2019).

The term *exercise* is used interchangeably with the term *physical exercise* and is defined by the American College of Sports Medicine guidelines as planned, structured and repeated physical activity to maintain or improve one or more areas of physical fitness (Pescatello, 2014). Patients with depression often have a severe lack of physical activity and a stronger tendency to sedentary behavior, which is why up to 80% of patients do not meet the prescribed weekly activity guidelines under objective measures (Schuch et al., 2017).

An influential meta-analysis by Schuch et al. (2018) found that individuals who are more physically active are less likely (OR = 0.83, CI [0.79, 0.88]) to develop depression than those who are less physically active. Numerous other (meta-)analyses have also demonstrated that physical exercise training has an antidepressant effect with response rates similar to mainstream

therapies such as antidepressant medication and cognitive behavioral therapy (Cooney et al., 2013; Heinzel et al., 2015; Krogh et al., 2011; Kvam et al., 2016; Morres et al., 2019; Rethorst et al., 2009; Silveira et al., 2013). Moreover, a recent umbrella review conducted by Singh et al. (2023), which encompassed ninety-seven reviews, clearly showed that physical exercise training interventions have a positive impact on alleviating symptoms of depression. The effect size was medium, with a median effect size of -0.43 (IQR: -0.66 to -0.27), as compared to conventional care.

According to a recent review (Ross et al., 2023), aerobic exercise stands out as the most widely utilized form of physical exercise treatment. This popularity can be attributed to its convenient accessibility (requiring little to no equipment) and the ease of prescribing the right intensity. On the other hand, resistance exercise has shown potential in reducing depressive symptoms, but it has received less attention in research compared to aerobic exercise (Ross et al., 2023). Although there is limited evidence available, it suggests that both aerobic and resistance exercises can yield similar antidepressant effects. To maximize benefits in cardiovascular and muscular fitness, a combination of both aerobic and resistance exercises should ideally be recommended. With regards to the necessary intensity of physical activity required to produce an antidepressant effect, the current consensus in the research field (reviews and meta-analyses) and public health guidelines (Piercy et al., 2018) is that physical exercise should be done regularly, 3 to 5 sessions per week, for 45 to 60 minutes per session, and at a moderate to vigorous intensity, although this can be adjusted based on a particular individual's initial fitness level (Dishman et al., 2021; Pearce et al., 2022; Rethorst & Trivedi, 2013; Schuch et al., 2016; Stubbs et al., 2018). Ross et al. (2023) points that physical exercise prescription parameters (i.e., frequency, intensity, time, type) were often not consistently reported in studies, making accurate replication of studies or clinical application difficult.

1.3.1. Mechanisms of Action

The current state of research suggests that physical exercise training triggers numerous biological and psychological processes in complex ways (Voss et al., 2013). Some of these processes have a positive impact on depressive symptoms, as they may directly or indirectly influence dysfunctions associated with depression. It should be noted, however, that some of the exercise-induced mechanisms are probably not specific to depression, as effects have also been shown in other mental disorders (e.g., anxiety disorders, dementia, and schizophrenia). There are several biological and psychological mechanisms of action that are well studied (for review, see Heinzel, 2020; Ross et al., 2023). However, since I am focusing on the biological mechanisms of action of physical exercise in MDD. I will only briefly mention the psychological ones, specifically, studies on self-efficacy expectancy (Higgins et al., 2014) and self-esteem (Legrand, 2014). In the following, I briefly describe the existing research on the biological mechanisms of action in MDD. It should be noted that the potential mechanisms of action of physical activity/exercise on depressive symptoms are not yet well understood and much research is still needed (Kandola et al., 2019). Since there are so few studies using individuals with MDD, studies in healthy individuals and basic research on animal models are also included.

1.3.1.1. Neurobiological Underpinnings - Neuroplasticity

Regarding the neurobiological effects of physical exercise, there are a multitude of mechanisms or pathways by which physical exercise may moderate depression. The complexity of the biological basis of depression (see chapter 1.1.3.), combined with the intricate molecular cascade triggered by physical activity, presents a significant obstacle in attempting to unravel the effects of physical activity/exercise on depression (Ross et al., 2023). Serotonergic and noradrenergic pathways play an essential, albeit complex, role in the pathophysiology of depression and are the primary targets of initial pharmacotherapeutic treatment (i.e., SSRIs, SNRIs) (Schatzberg, 2002). Although the antidepressant effects of physical activity/exercise

may also result from serotonergic and noradrenergic signaling, there is also substantial evidence that it affects the HPA axis, BDNF, and immunological-inflammatory function (Ross et al., 2023). Physical activity induced contractions of skeletal muscle release cytokines into circulation. Briefly, cytokines are proteins produced in response to infection, inflammation, and stress (e.g., physical exercise) that affect tissues throughout the body, including the brain (Enache et al., 2019). Cytokines are released from muscle fibres in response to physical exercise (Pedersen et al., 2007). These substances, known as myokines, can exert anti-inflammatory effects locally (e.g., in muscle tissue) and distally (e.g., in the heart, liver, and brain) and play a major role in the health benefits triggered by physical exercise (Petersen & Pedersen, 2005). In this sense, skeletal muscle serves as a secretory organ, and physical exercise is a catalyst for the release of myokines that stimulate anti-inflammatory and antidepressant effects (Pedersen, 2011). Furthermore, current physiological models of exercise in depression (Heinzel, 2020; Kandola et al., 2019) suggest that physical exercise leads to an increase in physical fitness (e.g., maximum oxygen uptake, strength), that, in turn, triggers several biological mechanisms including the enhancement of neuroplasticity. As described in 1.1.3. biological features of depression, it has been found that reduced hippocampal volume is evident in MDD (Arnone et al., 2012; Schmaal et al., 2016). The hippocampus is among others crucial for memory processes as well as involved in emotion and stress processing. These morphological changes, in turn, could be related to disrupted neurogenesis, as evidenced by findings of decreased blood serum concentrations of the growth factor BDNF in depression (Phillips, 2017). Initial findings on the relationship between physical exercise, the increase in neurotrophic growth factors, and the proliferation of neurons, e.g., in the dendate gyrus and hippocampus, were found in animal models (Dietrich et al., 2008; Pereira et al., 2007; Yau et al., 2011) and later in healthy humans (Vivar et al., 2013). It is assumed that physical exercise initiates a cascade of adaptive processes that improve blood flow and the supply of oxygen and neurotrophins to the brain. It has been shown that physical exercise increases intracerebral angiogenesis (growth of new blood

vessels), which promotes neurogenesis (formation of new neurons) in the hippocampus and other brain regions (Heinzel, 2020). Animal findings suggest that physical exercise-induced neurogenesis is influenced in part via modulation of serotonin and norepinephrine (Lin & Kuo, 2013), which may also explain the antidepressant effect of physical exercise. In addition to alterations in brain structure, physical exercise can also induce modifications in brain function during both rest and task processing, particularly in the prefrontal cortex (Voelcker-Rehage & Niemann, 2013). Methods like resting-state functional connectivity in healthy individuals offer valuable insights into (hippocampal) circuitry health. Stillman et al. (2018) discovered a positive correlation between heightened cardiorespiratory fitness and increased resting-state functional connectivity from the left anterior hippocampus to various brain regions, including the frontal pole, middle frontal gyrus, and parahippocampus in healthy individuals. Aghjayan et al. (2021) emphasized in their review that both cardiorespiratory fitness and aerobic exercise play crucial roles in influencing the functional connectivity within medial temporal regions, including the hippocampus, and other brain structures associated with memory and executive functions in adults. In the context of depression, the effects of physical exercise on brain morphology and functionality are almost unexplored. There is one study that investigated the effects of physical exercise intervention on hippocampal volume (Krogh et al., 2014) but could not demonstrate a clear exercise-induced change. Studies have been able to demonstrate the acute effect of an endurance exercise session on BDNF concentration in blood serum (Kallies et al., 2019), but effects of a multi-week exercise intervention on BDNF concentration provide inconsistent findings (Kurebayashi & Otaki, 2018). Further research, including studies with MDD patients, is necessary to clarify the conditions (e.g., duration, type, or intensity of the intervention) that have causality (Heinzel, 2020).

In addition to neuroplasticity processes, neuroendocrinological and antiflammatory processes initiated by physical exercise are shown to have antidepressant effects (Heinzel, 2020; Kandola et al., 2019; Ross et al., 2023). While only a few key aspects and outcomes of

the overall neurobiological response to physical exercise are currently considered, it may become clear, that there is a complex relationship of serotonergic and noradrenergic pathways, BDNF, HPA axis function, immuno-inflammation and the antidepressant benefits of physical exercise regarding the underlying pathophysiology of depression.

1.4. Physical Exercise, Working memory and Depression

In addition to affecting various neurobiological connections, physical exercise interventions also have effects on a variety of cognitive domains. It is assumed that the antidepressive effect of physical exercise is mediated by its effect on brain functions supporting cognitive control and emotion regulation (Voelcker-Rehage & Niemann, 2013; Yu et al., 2021). Studies in healthy individuals have shown that physical exercise leads to improvements in cognitive control, memory, and emotion regulation, resulting in improved performance in these domains (Bherer et al., 2013; Herold, Törpel, et al., 2019; Hillman et al., 2008; Liu-Ambrose et al., 2018; Stimpson et al., 2018). Studies with MDD patients examining cognitive domains after physical exercise training have shown little to no substantial benefits in alleviating cognitive symptoms (Brondino et al., 2017; Sun et al., 2018). In contrast, a recent study examined the impact of a 6-week aerobic exercise intervention on various cognitive domains, including WM functions and observed a significant positive effect on WM in individuals with MDD, in addition to the antidepressant effects (Imboden et al., 2020). In a recent meta-analysis by (Contreras-Osorio et al., 2022), the researcher focused explicitly on the individual domains of executive functions, which are especially relevant to this population's symptomatology and functional performance (Kriesche et al., 2023). Results indicate that physical exercise training improves WM in adults with depression, with a small but significant positive effect (ES = 0.33, p = 0.026). No significant effect was found on the other cognitive dimensions, inhibition or cognitive flexibility.

In this growing field of research on physical exercise interventions on cognition, it is difficult to make comparable statements. The research designs are often very inconsistent in

terms of the exercise intervention conducted (frequency, duration, intensity) (Ross et al., 2023) but also in terms of the cognitive paradigm and outcome measurements (e.g., processing speed, attention/vigilance, verbal learning and memory, and visual learning and memory) (Contreras-Osorio et al., 2022).

2. Aims and Design of the Dissertation project

This dissertation project focuses on investigating the effects of physical activity/exercise training in patients with major depression, particularly on WM functions, and to better understand the neural mechanisms underlying MDD pathophysiology and its treatment.

In Study I (Heinzel et al., 2022) we investigated if a preceding physical exercise training intervention will increase the success of a subsequent CBT and if this augmentation effect is associated with specific physiological changes. In Study II (Schwefel et al., 2023), we analysed a cross-sectional fMRI-analysis of both neural activity during the performance of a WM task and physical fitness during exercise electrocardiography in a large sample of patients with MDD. Finally, in Study III (Schwefel et al., sub), we used a longitudinal fMRI experiment to examine functional and structural neural changes during a WM task after physical exercise training, in particular hippocampal function in MDD.

Section 2.1. presents the research questions and hypothesis for each study. Section 2.2. explains the rationale for the three studies, including the SPeED project, in order to understand the design and methodology of the studies that address the research questions and test the hypothesis. All studies are part of the large-scale SPeED project, with the methodology for this presented in section 2.2.

2.1. Research questions and Hypotheses

In the following I will briefly outline the considerations and current state of research leading to the formulation of the research questions and the associated hypotheses for studies I, II, and III.

2.1.1. Study I

As presented in sections 1.3. physical exercise seems to be beneficial for MDD. However, the physiological mechanisms of these effects are still poorly understood (see chapter 1.3.1.). Furthermore, it is unclear whether and how the additional implementation of structured,

supervised exercise programs in psychotherapy for MDD can improve clinical outcomes. This study aimed to enhance our understanding of the underlying mechanisms involved in the combination of physical exercise training and CBT in MDD. Physical exercise may be effective in MDD because it can counteract certain psychological and physiological pathologies. Therefore, physical exercise training is thought to be an effective pretreatment for subsequent CBT (Heinzel et al., 2018).

Research questions:

- Does a previous exercise intervention increase the success of as subsequent CBT in the treatment of MDD?
- Is this augmentation effect associated with specific physiological change?

Hypotheses:

(1) After the exercise intervention/ waiting period, the high intensity exercise group compared to the low intensity exercise group (dose-response relation) and the waiting list control group is expected to show an increase in physical fitness.

(2) The outcome of CBT as measured by symptom assessments is expected to be better in the high - compared to the low - intensity exercise group (dose-response relation) and the waiting list control group.

(3) Within the exercise groups, CBT outcome can be predicted by improvements in physical fitness during the exercise intervention.

2.1.2. Study II

As presented in section 1.2. neuroimaging research with MDD patients completing WM tasks has shown that performance is impaired in the form of reduced accuracy and slowed response times and that these impairments are mediated by frontoparietal circuitry abnormalities by virtue of hyper- and hypoactivity in frontoparietal regions. In section 1.4. we examined studies that reported effects of physical activity/exercise training on frontoparietal

brain activity during the performance of cognitive tasks in healthy individuals. Given the scarcity of previous research on the effects of physical fitness on the pathophysiology of WM impairments in MDD and their neural patterns, this study aimed to address this gap. We investigated both neural activity during the performance of a WM task and physical fitness during exercise electrocardiography in patients with MDD. To test WM load-dependent hypotheses, we used an n-back task with four WM load levels as previously reported (Heinzel et al., 2018).

Research questions:

- Can a WM load-dependent specificity be observed in individuals with MDD compared to healthy individuals in both behavioral and neural measures?
- Is there a relationship between physical fitness and brain functioning during WM task performance in MDD?

Hypotheses:

(1) Compared to healthy controls, patients with MDD show both lower performance and higher reaction times in an n-back task specifically at high WM load.

(2) Patients with MDD show increased activation at low and decreased activation at high WM load in frontoparietal WM regions indicating reduced WM load-dependent modulation of neural activity compared to healthy controls.

(3) Whole Brain-Analyses within the MDD group show a fitness correlate in parietal regions. Fourth, Region-of-Interest (ROI) analyses within the MDD group that performed a graded exercise test show, on one hand, a positive relationship between behavioral n-back performance and physical fitness and, on the other hand, a positive relationship between parietal n-back activity and physical fitness.

2.1.3. Study III

As discussed in section 1.3.1.1., neuroplasticity is frequently invoked to explain the antidepressant effects observed after physical exercise training. The finding that the hippocampus volume, which plays an important role in emotions and memory, is reduced in MDD is also well studied (see chapter 1.1.3.). The effects of physical exercise training on brain morphology and functionality, especially WM functioning, in patients with MDD are basically unexplored. The aim of this exploratory longitudinal fMRI study was to investigate the neuronal changes during a WM task after physical training, especially the hippocampal function, and to investigate at a structural level the brain volume changes in MDD patients.

Research question:

- Are there changes in neural activation during a WM task or changes in brain volume evident in MDD patients after 12 weeks of physical exercise training, particularly in hippocampal function/volume?

Hypotheses:

(1) In an fMRI analysis, increased hippocampal activations during WM tasks are visible for the exercise groups compared to the control group after 12 weeks of training.

(2) Furthermore, a voxel-based morphometry analysis reveals a structural change in brain volume, especially hippocampal volume, in the exercise groups compared to the control group after exercise intervention.

2.2. Rationale of the studies - The SPeED study

The SPeED study is a randomized controlled trial investigating the effects of physical activity/exercise training and CBT in MDD (Heinzel et al., 2018). Using a longitudinal design (Figure 3), the study examined whether a previous physical exercise intervention increases the success of subsequent CBT and whether it is associated with specific physiological changes. The study was led by Prof. Dr. Stephan Heinzel from the Department of Clinical Psychology

and Psychotherapy at Freie Universität Berlin, Prof. Dr. med. Andreas Ströhle from the Department of Psychiatry and Psychotherapy at Charité, Campus Mitte and Prof. Dr. Thomas Fydrich from the Department of Psychology, Humboldt-Universität Berlin. In addition to the Freie Universität in Berlin and the University of Potsdam, the study's cooperation partners include the Center for Psychotherapy at the Psychological Institute of Humboldt University and the Sport- und Gesundheitspark Berlin/Zentrum für Sportmedizin Berlin. Funding and support was provided by the Emanuela Dalla Vecchia Foundation for Depression Research and the German Research Foundation (DFG). The study was approved by the local ethics committee of the Charité Universitätsmedizin Berlin, Germany (No EA1/113/15) and the ethics committee of the Freie Universität Berlin, Germany (No 133/2016). The study was registered at German register for clinical studies (DRKS) and the International Clinical Trials Registry Platform of the World Health Organization (https://trialsearch.who.int/Trial2.aspx?TrialID=DRKS00008869) and the study rationale, design, and methodological issues were reported in Heinzel et al. (2018).

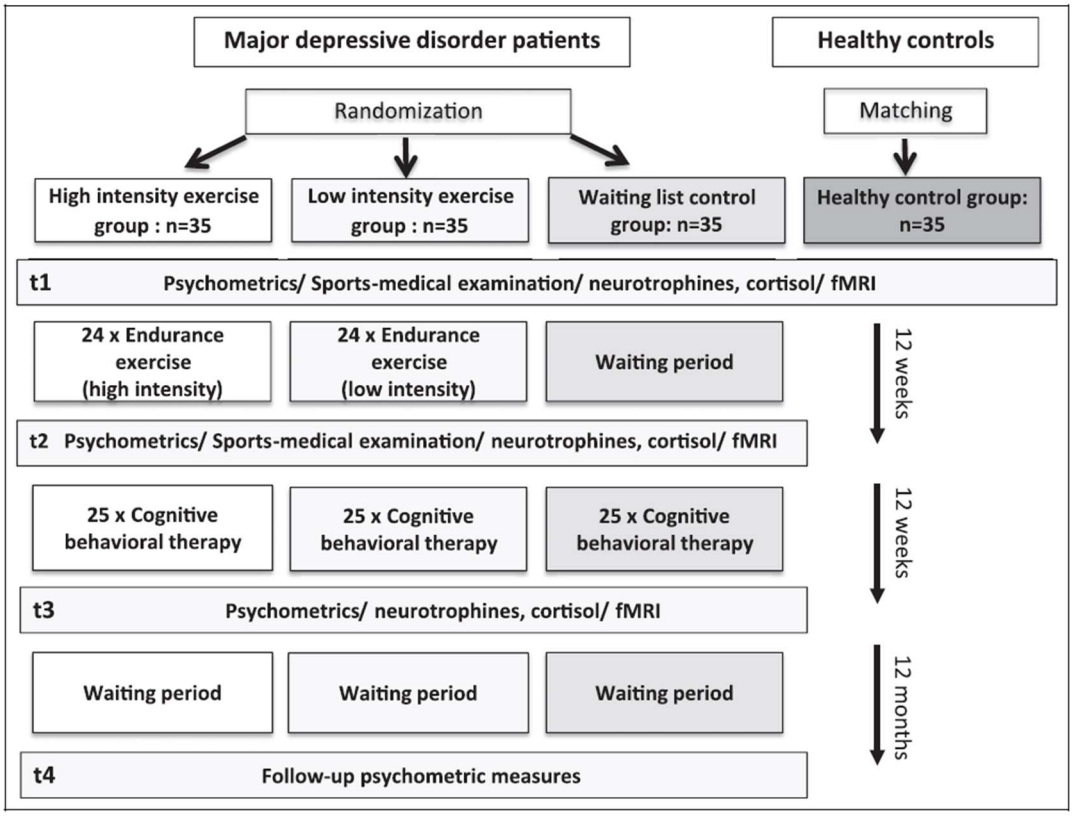

Figure 3. Study design. Graphic from Heinzel et al. (2018).

In order to provide a comprehensive insight into the methods used in the studies, this section focuses on the methods relevant to this dissertation project, while more in-depth information (including flow chart of patient flow and dropout reason) can be found in the respective papers.

2.2.1. Participants

Participants were recruited at the Center for Psychotherapy at Humboldt Universität zu Berlin, Germany, and via flyers and online advertisements. Written informed consent was obtained from all participants. All patients were randomly assigned to one of three groups: a high intensity exercise (HEX) group, a low intensity exercise (LEX) group, or a waiting list (WL) control group. After completion of exercise therapy/waiting list, all patients received the same manualized individualized CBT. Because dropout rates are generally higher in exercise groups than in a waiting list (Reljic et al., 2019), we chose a 3:3:2 allocation to the HEX, LEX, and WL groups, respectively. Random assignment sequences were generated prior to assignment by a computer program (MATLAB, The Mathworks Inc., Natick, USA) applied by a researcher not involved in the study. Participants were blinded to their assignment to HEX or LEX, but not to their assignment to an exercise group or WL. All participants were asked not to initiate additional regular and intensive physical exercise outside of the study protocol. All study participants complied with this request. All WL participants were offered participation in exercise treatment after t3 assessment. While the CBT therapists were blinded, the exercise instructors had to be unblinded because they used different training methods for HEX and LEX. The following inclusion criteria were used: A diagnosed mild or moderate depressive episode, age between 18 and 65 years, and passing a sports medicine physical examination. Past and current mental disorders were assessed in all participants by trained psychologists using the German version of the Structured Clinical Interview for DSM-IV TR (SCID, First et al., 1995). Some relevant exclusion criteria were current major depressive episode, current borderline or antisocial personality disorder, current suicidality, body mass index of >35 or <18, ineligibility for MRI, use of benzodiazepines or beta-blockers within the past 7 days, >2 × 45 min of

vigorous physical activity per week. For a list of all exclusion criteria or further study information, see Heinzel et al. (2018).

2.2.2. Supervised exercise interventions

Following the existing literature (see section 1.3), the subjects of our study completed a 12-week training program in the exercise groups. This consisted of two weekly sessions of 60 min training. According to the guidelines for endurance training from the American Heart Association (Fletcher et al., 2013), one session of the HEX group consisted of 20 min of bicycle ergometer, 20 min of running or Nordic walking, and 20 min of aerobic physical training at 55-85% of individual maximal heart rate reserve. The LEX group completed a similar program but consisting of much lower intensities of about 20-30% of individual maximal heart rate reserve. The training included 20 minutes of bicycle ergometer, 20 minutes of walking, and 20 minutes of stretching and relaxation. Heart rate was recorded with a heart rate monitor during the exercise sessions, and the Borg scale (Borg, 1982) was used as a measure of effort. Both groups were instructed by the same professional sports therapist to reduce trainer effects.

2.2.3. Assessment of Physical Fitness

Physical fitness was assessed at t1 and t2 (before and after exercise training) by stress electrocardiogram (ECG) during bicycle ergometry (Ergoselect 100; Ergoline GmbH, Bitz, Germany). Starting at 25 watts, workload was gradually increased with a repetitive progression of 25 W after every 2 min until reaching the maximum physical exertion (Borg, 1982). The finally reached level determined the maximum workload in Watt (W). The maximum effort was corrected for body weight in kilograms to obtain a measure of physical fitness that is comparable across individuals (Watts per kg) (Rost et al., 1982) This parameter is most relevant for Study II and serves as an indicator of successful intervention in Study I and II (longitudinal analysis).

2.2.4. N-back Paradigm during f-MRI

Analyzing WM function in study II and III, I will briefly describe the n back paradigm we used. We applied a modified version of the n-back task using numerical stimuli, following the methodology outlined by Heinzel et al. (2018). The task consisted of sixteen blocks, with four blocks each for 0-back, 1-back, 2-back, and 3-back. These blocks were visually presented in three different pseudo-randomized orders, which were counterbalanced across participants, resulting in a total duration of 9 minutes (for more details on the task design, please refer to the supplementary methods of Study II). For behavioral analyses, we used reaction time during correct responses and n-back performance, which was defined as the hit rate minus the false alarm rate. The n-back task is a well-established measure of WM processes in individuals with MDD, particularly in fMRI studies focusing on updating or manipulation processes (Nikolin et al., 2021). The 0-back condition served as a baseline, where no items needed to be updated in WM, primarily measuring attentional processes (Harvey et al., 2004). As the task's load factor increased, higher order WM functions, such as updating and manipulation, became more prominent. Hence, potential impairments in cognitive subprocesses can be inferred in MDD based on the pattern of performance and neural activity across the different n-back stages (Nikolin et al., 2021). Specifically, the 1-back condition can be defined as representing low (WM) load, the 2-back as medium load, and the 3-back as high load.

2.2.5. Measurement of brain imaging

For Study II and III, fMRI data was collected at Charité Campus Mitte, Berlin, with a 3TMagnetom Trio MRsystem and a 32-channel-headcoil (Siemens, Erlangen, Germany). A T1-weighted 3D pulse sequence was obtained (repetition time (TR) = 2440 ms, echo time (TE) = 4.81 ms, flip angle = 8 deg, matrix size = 256x258x192, sagittal slices with isotropic voxel size of 0.91 mm). Additionally, a T2-weighted 3D pulse sequence was measured (TR = 5000 ms, TE = 499 ms, flip angle = 120 deg, acquisition matrix = 256x258x192, sagittal slices with isotropic voxel size of 0.91 mm). Functional data was obtained using a gradient echo-planar

imaging (GE-EPI) pulse sequence (TR = 2000 ms, TE = 30 ms, flip angle = 78 deg, matrix size = 64 × 64, voxel size = 3.0 × 3.0 × 3.75 mm). 33 slices were acquired descending parallel to the bicommissural plane.

Additionally, voxel-based morphometry (VBM) was used in Study III to estimate changes in the volume of gray matter using high-resolution T1-weighted MPRAGE images. To implement this method, we employed the Computational Anatomy Toolbox (CAT12) (https://www.neuro.uni-jena.de/cat/), 'longitudinal model for small changes' within the Statistical Parameter Mapping (SPM12) software version 7771 (https://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB version R2022b.

Having introduced the aims, design and rationale of the three studies, the original publications of the studies (chapter 3, 4 and 5) will presented below. Supplementary material of the studies can be found in the appendix.

3. Study I: Physical exercise training as an add-on treatment to cognitive behavioral therapy in major depressive disorder: A randomized controlled trial.

This chapter has been published as „Heinzel, S., Schwefel, M., Sanchez, A., Heinen, D., Fehm, L., Henze, R., Terán, C., Kallies, G., Rapp, M. A., Fydrich, T., Ströhle, A., & Heissel, A. (2022). Physical exercise training as preceding treatment to cognitive behavioral therapy in mild to moderate major depressive disorder: A randomized controlled trial. *Journal of affective disorders*, *319*, 90–98.” https://doi.org/10.1016/j.jad.2022.09.024

4. Study II: Physical fitness is associated with neural activity during working memory performance in major depressive disorder

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Physical fitness is associated with neural activity during working memory performance in major depressive disorder

M.K. Schwefel [a,*], C. Kaufmann [b], G. Gutmann [a], R. Henze [a,b], T. Fydrich [b], M.A. Rapp [c], A. Ströhle [d], A. Heissel [c], S. Heinzel [a]

[a] Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany
[b] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany
[c] Social and Preventive Medicine, University of Potsdam, Potsdam, Germany
[d] Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité –Universitätsmedizin Berlin, Berlin, Germany

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ABSTRACT

Background: Deficits in cognition like working memory (WM) are highly prevalent symptoms related to major depressive disorder (MDD). Neuroimaging studies have described frontoparietal abnormalities in patients with MDD as a basis for these deficits. Based on research in healthy adults, it is hypothesized that increased physical fitness might be a protective factor for these deficits in MDD. However, the relationship between physical fitness and WM-related neural activity and performance has not been tested in MDD, to date. Understanding these associations could inform the development of physical exercise interventions in MDD.
Methods: Within a larger project, 111 (53female) MDD outpatients and 56 (34female) healthy controls performed an n-back task (0-, 1-, 2-, 3-back) during functional Magnetic Resonance Imaging. Physical fitness from a graded exercise test on a cycle ergometer was performed by 106 MDD patients.
Results: Patients showed reduced performance particularly at high loads of the n-back WM task and prolonged reaction times at all n-back loads. A whole-brain interaction analysis of group by WM load revealed reduced neural activity in six frontoparietal clusters at medium and high WM loads in MDD patients compared to healthy controls. Analysis of covariance within the MDD sample showed that physical fitness was associated with neural activity in right and left superior parietal lobules. Externally defined Regions of Interest confirmed this analysis.
Conclusions: Results indicate frontoparietal hypoactivity in MDD at high demands, arguing for decreased WM capacity. We demonstrate a parietal fitness correlate which could be used to guide future research on effects of exercise on cognitive functioning in MDD.

1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders, affecting approximately 322 million people worldwide (World Health Organization, 2017), and is characterized by affective, cognitive, and somatic symptoms. MDD patients frequently exhibit cognitive deficits, such as impaired attentional processes, executive functions (Shenal et al., 2003) and working memory (Semkovska et al., 2019; Snyder, 2013). WM is a cognitive system that is essential to the performance of cognitive tasks and everyday activities (Wager and Smith, 2003). It is defined as a limited capacity processing system that serves to retain and process information (Baddeley et al., 2012; Rottschy et al., 2012), e.g., content manipulation and updating (Engle et al., 1999). A commonly reported measure of WM is the n-back-task which allows to manipulate WM load. Studies using this measure in MDD showed that performance is impaired in the form of reduced accuracy and slowed response times (Harvey et al., 2004; Nikolin et al., 2021; Rose and Ebmeier, 2006). Such WM impairments are mediated by frontoparietal circuitry abnormalities (Wang et al., 2015) by virtue of hyper- and hypoactivity in frontoparietal regions. Some authors found hyperactivations in frontal areas (Harvey et al., 2005; Matsuo et al., 2007; Wagner et al., 2006; Walter et al., 2007) which might compensate for reduced neural efficiency (Barulli and Stern, 2013; Heinzel et al., 2014). Other studies found frontoparietal hypoactivations in MDD (Garrett et al., 2011; Meusel et al., 2013; Xia et al., 2019; Zhu et al., 2018), suggesting capacity-limited activity (Garrett et al., 2011; Meusel

* Corresponding author at: Clinical Psychology and Psychotherapy, Freie Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin, Germany.
E-mail address: melanie.schwefel@fu-berlin.de (M.K. Schwefel).

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et al., 2013) depending on task difficulty and performance. Therefore, the extent of WM load as an indicator of task demand seems to be an important factor. Taken together, these results suggest that MDD patients exhibit increased frontal activity at low WM loads. However, at high WM loads, MDD patients show decreased frontoparietal activity, indicating a reduced WM capacity limit. Thus, the first aim of this study is to investigate WM load-dependent specificity in MDD compared to healthy individuals in behavioral measures and neural activity, as a basis for developing adequate treatment approaches.

However, relatively low remittance rates of 50% and below indicate that there is room for improvement and additional treatment options should be investigated (Cuijpers et al., 2021; Shinohara et al., 2013). Meta-analyses suggest that antidepressant effects can be demonstrated for physical activity and exercise interventions (Cooney et al., 2013; Heinzel et al., 2015; Schuch et al., 2018). Physical exercise has been defined as a planned, structured, repetitive and purposeful subcategory of physical activity (Caspersen et al., 1985). Some approaches with healthy young as well as elderly individuals emphasize the role of regular physical activity and exercise to maintain cognitive functioning (Bherer et al., 2013; Hillman et al., 2008; Liu-Ambrose et al., 2018). To develop optimized physical exercise treatments that serve as clinically useful additional treatment options for MDD, it is important to gain a better understanding of biological mechanisms of physical activity and their effect on cognitive functions and depressive symptoms. Therefore, as a first step, this cross-sectional study is focused on physical activity and individual physical fitness without an intervention. It is thought that antidepressive effects of increased physical activity and fitness are mediated by neuroplasticity that supports cognitive functioning. However, most research on neurobiological mechanisms of physical activity has been done in healthy individuals (Herold et al., 2019; Voelcker-Rehage and Niemann, 2013; Yu et al., 2021) and model assumptions need to be tested in participants with MDD. In this endeavour, it would be an important step to investigate the relationship between physical fitness and brain functioning during cognitive task performance in MDD, which is the second aim of the current cross-sectional study.

Previous qualitative reviews of neuroimaging studies in healthy individuals reported effects of physical activity on frontoparietal brain activity during the performance of cognitive tasks (Herold et al., 2019; Voelcker-Rehage and Niemann, 2013). With the first quantitative meta-analysis in this specific field of research, Yu and colleagues (Yu et al., 2021) showed that physical activity interventions led to increased functional activations primarily located in precuneus, superior and inferior parietal lobule (Table 3) in healthy subjects. These regions are part of the frontoparietal and attention networks and have been related to executive control and working memory (Nee et al., 2013). In MDD, the precuneus has been associated with decreased activity in the n-back task (Wang et al., 2015). Furthermore, it is suggested that cognitive improvements are mediated by improvements in physical fitness (Colcombe and Kramer, 2003) in healthy individuals. Thus, if these mechanisms prove true in MDD, increased physical activity and fitness may counteract cognitive dysfunctions by means of specific functional brain changes.

In the current study, for the first time, we investigated both neural activity during the performance of a WM task and physical fitness during exercise electrocardiography in a large sample of patients with MDD. To test WM load-dependent hypotheses, we used an n-back task with four WM load levels as previously reported (Heinzel et al., 2018).

We hypothesized that

1) Compared to healthy controls, patients with MDD show both lower performance and higher reaction times in an n-back task specifically at high WM load,
2) Patients with MDD show increased activation at low and decreased activation at high WM load in frontoparietal WM regions indicating reduced WM load-dependent modulation of neural activity compared to healthy controls,
3) Whole Brain-Analyses within the MDD group show a fitness correlate in parietal regions.
4) ROI-Analyses within the MDD group that performed a graded exercise test show a
   a. positive relationship between behavioral n-back performance and physical fitness,
   b. positive relationship between parietal n-back-activity and physical fitness.

2. Methods and materials

2.1. Participants and behavioral data

111 MDD outpatients and 56 healthy control (HC) subjects participated in the current study. This analysis is a cross-sectional study in the context of a larger longitudinal project on the long-term effects of physical exercise (Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients = SPeED-Study (Heinzel et al., 2018). The MDD group was diagnosed using the German version of the Structural Clinical Interview for DSM-IV (SCID) by clinical psychologists. Participants were included if their amount of weekly vigorous physical exercise did not exceed 90 min. to be able to achieve exercise gains within the longitudinal part of the project. The rational for this criterion is based on guidelines of the American Heart Association for endurance exercise (Fletcher et al., 2013). A list of all inclusion and exclusion criteria is reported in Heinzel et al. (2018) and in the supplementary methods. One participant in the HC and one in the MDD sample showed WM performance at chance level (performance below 30% hit rate or above 30% false alarm rate) in the 3-back condition in the WM-task and had to be excluded from analyses. Therefore, the final analysis sample consisted of 110 patients with MDD and 55 HC (see Table 1 for demographic data). All participants had normal or corrected-to-normal vision, and no history of any neurological diseases or brain injuries. The study was approved by the local ethics committees of Charité Universitätsmedizin Berlin, Germany (No EA1/113/15), and of the Freie Universität Berlin, Germany (No 133/2016) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after the procedures had been fully explained.

Table 1
Demographics of healthy control (HC) and major depression disease patient (MDD) samples.

Measure	HC (N = 55)	MDD (N = 110)	P Value
Age	30.5 (7.3)	36.4 (10.0)	<0.001
Sex	21 m/34 w	57 m/53 w	0.136
Verbal test score	32.3 (3.7)	32.4 (3.8)	0.606
BDI-2	1.9 (2.6)	27.3 (7.7)	<0.001
Body-Mass-Index	n.a.	24.6 (4.1)	n.a.
MDD, Recurrent	n.a.	81[a]	n.a.
Current medication	n.a.	44[b]	n.a.
Physical fitness	n.a.	2.3[c] (0.5)	n.a.
Performance 0-Back	99.5 (1.5)	98.6 (3.5)	0.084
Performance 1-Back	96.6 (5.9)	95.8 (6.8)	0.484
Performance 2-Back	82.7 (16.7)	77.7 (15.3)	0.060
Performance 3-Back	81.3 (20.4)	66.8 (20.5)	<0.001
Reaction time 0-Back	397 (74)	446 (65)	<0.001
Reaction time 1-Back	461 (88)	529 (89)	<0.001
Reaction time 2-Back	564 (96)	629 (112)	<0.001
Reaction time 3-Back	553 (119)	653 (109)	<0.001

Note. Means and standard deviations (in parentheses) are shown. Units: Age [years]; verbal test score [sumscore]; BDI-2 [sumscore]; Performance [% correct]; Reaction time [ms]; Physical fitness [W/kg].

[a] Number of recurrent depressive patients.

[b] 29 SSRIs, 11 SSNRIs, 10 tetracyclic antidepressents, 6 neuroleptics, 4 tricyclic antidepressants, 1 tranquilizer. 1 MAO-inhibitor, 1 lithium.

[c] data available for 106 MDD patients.

2.2. N-back Paradigm during fMRI

We used a modified version of a n-back paradigm with numerical stimuli as described in Heinzel et al. (2018). Sixteen blocks, four blocks of 0-, 1-, 2-, and 3-back, were visually presented with three different pseudo-randomized orders counterbalanced across subjects with a total duration of 9 min. (more details on the task design please refer to the supplementary methods). N-back performance (defined as hit rate minus false alarm rate) and reaction time during correct responses were used as outcome scores for behavioral analyses. The n-back task has been widely used in MDD to measure working memory processes in fMRI such as updating or manipulation (Nikolin et al., 2021; Wang et al., 2021). The simplest level (0-back) serves as a baseline since no items need to be updated in working memory and mainly attentional processes are measured (Harvey et al., 2004). As the load factor increases, higher order WM functions such as updating and manipulation are required. Thus, assumptions about possibly impaired cognitive subprocesses in MDD can be made based on the pattern of performance and neural activity at the different n-back stages (Nikolin et al., 2021). In the following, the 1-back condition is defined as low WM load, 2-back as medium WM load, and the 3-back as high WM load.

2.3. MR image acquisition

FMRI data were collected at Charité Campus Mitte, Berlin, with a 3TMagnetom Trio MRsystem and a 32-channel-headcoil (Siemens, Erlangen, Germany). At first a T1-weighted 3D pulse sequence was obtained (repetition time (TR) = 2440 ms, echo time (TE) = 4.81 ms, flip angle = 8 deg, matrix size = 256x258x192, sagittal slices with isotropic voxel size of 0.91 mm). Additionally, a T2-weighted 3D pulse sequence was measured (TR = 5000 ms, TE = 499 ms, flip angle = 120 deg, acquisition matrix = 256x258x192, sagittal slices with isotropic voxel size of 0.91 mm). Functional data were obtained using a gradient echo-planar imaging (GE-EPI) pulse sequence (TR = 2000 ms, TE = 30 ms, flip angle = 78 deg, matrix size = 64 × 64, voxel size = 3.0 × 3.0 × 3.75 mm). 33 slices were acquired descending parallel to the bicommissural plane. MR image processing and analysis are described in detail in the supplementary methods.

2.4. Estimation of BOLD effects in n-back

The n-back experiment was analyzed within the framework of the General Linear Model (GLM). At the single subject level, we created design matrices comprising the experimental conditions of 0-, 1-, 2-, and 3-back as separate regressors of interest and all other conditions (cue, button press as well as six rigid body realignment parameters) as regressors of no interest. The GLM was fitted voxel-wise into the high-pass frequency filtered time series using the restricted maximum likelihood algorithm implemented in SPM12. Contrasts of each WM condition (1-, 2-, and 3-back) to baseline (0-back) were then calculated.

On the second level, a random effects model as implemented in the GLM_Flex_Fast4 toolbox (https://mrtools.mgh.harvard.edu/index.php?title=GLM_Flex) was applied to test a repeated measures ANOVA with the between-subjects factor group (MDD vs. HC) and the within-subjects factor WM load (1-, 2-, and 3-back respectively contrasted to 0-back). Because age differed significantly between groups, age was included as a control variable. For the whole-brain-effect of the analyses we used probabilistic threshold-free cluster enhancement (pTFCE) as implemented according to Spisák et al. (Spisák et al., 2019) in addition to whole brain peak-level (voxel-wise) FWE correction with $p < 0.05$ and a minimum cluster size threshold of $k > 10$. Because we were specifically interested in WM activations for the WM load-dependent hypothesis in MDD, we chose a more restrictive approach. For this, a WM-mask was created with the tool *Neurosynth* (Yarkoni et al., 2011) which is a platform for automatically synthesizing the results of different neuroimaging studies. Using the term *working memory*, the tool summarized data from 1091 studies and created a tissue probability map (including 12,010 voxels) at a probability threshold of 0.1 to filter out the most common WM activations (see supplementary figures S1**)**. For the physical fitness specific hypothesis, we used physical fitness as an additional regressor in our ANCOVA. As we had no specific expectations for the activation pattern for this analysis, a binary whole-brain mask was created using the gray matter tissue probability map (including 150,571 voxel) available in SPM at a probability threshold of 0.3.

2.5. ROI-analyses

Additionally, we used the findings of the recent meta-analysis by Yu et al. (2021) (Table 3) in a Region-of-Interest-(ROI) analysis as described in de Vries et al. (2014) to compare the results from our whole-brain analysis with a hypothesis-driven ROI approach, using ROI-coordinates based on external criteria from independent data. Thus, we built four ROIs using 5 mm spheres around the coordinates reported in Yu et al. (Yu et al., 2021) with the MATLAB tool FIVE. The activity of the included voxels was averaged for each WM load and then correlated with performance, reaction time and physical fitness measure.

2.6. Assessment of physical fitness

Data of a graded exercise test on a cycle ergometer was available in 106 patients with MDD (see Table 1 for demographic data). Subjects completed the graded exercise test and fMRI examination within one week. To measure physical fitness, the participants completed a stress electrocardiogram (ECG) during bicycle ergometry. Starting at 25 W, load was gradually increased until reaching the maximum physical exertion. The maximum effort is adjusted by kg body weight (Watts per kg) (Rost et al., 1982).

2.7. Statistical analysis

All non-imaging data related analyses were carried out using IBM SPSS Statistics 27 for Windows (SPSS Inc., Chicago, IL, USA). Demographic and clinical data were analyzed with two sample t-tests or chi-square tests (Table 2). Because age differed significantly between groups, age was included as a control variable in all group analyses. To compare performance and reaction times between the groups in the n-back-task, a two (group) by four (load) repeated-measures analysis of covariance (ANCOVA) with age as a covariate was performed for each

Table 2
Significant whole-brain-interaction effect (load × group) in n-back-task.

Cluster/Region	Hem	BA	MNI Coordinates			t-Value	clustersize
			x	y	z		
C1: Superior Parietal Lobule / Inferior Parietal Lobule	L	7/40	−30	−48	38	4.6	324
C2: Inferior Frontal Gyrus / Precentral Gyrus	L	6/9	−46	8	16	4.6	103
C3: Lateral Occipital Cortex / Superior Parietal Lobule	R	7	14	−64	56	4.01	32
C4: Superior Frontal Gyrus/ Middle Frontal Gyrus	L	6	−24	−2	62	3.83	24
C5: Frontal Lobe /Middle Frontal Gyrus	R	9	36	42	30	3.96	23
C6: Superior Parietal Lobule / Supramarginal Gyrus	R	40/7	34	−40	42	4.11	10

Note. pTFCE and FWE peak-corrected, $p < 0.05$, cluster ≥ 10 Voxel. C = Cluster, BA = Brodmann Areal, L = left, R = right.

Table 3
Correlations physical fitness to predefined parietal ROIs (Peak1-4, all loads combined).

	MNI	location	fitness W/kg	
			r	p
Peak1	−18 66 48	Left Parietal Lobe, Precuneus, BA 7	0.151	0.122
Peak 2	−30–48 44	Left Parietal Lobe, Superior Parietal Lobule, BA 7	**0.287**	**0.003**
Peak 3	–32–58 46	Left Parietal Lobe, Inferior Parietal Lobule, BA 39	0.150	0.125
Peak 4	−40–48 42	Left Parietal Lobe, Inferior Parietal Lobule, BA 40	**0.275**	**0.004**

Note. r = pearson's correlation, p = significance, bold = sig. correlations.

outcome. To control the influence of medication, the same analysis without the medicated MDD patients (N = 66) was calculated. If the Mauchly sphericity test was significant, we corrected accordingly with the Greenhouse-Geisser correction or the Huynh-Feldt correction, depending on how much sphericity was violated. All correlation analyses with physical fitness were performed with all available physical fitness data (N = 106) in MDD. To all tests Bonferroni correction for multiple comparisons was applied.

3. Results

3.1. Behavioral results during n-back

A two (group) by four (WM load) ANCOVA of the n-back performance showed a significant interaction ($F(1.9,486) = 6.74$, $p = 0.002$, partial $n^2 = 0.04$) as well as a significant main effect of group ($F(1,162) = 6.23$, $p = 0.014$, partial $n^2 = 0.037$). There was a main effect of the covariate age ($F(1,162) = 12.23$, $p = 0.001$, partial $n^2 = 0.07$). The Greenhouse–Geisser adjustment was used to correct for violations of sphericity. Follow-up two-sample t-tests indicated that compared to patients with MDD, healthy control participants revealed better performance at 0-back ($t(160,6) = -2.19$, $p = 0.03$), 3-back ($t(1\,6\,3) = -4.28$, $p = 0.00$) and by trend also 2- back ($t(1\,6\,3) = -1.89$, $p = 0.06$) but not at 1-back (see Fig. 1, Panel A).

Compared with the results of the n-back performance, reaction time analyses showed a tendency of a two (group) by four (WM load) interaction ($F(2.4, 486) = 2.59$, $p = 0.066$, partial $\eta2 = 0.016$), a significant main effect of WM load ($F(2.4, 486) = 21.15$, $p < 0.001$, partial $\eta2 = 0.115$) and also a main effect of group ($F(1, 162) = 20.01$, $p < 0.001$, partial $\eta2 = 0.110$). There was also a main effect of the covariate age ($F(1, 162) = 5.93$, $p = 0.016$, partial $\eta2 = 0.035$). The Huynh-Feldt adjustment was used to correct for violations of sphericity. Follow-up two-sample t-tests indicated that compared to patients with MDD, healthy control participants had faster RTs in all conditions (0-back: $t(1\,6\,3) = 4.37$, $p < 0.001$; 1-back: $t(1\,6\,3) = 4.63$, $p < 0.001$; 2-back: $t(1\,6\,3) = 3.72$, $p < 0.001$; 3-back: $t(1\,6\,3) = 5.36$, $p < 0.001$; see Fig. 1, Panel B).

To control for the influence of medication on our approach, we repeated the same analysis without the medicated MDD patients (MDD = 66, HC = 55). Similar effects of group and interaction (group by load) emerged in performance and reaction time, so we can assume a negligible influence of medication (see supplementary Tables S1-S2 for ANCOVA and t-tests).

3.2. FMRI results during n-back

As shown in Table 2, whole-brain analyses (pTFCE and peak-level FWE $p < 0.05$ corrected) of the two (group) by three (WM load) interaction revealed a significant interaction effect in six clusters indicating reduced activation in the MDD group compared to the HC group at medium and high WM load. Fig. 2 shows the activation pattern in the two largest clusters, the other clusters with similar patterns can be found in the supplementary material (Figure S2).

3.3. FMRI results of physical fitness

Analysis of covariance with 106 MDD patients and physical fitness as a regressor revealed a significant effect of physical fitness in two parietal clusters (pTFCE and peak-level FWE $p < 0.05$ corrected, see Fig. 3), suggesting that the higher the physical fitness index in MDD, the higher

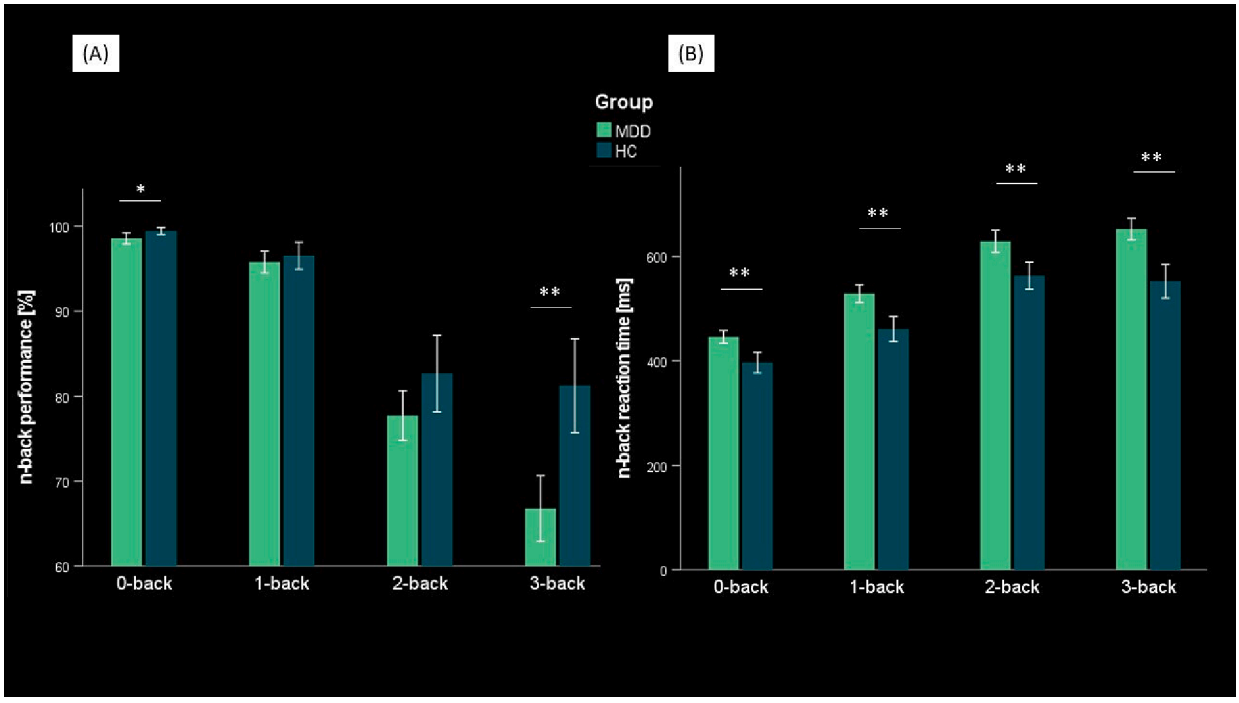

Fig. 1. Behavioral n-back data in healthy controls (HC) and major depressive disorder (MDD). Means and standard errors are reported for A) performance and B) reaction time. *p < 0.05; **p < 0.01.

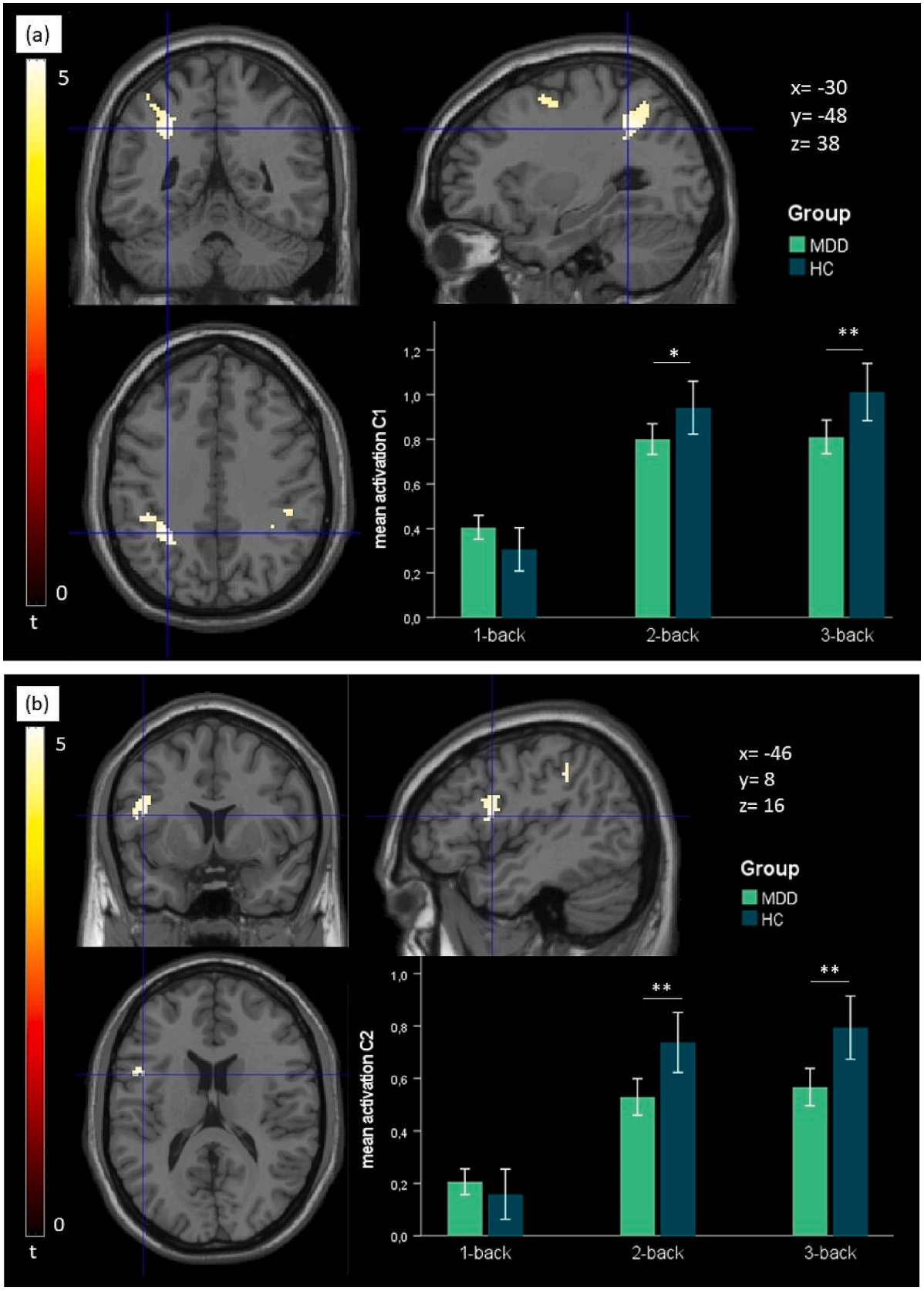

Fig. 2. Significant interaction clusters (pTFCE and peak-level FWE corrected, $p < 0.05$, cluster > 10 voxel) and their activation patterns in the n-back task. Mean and standard error of the mean for the average activation divided by group and WM load for each cluster. a) C1: Superior Parietal Lobule / Inferior Parietal Lobule, b) C2: Inferior Frontal Gyrus / Precentral Gyrus. *$p < 0.05$, *$p < 0.01$.

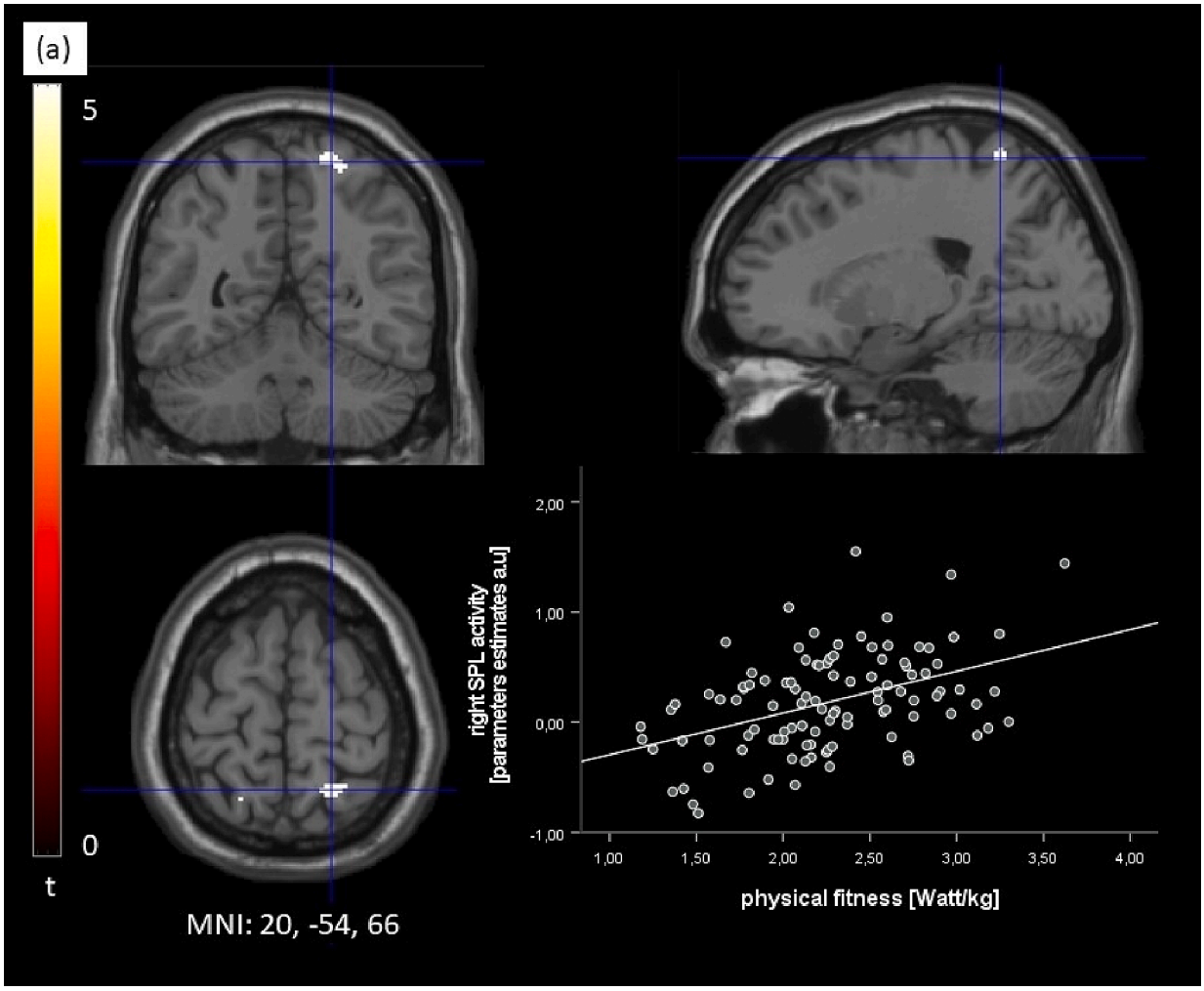

Fig. 3. Significant clusters of fitness (pTFCE and peak-level FWE corrected, $p < 0.05$, cluster ≥ 10 voxel) and their activation patterns in the n-back task. a) Right Superior Parietal Lobule / Lateral Occipital Cortex, $t = 4.84$, 37 voxels. Fitness and right SPL-activity in n-back in the MDD sample, R^2 linear = 0.19, b) Left Superior Parietal Lobule / Lateral Occipital Cortex, $t = 4.5$, 16 voxels. Fitness and left SPL-activity in n-back in the MDD sample, R^2 linear = 0.167.

the activation in the right and left superior parietal lobule.

3.4. Relationship between physical fitness, n-back performance, and BOLD response

To substantiate whole brain imaging findings against external criteria, we related physical fitness to behavioral (performance and reaction time) and neural measures (BOLD response in load-dependent predefined ROIs). For the MDD patients who performed the graded exercise test, we did not find a significant correlation between behavioral n-back data and physical fitness. However, there was a correlation by trend in performance for 1- and 3-back (1-back: $r = 0.19$, $p = 0.053$, 3-back: $r = 0.18$, $p = 0.070$,) but not for 0- and 2-back (0-back: $r = 0.09$, $p = 0.354$, 2-back: $r = 0.02$, $p = 0.846$).

For predefined parietal ROIs, we found significant correlations with physical fitness. After Bonferroni-correction the relationship to the left superior parietal lobule (Peak2) and left parietal inferior lobule (Peak4) became obvious, especially in medium and high load conditions, indicating a positive relation between higher physical fitness and increased BOLD response (Table 3; see Table S3 in the supplement material for post hoc tests for single n-back-loads).

4. Discussion

Our results indicate reduced performance especially for high n-back load and prolonged response times for all n-back loads for MDD patients in comparison to HC. Furthermore, our results reflect a WM load-dependent performance decrement in MDD patients. Whole-brain analysis of group by WM load revealed significant interaction effects in six frontoparietal clusters. The interaction effects were driven mainly by reduced BOLD response at medium and high WM load in MDD patients compared to HC subjects. A covariance analysis with 106 MDD patients showed that physical fitness was associated with activity of the superior parietal lobule (SPL) bilaterally suggesting that the higher the physical fitness, the higher the BOLD response in parietal cortices at high WM load. ROI analyses verified this finding.

The behavioural results confirmed our hypotheses and are largely in line with previous findings of a current meta-analysis by Nikolin et al. (Nikolin et al., 2021), suggesting a WM deficit in patients with MDD. Higher RTs in all n-back conditions reflect a psychomotor slowing in MDD during the performance of the n-back task regardless of WM load and are consistent with previous findings (Nikolin et al., 2021; Bennabi et al., 2013; Buyukdura et al., 2011) and have been interpreted in terms of psychomotor retardation in depression. Performance decrements at high WM load during n-back indicate that patients with MDD have difficulties especially when higher-order executive functions such as

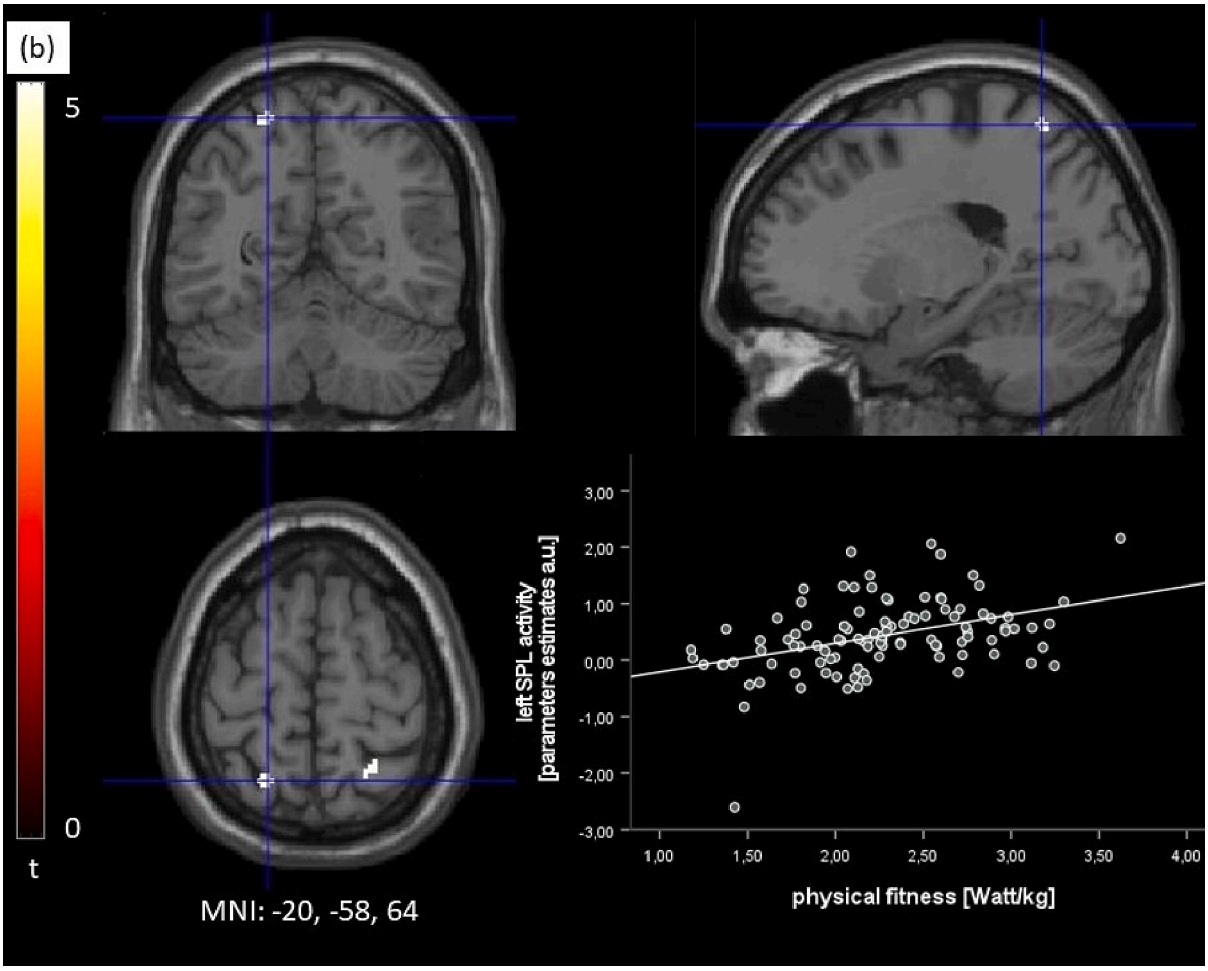

Fig. 3. (*continued*).

updating (Owen et al., 2005) are involved (Harvey et al., 2004; Bartova et al., 2015; Fitzgerald et al., 2008). This may reflect deficient executive control functions, affecting the ability to coordinate different WM subprocesses (Nikolin et al., 2021).

To test the WM load-dependent hypothesis in MDD compared with HC, we computed a whole-brain analysis with a brain mask of regions that are involved in working memory task. Results of the group by WM load interaction, showed significant interaction effects in six frontoparietal clusters, indicating reduced activity at high WM load in MDD. Consistent with previous (Owen et al., 2005) and current meta-analyses (Mencarelli et al., 2019) on neural activations related to the n-back task, the identified clusters belong to a frontoparietal WM network. Thus, MDD-related alterations in neural activity during WM performance point towards a malfunctioning network instead of a specific region. The largest cluster was located in left parietal cortex (SPL and inferior parietal lobule (IPL)) supporting previous results reported in Wang et al. (Wang et al., 2015). The SPL is critically important for the manipulation and rearrangement of information in WM (Koenigs et al., 2009)) and is associated with shielding external distractors and updating WM content, whereas the IPL is associated with shifting attentional focus within activated WM content during WM tasks (Nee et al., 2013). Additional clusters were located in frontal areas (middle frontal gyrus and inferior frontal gyrus) and may indicate MDD-associated impairments in executive components of WM, such as mental refreshing of recently presented triggers and updating (continuous removal and addition of information to WM) (Nee et al., 2013). These findings are in line with previous studies (Garrett et al., 2011; Meusel et al., 2013; Xia et al., 2019; Zhu et al., 2018; Wang et al., 2021; Vasic et al., 2009). Divergent from Wang's et al. (Wang et al., 2015) meta-analysis, no frontal hyperactivations were detected in our MDD sample. While neural activity in MDD is slightly higher at low WM load compared to HC in our study, these differences were not significant in the regions that showed significant group by WM load interaction effects. It must be noted that our analyses were set up to identify MDD-related alterations in WM load-dependent activation patterns and we did not investigate group differences for individual n-back loads separately. Thus, our results show a reduced WM-dependent modulation of neural activity in MDD that is driven by reduced activation at medium and high WM load. Most studies in Wang's et al. (Wang et al., 2015) meta-analysis used WM tasks with relatively lower task demand that did not reveal any performance deficits in MDD (8 out of 10 studies). Studies that have reported frontal hyperactivations (Harvey et al., 2005; Matsuo et al., 2007; Wagner et al., 2006; Walter et al., 2007) interpreted these findings in terms of compensatory activations to maintain a normal level of performance. As described within models of compensatory activity in relation to task demand (e.g., the *CRUNCH*-model, (Reuter-Lorenz and Cappell, 2008)), performance decrements and associated reduced neural activity are expected at high task demand when compensatory attempts fail and capacity limits are exceeded (Barulli and Stern, 2013; Heinzel et al., 2014; Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010). Thus, our findings point towards a reduced neural capacity in the WM network in MDD that becomes visible especially at high WM load. Although we had a very large sample of MDD patients compared to other WM MDD studies (Wang et al., 2015), we cannot conclude that alterations in the load-dependent modulation of neural activity are specific to MDD. To answer this question, large transdiagnostic samples need to be

tested in future research.

To specifically capture the neurobiological relationship between physical fitness and brain function during cognitive task performance, we used physical fitness as an additional regressor in our ANCOVA in the MDD sample. Thus, we demonstrated a distinct positive correlation of physical fitness with WM-related functional activation of the SPL bilaterally in patients with MDD. On a behavioural level, there was a positive trend between physical fitness and 3-back performance. The SPL in general is associated with shielding external distractors and updating WM content (Nee et al., 2013). Our finding can be localized within the dorsal attentional network, which is involved in internally or externally oriented attention and appears to be associated with reduced connectivity with the frontoparietal network in depression (Kaiser et al., 2015). Our finding suggests that physical fitness might be an important factor to prevent WM impairments in depression via effects on SPL activation. Our results are in line with the meta-analysis of Yu et al. (Yu et al., 2021), who integrated the findings of 20 neuroimaging studies in healthy subjects, testing the influence of physical exercise on cognitive brain activation. They suggest that physical exercise prevents cognitive decline in healthy individuals by enhancing functional integration of the frontoparietal control network via effects on the precuneus located in the SPL. In our ROI-analysis, a positive association was found between parietal n-back activity in the left SPL and IPL and physical fitness in patients with MDD. The related ROIs are part of the dorsal attentional network and frontoparietal network (Yu et al., 2021). Another supporting finding for our observed positive correlation between physical fitness and parietal activation comes from studies with healthy older adults. Prakash et al. (Prakash et al., 2011) conducted a cross-sectional study comparing high- and low-fit participants using a VO2max test. They revealed that cardiovascular physical fitness was associated with higher recruitment in frontal areas (middle frontal gyrus, superior frontal gyrus) and SPL in the most challenging condition of a Stroop task (color reading interference: word content conflicts word color). Using a flanker paradigm, Colcombe et al. (Colcombe et al., 2004) also provided evidence that increased physical fitness levels are associated with greater neural recruitment of regions involved in executive function including prefrontal and parietal cortex. In short, these studies suggest that higher physical fitness is related to enhanced cognitive performance and increased activation of fronto-parietal areas in healthy adults. To our knowledge, this is the first study dedicated to the relationship between functional brain activity in a WM task and physical fitness in MDD. The present results can be used to guide future research on physical fitness or exercise effects on mental health and cognition to develop optimized physical exercise treatments that serve as clinically useful additional treatment options for MDD.

There are several limitations to this study. It is important to note that the present study is a cross-sectional analysis, so it's important to highlight that no causal conclusion can be drawn. It could be that fit individuals are protected to some degree from exceptionally severe depressive symptoms as well as the associated cognitive deficits, rather than that fitness mitigates cognitive deficits. Results of the upcoming longitudinal study (Heinzel et al., 2018) will be valuable to determine whether improved fitness has cognitively enhancing or protective effects in depressed individuals. Moreover, physical fitness index was measured by means of the power output during an exercise ECG on a bicycle ergometer. In future studies, this index could be extended by additional indicators of fitness to obtain a more comprehensive picture of individual physical fitness. We had to apply several exclusion criteria for security and practical reasons (e.g., exclusion of MDD patients with severe MDD), thus our results are not representative for the entire spectrum of MDD. Because a subset of our MDD sample was supposed to participate in a subsequent exercise intervention, we did not include participants that exercised regularly and vigorously more than twice a week. Therefore, we may have excluded particularly physically fit individuals. However, only a very small proportion of MDD patients were not included for this reason. Groups showed small but significant differences in age, however, results were corrected for age differences and both behavioral and fMRI results remained significant when controlling for age. Furthermore, we did not assess the duration of the disorder systematically. In future studies, this information should be obtained and included in the statistical analyses because disease duration may have an influence on working memory performance, physical fitness and associated brain functioning.

As this is the first study investigating neural correlates of cognitive task performance and physical fitness in MDD, it can only be a starting point for future research, testing other cognitive tasks to gain further understanding of the relationships between physical activity and cognitive functioning in MDD. It would be interesting, for example, to test different WM subprocesses separately or to investigate other executive tasks such as planning or inhibition tasks in future studies. Although the n-back task is a widely used and well-established measure of working memory functions and dysfunctions in depression (e.g. Nikolin et al., 2021), its sensitivity and specificity for detecting working memory deficits in depression have not been fully explored. Specifically, at higher working memory load (e.g., 2- and 3-back), the n-back task is a complex task that also requires higher executive functions such as updating, thus it is not considered a "pure" measure of working memory (e.g. Miller et al., 2009). Some studies have suggested that the n-back task may be less sensitive to detecting working memory deficits compared to other tasks, such as the Digit Span task or the Spatial Span task (Redick and Lindsey, 2013). Overall, while the n-back task is a promising tool for assessing working memory deficits in depression, more research is needed to fully understand its sensitivity and specificity in this population. It is important to consider that the n-back task should be used in conjunction with other measures and other clinical measures like duration of illness when interpreting the results of n-back task performance in individuals with depression.

5. Conclusion

In the current study, patients with MDD showed generally higher RTs during the performance of an n-back task as well as WM performance decrements specifically at high WM load. FMRI analyses revealed significant group by WM load interaction effects in six frontoparietal clusters, indicating reduced BOLD response at medium and high WM load. These results support the notion of a capacity limited WM processing in MDD. Moreover, we found a distinct positive correlation of physical fitness with cognition-related functional activation of the superior parietal lobe bilaterally in patients with MDD. This finding may inform the development and investigation of physical fitness interventions to prevent or counteract WM impairments in MDD.

CRediT authorship contribution statement

M.K. Schwefel: Data curation, Writing – original draft, Writing – review & editing. **C. Kaufmann:** Methodology, Software, Validation, Writing – review & editing. **G. Gutmann:** Software, Formal analysis, Writing – review & editing. **R. Henze:** Data curation. **T. Fydrich:** Funding acquisition, Supervision, Validation. **M.A. Rapp:** Supervision, Validation. **A. Ströhle:** Funding acquisition, Validation. **A. Heissel:** Conceptualization, Funding acquisition, Project administration. **S. Heinzel:** Conceptualization, Project administration, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103401.

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5. Study III: Effect of physical exercise training on neural activity during working memory in major depressive disorder

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. **Effect of physical exercise training on neural activity during working memory in major depressive disorder**

Schwefel, M.K. [1*], *Kaufmann, C.* [2], *Gutmann, G.* [1], *Henze, R.* [1,2], *Fydrich, T.* [2], *Rapp, M.A.* [3], *Ströhle, A.* [4], *Heissel, A.* [3], *& Heinzel, S.* [1,5]

[1] Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany;

[2] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany;

[3] Social and Preventive Medicine, University of Potsdam, Potsdam, Germany;

[4] Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitäts-medizin Berlin, Berlin, Germany;

[5] Institute of Psychology, Department of Educational Sciences and Psychology, TU Dortmund University, Dortmund, Germany.

*** Corresponding author:**

M.Sc. Melanie Schwefel, Clinical Psychology and Psychotherapy, Freie Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin, Germany

E-mail: melanie.schwefel@fu-berlin.de

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Abstract

Background: Deficits in working memory (WM) are common in patients with Major Depression Disorder (MDD). Previous research mainly in healthy adults indicated that physical exercise training may improve cognitive functions by stimulating neuronal plasticity particularly in hippocampal structures. Thus, the goal of this functional Magnetic Resonance Imaging (fMRI) study was to examine alterations in neuronal activity during a WM task and to investigate changes in brain volume and functioning following a physical exercise training in patients with MDD with a specific focus on hippocampal structures.

Methods: 86 (39 female) MDD outpatients were randomly assigned to one of three groups for a 12-week intervention: High intensity exercise training (HEX), low intensity exercise training (LEX) or waiting list control group (WL). An n-back task (with WM loads of 0, 1, 2, and 3) during fMRI was conducted before and after interventions/waiting period.

Results: Both exercise groups showed better performance and shorter reaction times at higher WM loads after 12-weeks of physical exercise training. Specifically in the HEX, we found an improvement in physical fitness and an increase in neural activation in the left hippocampus as compared to the WL following the exercise training. Training-related structural volume changes in gray matter or hippocampus were not detected.

Conclusions: Our results partly support the hypothesis that physical exercise training positively affects WM functions by improving neuronal plasticity in hippocampal regions. Exercise training seems to be a promising intervention to improve deficient WM performance in patients with MDD.

Clinical trials registration name: Neurobiological correlates and mechanisms of the augmentation of psychotherapy with endurance exercise in mild to moderate depression - SPeED, http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00008869, DRKS00008869

Introduction

Individuals with major depressive disorder (MDD) frequently report memory impairments that often continue even after antidepressant treatment (1; 2). These deficits appear especially when performing cognitively demanding memory tasks such as complex working memory (WM) (3; 4). WM is a limited capacity system for holding and processing information for a short period of time (5; 6) that is crucial for many everyday tasks (7). Complex WM tasks include the manipulation (e.g., updating) of content and a commonly used measure is the n-back task with various WM loads. In this task, patients with MDD show decreased performance and slowed reaction times specifically at high WM load (8; 9). While reasons for memory impairment in MDD are not yet clear, research suggests that the hippocampus, which is crucial in memory processes as well as in emotion and stress processing, may also be involved in the pathogenesis of MDD. A finding that has now been replicated several times in meta-analyses is a reduced hippocampal volume in patients with MDD (10; 11). In addition to these structural abnormalities, neurofunctional alterations have been identified within the hippocampus that relate to memory impairments in MDD (12–14; 10; 15). Moreover, functional neuroimaging studies have reported dysfunctionalities in fronto-parietal regions during WM processing (16; 17; 9).

As remission rates continue to stay below 50% after standard treatments (cognitive behavioral therapy and antidepressant medication) (18; 19), additional treatment options are needed that specifically address specific neurophysiological pathomechanisms of MDD. In recent years, physical exercise has come into focus. It has proven to be effective in reducing depressive symptoms (20–24) and may counteract certain underlying deficits in MDD including memory impairments (25; 26). Studies with healthy and elderly people indicate that regular physical training helps to maintain or improve cognitive performance (27–30). Less research exists for

individuals with MDD, but exercise has also been shown to be associated with large depression relief and benefits on WM (31).

Neurobiological models of physical exercise in MDD (25) consistently postulate that exercise initiates a cascade of (neuro)biological mechanisms, such as neuroplasticity at different levels (e.g., brain-derived neurotrophic factor (32–34)), as well as functional and structural brain changes particularly within hippocampus (35). In brief, it is hypothesized that the antidepressant effect of physical exercise is mediated by increased neuroplasticity that supports cognitive functioning. That exercise plays a crucial role in promoting neuroplasticity is evidenced by numerous studies conducted in animals and humans (36–39).

While the increase in hippocampal volume after exercise has been consistently observed in animal models (40), evidence in humans and specifically in patients with MDD is less conclusive to date. A meta-analysis conducted in human subjects (41) showed that aerobic exercise had a positive effect on left hippocampal volume compared to control conditions, but variance between studies seems to be large. More generally, it seems that many exercise studies do not show any effect on brain gray matter, as indicated by a recent systematic review (42). Research studying the relationships between exercise, hippocampal volume and depression has been sparse and unequivocal. Hippocampus volume increased after a running intervention in young adults (43) but did not change significantly after an aerobic exercise trial in patients with MDD (35). Structural MRI studies provide insights into associations between exercise and hippocampal morphology, while techniques like resting-state functional connectivity (rsFC) offer additional insights into hippocampal circuitry health. In a study involving 50 healthy young adults, it was found that increased cardiorespiratory fitness correlated with heightened rsFC from the left anterior hippocampus to the frontal pole, middle frontal gyrus, and parahippocampus (44). Summarizing findings, Aghjayan et al. (45) highlighted in their review that both cardiorespiratory fitness and aerobic exercise play crucial roles in the functional

connectivity among medial temporal regions, including the hippocampus, and other brain structures associated with memory and executive functions in adults.

Thus, since most research on neurobiological mechanisms of physical exercise has been done in healthy individuals (46; 27; 47), more research needs to be conducted in patients with MDD and model assumptions need to be tested in this population. In particular, neurofunctional effects of physical exercise have been almost unexplored in MDD. To our knowledge, the current study is the first to investigate neural activity during WM performance before and after a physical exercise intervention in patients with MDD.

To optimize exercise as a treatment for MDD, we need to understand how effects of exercise on cardiovascular fitness, neural functioning, and cognitive performance are related in MDD. Therefore, the aims of this (f-)MRI study were twofold: (I) on a functional level, to examine neural changes during a WM task following physical exercise training, in particular hippocampal functioning and (II) on a structural level, to examine changes of brain volume, especially hippocampus, after physical exercise training in MDD patients.

Methods and materials

Participants

Eighty-six MDD outpatients participated in the current study. This subsequent analysis is part of a larger longitudinal project on the long-term effects of physical exercise (Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients = SPeED-Study (48). Inclusion criteria were a diagnosed mild or moderate depressive episode, an age between 18 and 65 years, and passing a sport medical examination. Patients were diagnosed using the German version of the Structural Clinical Interview for DSM-IV (SCID) (49) by clinical psychologists to assess past and present mental disorders. A list of all inclusion and exclusion criteria is reported in Heinzel et al. (50) and in the supplementary methods. All patients were allocated randomly into one of three groups: a group with high intensity of the

exercises (high intensity exercise group, HEX) or a group with low intensity of the exercises (low intensity exercise group, LEX) or a waiting list control group (WL) with blinding regarding HEX or LEX allocation. See Heinzel et. al. (50) for detailed description of the study design, dropout reasons and results of the clinical trial. The final analysis included 26 HEX, 32 LEX, and 28 WL MDD patients (see Table 1 for demographics), excluding four due to unanalyzable MRI data. All participants had normal vision, no neurological history, and provided written informed consent. The study was approved by local ethics committees in accordance with the Declaration of Helsinki (Charité Universitätsmedizin Berlin, Germany, No EA1/113/15; Freie Universität Berlin, Germany, No 133/2016).

Table 1
Demographics of patients with major depressive disorder (MDD) pre and post exercise intervention.

Variable	HEX (n=26)	LEX (n=32)	WL (n=28)	p
Age (years)	36.5 (10.7)	34.6 (9.8)	40.8 (10.2)	.064
Sex (n men/women)	14/12	23/9	10/18	.388
School education (years)	11.9 (1.6)	12.33 (1.2)	11.93 (1.3)	.437
Fitness (W/kg bodyweight)				
Pre	2.23 (.40)	2.35 (.56)	2.22 (.58)	.235
Post	2.37 (.45)	2.37 (.53)	2.17 (.53)	.569
Relative change pre post [%]	4.46 (14.42)	-0.05 (10.58)	-5.88 (15.15)	.024
HAMD				
Pre	13.2 (3.9)	13.1 (3.4)	12.7 (4.1)	.845
Post	10.0 (5.2)	10.3 (4.0)	10.8 (5.7)	.883
Relative change pre post [%]	-23.0 (36.5)	-18.2 (38.1)	-13.1 (1.9)	.617
BDI-2				
Pre	26.0 (8.6)	28.1 (6.3)	26.8 (7.6)	.569

Post	20.7 (13.7)	20.7 (10.3)	21.1 (9.1)	.990
Relative change pre post [%]	-23.6 (35.2)	-24.6 (35.9)	-19.4 (34.5)	.829
Antidepressants[a]				
Yes/no (n)	12/14	9/23	11/17	.355
SSRI (n)	6	8	7	
SSNRI (n)	3	0	0	
SNDRI (n)	2	0	4	
Tricyclic (n)	0	1	1	
Tetracyclic (n)	4	4	0	
other (n)	2	2	3	

Note: If not stated otherwise, values represent means and standard deviations. P-values of the group comparisons between HEX, LEX, and WL (univariate ANOVAs / Chi^2 tests for categorical variables) are reported. Physical fitness is indicated by maximum achieved Watt per kg bodyweight during ergometry. BDI-2: Beck Depression Inventory 2; HAMD: Hamilton Rating Scale for Depression, HEX: High intensity exercise group; LEX: Low intensity exercise group; pre: measurement point before exercise training; post: measurement point after exercise training; WL: Waiting list group. Calculation for relative % change between pre and post: (post - pre)/pre * 100.
[b] The sum of n's for each substance group is larger than the total number of subjects receiving any kind of antidepressants because several subjects received more than one substance.

Depression Measurements

Before and after exercise training depressive symptoms were assessed via interviews by trained clinical psychologists using the 17-item version of Hamilton Rating Scale for Depression (HAMD) (51) and by the self-report measure Beck Depression Inventory 2 (BDI-2) (52). We used HAMD and BDI-2 sumscores for all further analyses.

Exercise training

As described in Heinzel et al. (48) and considering the results of various meta-analyzes (21; 53; 22; 23), participants in the HEX and LEX groups completed a 12-week training program involving two 60-minute sessions per week. Adhering to the American Heart Association guidelines (54), one session of the HEX group consisted of 20 min of bicycle ergometer, 20 min

of running or Nordic walking, and 20 min of aerobic body workout at 55-85% of the individual maximum heart rate reserve. LEX sessions had lower intensities (20-30%) and included 20 min of cycling, 20 min of walking, and 20 min of stretching and relaxation. To measure physical fitness, the participants completed a stress electrocardiogram (ECG) during bicycle ergometry (Ergoselect 100; Ergoline GmbH, Bitz, Germany) before and after exercise training (for details Schwefel et al. (9)). To get an inter-individually comparable measure of physical fitness, the maximum effort is adjusted by kg body weight (Watts per kg) (55).

N-back paradigm during fMRI

We employed a modified n-back paradigm with numerical stimuli, following the protocol as described in Schwefel et al. (9) and Heinzel et al. (56). The task comprised sixteen blocks (0-, 1-, 2-, and 3-back) presented in three pseudo-randomized orders across subjects, totaling 9 minutes (see supplementary methods for task design details). Behavioral analysis utilized n-back performance (hit rate minus false alarm rate) and reaction time during correct responses. The n-back task is commonly used in MDD to assess working memory (WM) processes in fMRI, reflecting updating and manipulation functions as the load factor increases (8; 17). The 0-back serves as a baseline, measuring attentional processes (57), while the 1-back, 2-back, and 3-back represent low, medium, and high WM loads, respectively. These conditions help identify potentially impaired cognitive subprocesses in MDD based on performance patterns and neural activity (8).

fMRI: MR image acquisition

FMRI data were collected at Charité Campus Mitte, Berlin, with a 3T Magnetom Trio MR system and a 32-channel headcoil (Siemens, Erlangen, Germany). At first a T1-weighted 3D pulse sequence was obtained (repetition time (TR)=2440ms, echo time (TE)=4.81ms, flip angle=8 deg, matrix size=256x258x192, sagittal slices with isotropic voxel size of 0.91 mm). Additionally, a T2-weighted 3D pulse sequence was measured (TR=5000 ms, TE=499 ms, flip

angle=120 deg, acquisition matrix=256x258x192, sagittal slices with isotropic voxel size of 0.91 mm). Functional data were obtained using a gradient echo-planar imaging (GE-EPI) pulse sequence (TR=2000 ms, TE=30 ms, flip angle=78 deg, matrix size=64×64, voxel size=3.0×3.0×3.75 mm). 33 slices were acquired descending parallel to the bicommissural line. MR image processing and analysis are described in detail in the supplementary methods.

fMRI: Estimation of BOLD effects in n-back

The n-back experiment was analysed within the framework of the General Linear Model (GLM (58)). At the single-subject level, design matrices included separate regressors for 0-, 1-, 2-, and 3-back conditions as well as regressors for other conditions (cue, button press, and six realignment parameters). The GLM was fitted voxel-wise into the high-pass frequency filtered time series using the restricted maximum likelihood algorithm implemented in Statistical Parametric Mapping version 12 (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab (The Mathworks Inc., Sherborn, MA, USA). Contrasts of each WM condition (1-, 2-, and 3-back) to baseline (0-back) were then calculated.

Second-level analysis allowed us to determine differences in activation between interventions and time points at the group level. Contrast images e.g., '1-back<0-back' were entered into a 2 (time: pre/post) × 3 (intervention: HEX/LEX/WL) repeated measures ANOVA. Each load was analysed in a separate ANOVA. Post hoc comparisons were calculated as t-contrasts in our ANOVA design. Analyses were performed for the whole brain, restricted to gray matter according to the tissue probability map (including 150571 voxel) thresholded at 0.3 as implemented in SPM12. We used a Monte Carlo simulation correction (10,000 iterations) with an initial voxel-wise threshold of $p < 0.001$ (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). Clusters with a minimum cluster size of 85 voxels for 1-back and 98 for 3-back voxels (depending on full-width at half-maximum (FWHM) -value) yielded a cluster-level FWE threshold of $p < 0.05$.

Anatomical localizations of the activation peaks were determined using xjView (https://www.alivelearn.net/xjview) and the MATLAB tool FIVE.

MRI: Volume-based morphometry

Voxel-based morphometry (VBM) using high-resolution T1-weighted MPRAGE images was performed with Computational Anatomy Toolbox (CAT12) (https://www.neuro.uni-jena.de/cat/), within Statistical Parameter Mapping (SPM12) software version 7771 (https://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB version R2022b. Following CAT12 manual guidelines (59), we modulated, normalized, and segmented 3D T1-weighted MRI scans into white matter, gray matter, and cerebrospinal fluid (CSF), estimating total intracranial volume (TIV). Quality assurance checks were conducted to ensure minimal noise and distortion. Scans with ratings below 'B' ('B-': n = 4; 'C+': n = 2) were closely monitored and included. In the process, one patient was excluded. After quality check, a 6 mm Gaussian full-width at half-maximum (FWHM) kernel was applied. Normalized and smoothed gray matter maps were used for statistical parametric mapping. A basic model for three-group longitudinal data was built, investigating group-by-time interaction and main effects using Automated Anatomical Atlas (AAL3) (60).

Statistical group analysis

All non-imaging data related analyses were carried out using SPSS version 27 (IBM Corporation, Armonk NY, USA). Demographic and clinical data were analyzed with two sample t tests or $\chi 2$ tests. Group comparisons were performed using two-sample t-tests. To test training-related improvements in physical fitness and compare effects between the three groups, a 3 (group) x 2 (time) analysis of variance (ANOVA) was performed. Symptom outcomes were tested using 3 (group) x 2 (time) ANOVAs. To compare performance and reaction times between the groups in the n-back-task, a 3 (group) x 4 (load) x 2 (time) repeated-measures analysis of covariance (ANCOVA) was performed for each outcome. Voxel-based

morphometry analyses using SPM12 used a flexible factorial analysis of variance (ANOVA) to assess changes in GM volumes over two time points (pre, post-exercise training) within the three MDD groups.

Results

Exercise training (measured by fitness improvement)

A 3 (group) by 2 (time) ANOVA showed an interaction effect ($F(2, 83) = 4.93$, $p = .009$, partial $\eta^2 = .106$). There was a trendwise main effect of time ($F(1, 83) = 3.00$, $p = .087$, partial $\eta^2 = .035$) and no main effect of group ($F(2, 83) = 0.81$, $p = .448$, partial $\eta^2 = .019$). As shown in Figure 2 and confirmed by follow-up paired t-tests, physical fitness improved from t1 to t2 in HEX ($t(25) = -2.51$, $p = .01$, $d = -.49$), did not change in LEX ($t(31) = -.86$, $p = .200$, $d = -.15$) and WL ($t(27) = 1.30$, $p = .10$, $d = .25$).

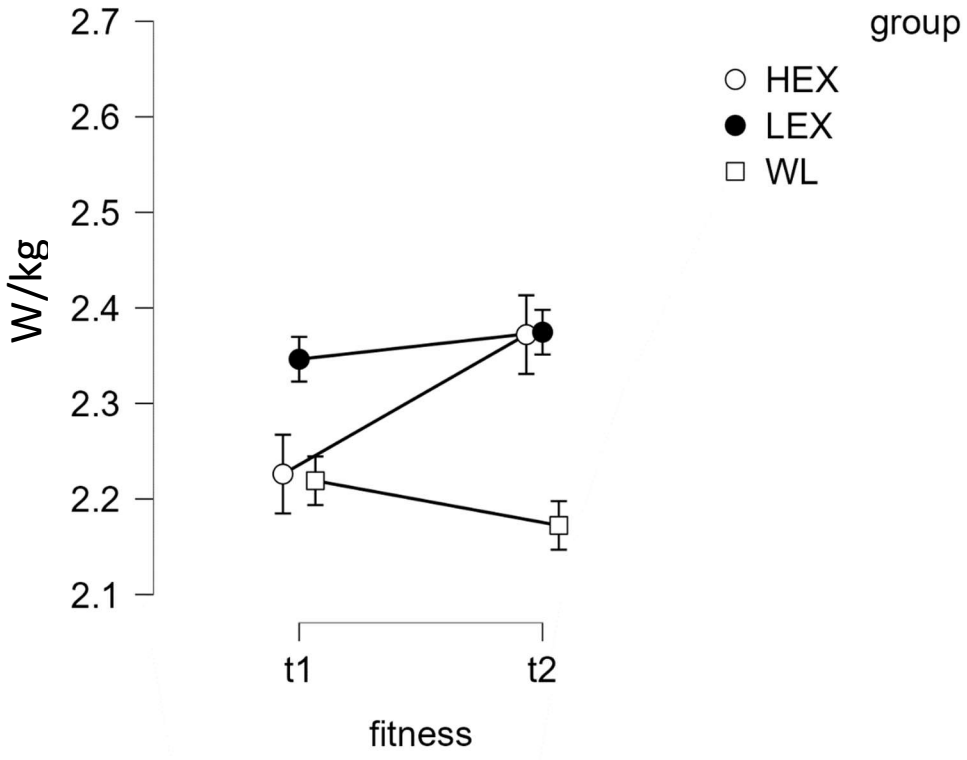


Figure 1. Change in fitness from t1 to t2.

Note: W/kg = Watt per kilogram body weight; HEX = high intensity exercise group; LEX = low intensity exercise group; WL = waiting list. Error-bars indicate standard errors of the mean.

Depressive Symptoms

The 3 (group) by 2 (time) ANOVAs with BDI-2 and HAMD as outcome variable did not reveal any significant interaction or group effect. There was a significant main effect of time in BDI-2 and HAMD, indicating a general improvement from t1 to t2 (BDI-2: $F(1, 82) = 30.77$, $p < .001$, partial $\eta^2 = .27$; HAMD: $F(1, 82) = 28.05$, $p < .001$, partial $\eta^2 = .26$). Follow-up t-tests show that depressive symptoms measured with HAMD and BDI-2 improved significantly from t1 to t2 in all three groups (HAMD: HEX: $t(25) = 3.70$, $p < .001$, $d = .73$; LEX: $t(31) = 3.73$, $p < .001$, $d = .66$; WL: $t(26) = 1.93$, $p = .032$, $d = .37$; BDI-2: HEX: $t(25) = 2.64$, $p = .007$, $d = .52$; LEX: $t(30) = 3.90$, $p < .001$, $d = .70$; WL: $t(27) = 3.14$, $p = .002$, $d = .59$).

Behavioral results during n-back

For the performance during n-back, the 3 (group) × 4 (load) ×2 (time) ANOVA revealed a significant main effect of time, load and time x load interaction (see table 2). Latter means a stronger performance change in higher WM loads. There were no significant main effects of group and no significant interactions for time × group, load × group or time × load × group (see supplements for detailed statistic).

Table 2.
Significant main effect of time, load and interaction effect of n-back performance.

	df	*F*	*p*	η^2
time	1	14.07	<.001	.145
load	3	63.51	<.001	.702
time × load	3	6.71	<.001	.199

Post hoc comparisons revealed a significant increase in performance from pre to post in 2- and 3-back only in HEX (2-back: $t(25) = -2.17$, $p = .020$, $d = -.43$; 3-back: $t(25) = -2.50$, $p = .010$, $d = -.49$) and LEX (2-back: $t(31) = -2.47$, $p = .010$, $d = -.44$; 3-back: $t(31) = -2.57$, $p = .008$, $d = -.45$), not in WL (Figure 2 A).

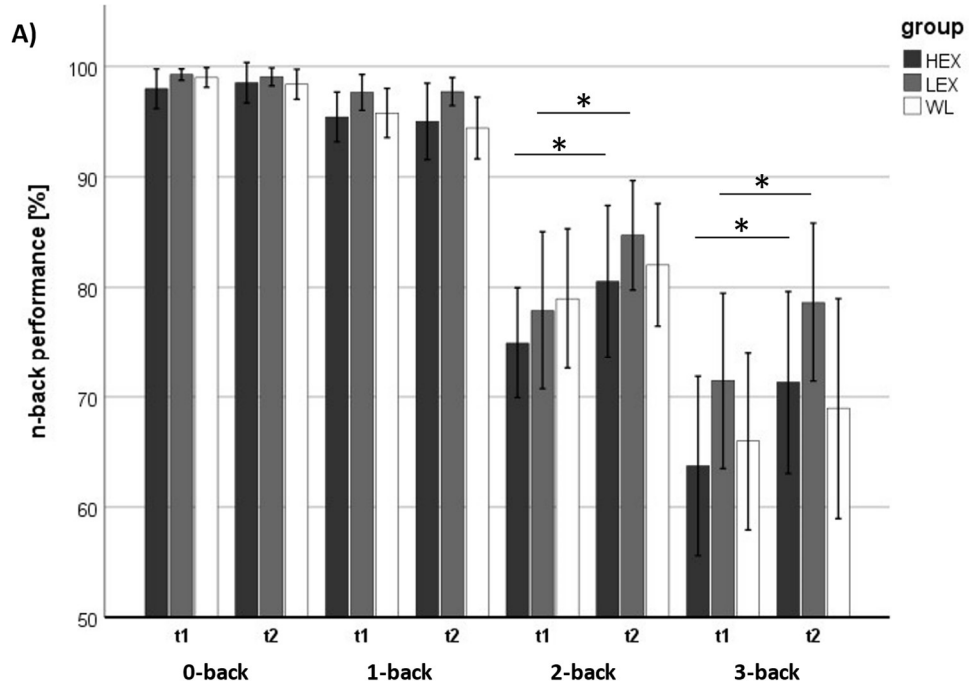


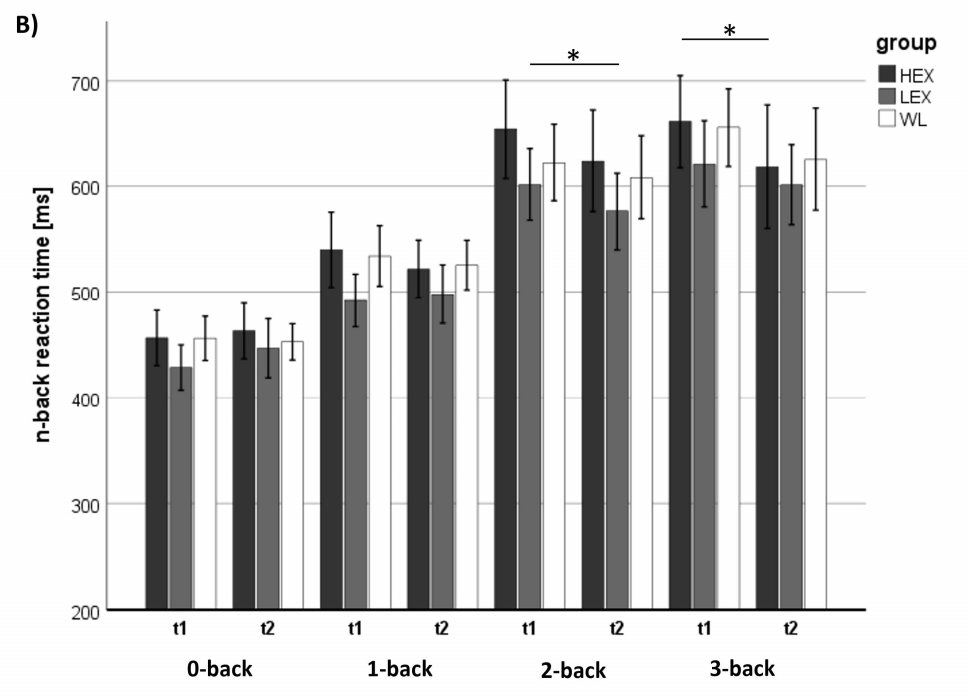
Figure 2. Behavioral n-back data in major depressive disorder (MDD). Means and standard errors are reported for A) performance and B) reaction time. *p < 0.05. HEX = high intensity exercise group; LEX = low intensity exercise group; WL = waiting list.

Similar effects were observed for reaction time, as the 3 (group) x 4 (load) x 2 (time) ANOVA showed a significant main effect of time, load and time x load interaction (see Table 3). The interaction effect describes a greater change after exercise in reaction time during higher loads. There were no significant main effects of group and no significant interactions for time × group, load × group or time × load × group (see supplements for detailed statistics).

Table 3.
Significant main effect of time, load and interaction effect of n-back reaction time.

	df	*F*	*p*	η^2
time	1	6.25	.014	.070
load	3	135.07	<.001	.833
time × load	3	6.09	<.001	.183

Post hoc comparisons revealed a significant decrease in reaction time from pre to post in HEX and LEX in higher load-conditions (HEX in 3-back: t(25) = 1.99, p = .029, d = .39; LEX in 2-back: t(31) = 2.07, p = .023, d = .37), not in WL (Figure 2 B).



FMRI results during n-back

T-tests contrasting high, low, and no-exercise training for each load-condition showed significant activation increases from pre to post in 1-back and 3-back load (Table 2). The largest cluster was found in the 3-load condition in the HEX>WL contrast. At the 1- and 3-back load condition, there was an increase in activation in the left hippocampus in the HEX>WL contrast after exercise training. No effects were seen in 2-back.

Table 4.
Significant whole-brain effects in the n-back task.

region	side	MNI-coordinate x	y	z	Peak t-value	clustersize
1-back k>85						
HEX>WL, post>pre						
Hippocampus	L	-28	-38	-8	4.13	90
3-back k>98						
HEX>WL, post>pre						
Hippocampus	L	-30	-42	-4	3.73	138

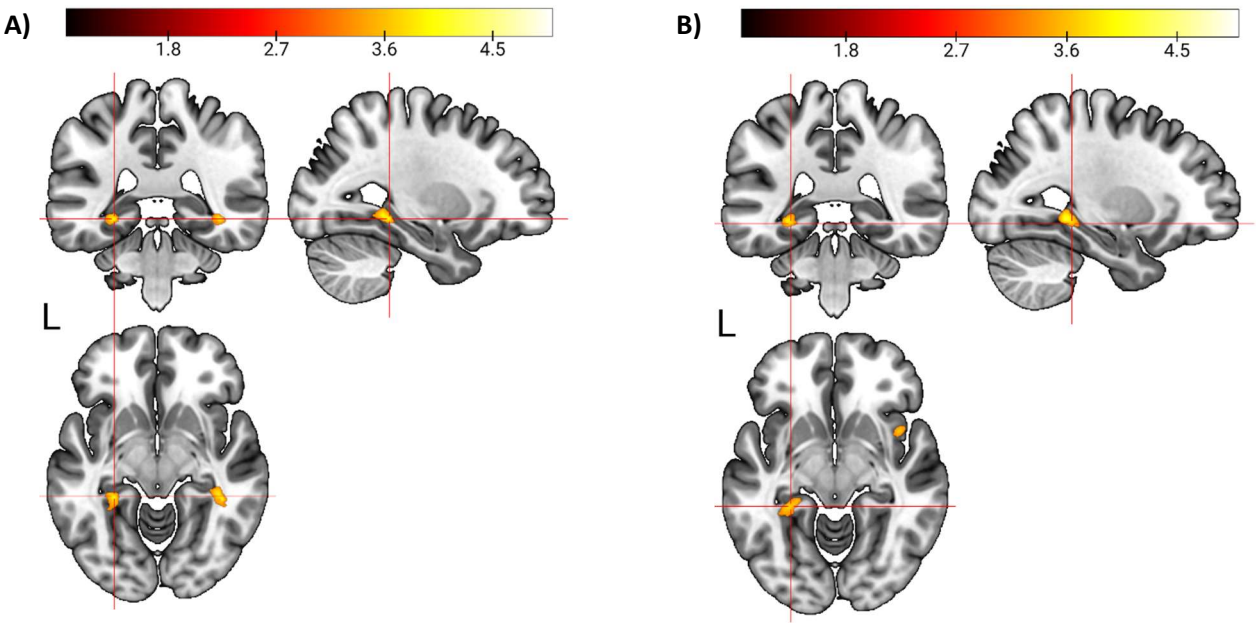


Figure 3. Significant interaction clusters (*p<.05, FWE cluster-corrected*), A) 1-back: left Hippocampus, B) 3-back: left Hippocampus.

Volume-based morphometry

Post-intervention, there were no differences in right or left hippocampal, parahippocampal or total brain gray matter volume, as shown in Table 3. Thus, the intervention did not result in a change in hippocampal volume or gray matter in total.

Table 5.
Intervention effects on hippocampal, total and gray matter volume. Mean and standard deviation are reported.

Brain Volumes in cm^3	HEX	LEX	WL	% change HEX[a]	% change LEX[a]	% change WL[a]	Effect Size[b]
Left Hippocampal	N=26	N=32	N=28				
Pre	4.22 (0.4)	4.31 (0.4)	4.02 (0.4)				
Post	4.23 (0.4)	4.32 (0.5)	3.99 (0.4)	0.20	0.06	-0.62	0.03
Right Hippocampal							
Pre	4.10 (0.4)	4.22 (0.4)	3.94 (0.4)				
Post	4.10 (0.5)	4.22 (0.4)	3.92 (0.4)	-0.28	0.05	-0.28	0.01
Left Parahippocampal							
Pre	4.21 (0.5)	4.45 (0.5)	4.09 (0.4)				
Post	4.22 (0.5)	4.44 (0.5)	4.09 (0.4)	0.41	-0.13	0.00	0.01
Right Parahippocampal							
Pre	4.57 (0.5)	4.95 (0.6)	4.53 (0.5)				
Post	4.56 (0.5)	4.93 (0.6)	4.51 (0.4)	-0.18	-0.45	-0.46	0.01
Grey Matter							
Pre	639.04 (63.0)	670.28 (61.8)	632.04 (68.0)				
Post	635.12 (63.0)	667.09 (63.6)	635.4 (64.6)[a]	-0.61	-0.50	-0.22	0.02
Total brain							
Pre	1485.18 (176.7)	1543.49 (135.2)	1482.56 (179.0)				
Post	1485.31 (176.5)	1543.80 (135.2)	1493.60 (172.5)[c]	0.01	0.02	0.01	0.00

[a] Effect Sizes were calculated by dividing Beta by the pooled SD at baseline, with positive ESs meaning a beneficial effect of the intervention on a specific outcome. ESs < 0.2 indicate “no difference”, ESs between 0.2 and 0.5 indicate “small differences”, ESs between 0.5 and 0.8 indicate “medium differences” and ESs ≥ 0.8 indicate “large differences” (61).

b Calculation for average % change between Pre and Post: (Post - Pre)/Pre * 100.

c Data of one additional patient from the WL group was missing due to segmentation errors.

Discussion

The primary aim of the current study was to assess neural (hippocampal) activations and volume in response to aerobic exercise in patients with MDD. On a behavioral level, we found higher performance and shorter reaction times especially in exercise groups at higher WM loads after a three-month aerobic exercise intervention. On a functional level, we found increased hippocampal activations in a group of mild to moderate depressed out-patients after a three-month aerobic exercise intervention. More precisely, we showed an increase in activation in the left hippocampus in the HEX > WL contrast after exercise training in low and high WM demands. Structural volume changes in gray matter or hippocampus after the exercise training were not found. In addition, the three-month aerobic exercise training resulted in an improvement in fitness specifically in the HEX group. This indicates that training above a certain intensity threshold was required to achieve fitness gains in the current study. As hippocampal activity changes were also restricted to the HEX, it is plausible to assume that these neural changes were related to the high intense exercise training. Reduced depressive symptoms were reported in all groups after three months.

To the best of our knowledge, this is the first study to assess functional brain activity in a WM task in response to aerobic exercise in patients with MDD. Our key finding reveals heightened hippocampal activity during the n-back task after exercise training in the HEX group compared to the WL group. This aligns with studies in healthy adults, such as Wagner et al. (62), who observed increased BOLD signals in the left anterior hippocampus following short-term intensive aerobic training. They attributed this to enhanced perfusion and neuronal responsiveness. Similar positive effects of aerobic exercise on the hippocampal memory system

have been consistently demonstrated in rodents (40; 63; 37). In young and fit individuals, a three-month aerobic exercise regimen increased relative cerebral blood volume in the dentate gyrus of the hippocampus, correlating with improved memory performance (64). Maass et al. (65) observed increased hippocampal perfusion exclusively in the exercise group of older adults, correlating with enhanced recognition memory. Notably, the alterations in hippocampal perfusion were found to be positively correlated with improvements in recognition memory evaluated using the Verbal Learning and Memory Test. Holzschneider et al. (66), focusing on middle-aged individuals, found that fitness levels influenced fMRI activations during a spatial learning task, involving various brain regions, including the hippocampus. In our study with individuals experiencing MDD, the heightened hippocampal activation, evident across low and high WM loads in the high exercise group compared to the no sport group (WL), indicates exercise-induced improvements in hippocampal blood flow and neuronal responsiveness during WM tasks. This aligns with research in healthy individuals and suggests that exercise-induced alterations in the vascular system may contribute to enhanced neuroplastic changes by facilitating the delivery of neurotrophic factors and oxygen through blood vessels more efficiently (67).

On the behavioral level, we found higher performance and shorter reaction times specifically in the exercise groups at higher WM loads after exercise training, which is in line with the current state of research. A recent meta-analysis (68) supports these findings, demonstrating a small but significant positive effect of physical exercise training on WM in depressed adults (Hedges's $g = 0.33$, $p = 0.026$) compared with the control group. Even though this effect does not show up in a significant interaction group x time effect in our study, it is evident in both reaction times and performance at t-tests level, with even higher effect sizes than in Contreas-Osorio et al. (68). Thus, aerobic exercise might improve WM especially at high demands.

For the finding that depressive symptoms were reduced in all three groups after exercise, various explanations are conceivable. Heinzel et al. (50) analyzed this phenomenon in more

detail. As possible explanations for the fact that the control groups also improved their symptoms, they mention fluctuations in illness severity, spontaneous improvement, regression to the mean, and therapeutic effects of the diagnostic procedures during the study assessments and "probationary" sessions.

Consistent with findings by Krogh et al. (35), this study indicates that exercise training induced behavioral and neural changes but did not impact brain structure in terms of overall or hippocampal volume in individuals with MDD. Despite a significant increase in maximal oxygen uptake after exercise intervention, no rise in hippocampal volume was observed in MDD patients. While research on aerobic exercise's impact on hippocampal volume is extensive in healthy controls (69; 65; 41; 43; 70) and other patient groups, such as schizophrenia (71), showing positive correlations, Hvid et al. (42) noted sparse and vague effects in their systematic review with healthy individuals. Consequently, the evidence supporting hippocampal volume increase following exercise training in MDD remains limited, leaving the relationship between exercise and hippocampal growth inconclusive.

The discrepancy between the functional hippocampal activation changes and behavioral improvements after exercise training on the one hand and the absence of findings on structural brain measures and symptom level on the other hand may suggest several explanations: The 12-week, twice-weekly intervention may not have been of sufficient duration or intensity to induce structural changes, given the critical role of these factors in antidepressant effects for individuals with depression (72; 73). Exercise is often part of a healthier lifestyle, which could increase the effects of physical activity on brain structure. Lifestyle factors associated with a healthier overall lifestyle, such as smoking, obesity, and alcohol consumption, are known to impact gray matter volume (74–78).

Additionally, rodent studies indicate that combining physical exercise with environmental enrichment enhances neurogenesis more than either condition alone, suggesting that physical

activity alone might not be potent enough to yield measurable effects on brain volume (79; 80). Another explanation is that a lifetime of higher physical activity and associated lifestyle factors are likely to have a greater effect on the brain than a three-month intervention. Research by Wilckens et al. (70) suggests that interventions lasting over 24 weeks show training effects, indicating that a three-month increase in physical activity might not be adequate for volumetric changes in certain populations. Thus both, environmental effects, and the duration of intervention, could contribute to intervention effects. Moreover, previous research on neuroplasticity confirms our finding that functional brain changes occur more frequently and faster than changes at the structural level (e.g., (81)).

The strengths of our study are the type of intervention (aerobic exercise), the fact that the LEX and HEX interventions were comparable in all parameters except exercise intensity, both training sessions took place at the same location, participants were blinded to participation in LEX and HEX and randomly assigned, and that patients adhered well to the program, resulting in improvements in physical fitness. A study limitation may be the relatively low training frequency, with attendance falling below recommended frequencies. Despite implementing two sessions per week at the recommended intensity (54), actual attendance rates were lower (HEX: 1.7, LEX: 1.6), contrasting with more recent guidelines suggesting 3-5 sessions weekly (73; 72; 82–85) Additionally, some participants were on medication, potentially influencing outcomes, although this mirrors real-world clinical scenarios.

The complexity of biological underpinnings of depression makes it difficult to fully understand the neural mechanisms of action of exercise training in MDD on the various cognitive processes. The results of this study support the hypothesis that exercise positively affects WM functions by improving neuroplasticity in hippocampal regions at neurofunctional, but not structural level. Exercise adaptations (such as duration and intensity) need to be investigated in future studies, as does the modulatory influence of additional environmental and individual

constitutional variables on neuroplasticity in training studies. Exercise training seems to be a promising treatment for MDD patients to improve cognition, but further research is needed to fully understand the underlying mechanisms of action.

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6. General Discussion

In the following chapter the findings, gain of knowledge and conclusions of this dissertation project on the effects of physical activity/exercise training on WM functions in major depression will be discussed. In section 6.1. the main results from our three studies will be summarized and discussed. Next in 6.2. the main strengths and limitations of the three studies will be focused. Further, in section 6.3. clinical implications derived from the results across all studies will be made. Additionally, in section 6.4. further suggestions for future research on physical exercise as a treatment for major depression disorder in the context of cognition will be made. Finally, section 6.5. will end this chapter with general conclusions on exercise interventions related to cognition in MDD.

6.1. Discussion of the main findings

The positive effects of physical exercise on MDD will be discussed first, as this was the main focus in Study I. Secondly, findings on the pathophysiology of WM processing and the effects of physical fitness/exercise training at the behavioural level obtained in Studies II and III are discussed. Finally, the findings on neuroplasticity in WM processing in MDD in the context of physical fitness (Study II) and physical exercise training (Study III) will be discussed. Figure 4 shows a schematic overview of the most important results of this dissertation. The results can be described on a behavioural, physical, and neuronal level, pre and post exercise intervention.

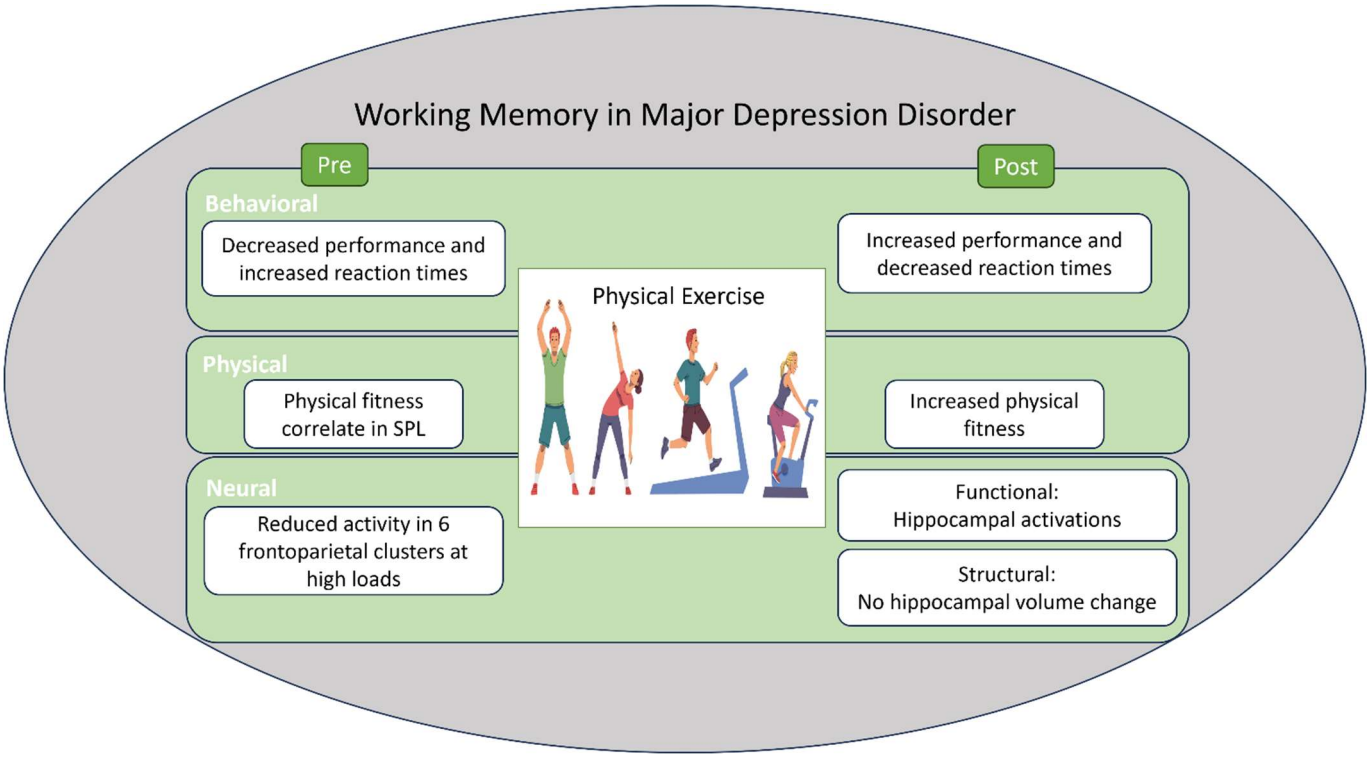

Figure 4. Summary of the main findings of physical exercise effects on WM in MDD. SPL=superior parietal lobe.

6.1.1. Beneficial effects of physical exercise in MDD

The results of Study I, the clinical trial of the SPeED project, indicated that engaging in HEX training led to improved physical fitness, while the LEX training group and the WL group did not show similar enhancements. Despite the notable increase in fitness post-exercise, the reduction in depressive symptoms was consistent across all groups. However, the degree of improvement in fitness was identified as a predictor for the subsequent response to CBT. In conclusion, the expected augmentation effect of an intensive exercise intervention did not occur, so the exercise interventions tested in our study did not result in a better outcome of CBT compared with a WL group receiving CBT alone. Similar intervention effects were found in Study III: fitness improvement only in HEX group and no group specific change in depressive symptoms after training was found.

In accordance with the majority of research on physical activity/exercise, the HEX group in our study exhibited enhanced physical fitness from t1 to t2. The magnitude of the fitness

improvement (d = -0.49) aligns with similar gains observed in previous aerobic exercise interventions for individuals with MDD (for review, see Stubbs et al., 2018). However, it falls short when compared to exercise programs of longer duration (e.g., Kruisdijk et al., 2019) and more frequent training sessions (for review, see Vancampfort et al., 2017). Importantly, results of Study I and III confirm that a certain level of intensity is required to achieve physical fitness improvements in MDD (Dunn et al., 2005; Fletcher et al., 2013; Heinzel et al., 2018). While physical fitness improved specifically in the HEX group from pre to post training, substantial symptom improvements were not exclusively observed in the HEX but in all groups (with moderate effect sizes). It is unlikely and rather not hypothesized that low intensity exercise leads to antidepressant effects (Schuch et al., 2016), yet some studies report significant effects even at low exercise intensities such as a subgroup analysis in Cooney et al. (2013). The pre-post effect sizes we observed in our WL group are similar to the effects typically seen in waiting list control groups in previous studies on psychotherapy trials MDD, where the effect size is typically around d = 0.50 (for review, see Rutherford et al., 2012).

Despite a minority of psychotherapy studies showing worsening depressive symptoms within the waitlist control group (e.g., Nezu, 1986), the prevailing body of research in this domain described symptom improvements. Variations in the severity of the illness, improvement on its own, regression to the mean, and the therapeutic benefits of the diagnostic procedures carried out during the study assessments and *probationary* sessions have all been credited for these improvements (Fava et al., 2003; Rutherford et al., 2012). These findings underscore the dynamic nature of depressive disorders and the importance of considering various contributing factors when evaluating treatment outcomes. In our study, all patients participated in so-called five *probationary sessions*. These sessions, which took place between t1 and t2, are mandatory in the German health care system and included further diagnostics via interview of the biography and behavioral analyses as well as discussion of treatment goals. Although these sessions were not therapy interventions in the strict sense, they may have

positively influenced outcome expectations and thereby reduced depressive symptoms (Holtforth et al., 2011; Schindler et al., 2011; Thiruchselvam et al., 2019). This highlights the complex interplay between psychological factors, patient engagement, and therapeutic expectations, which could impact treatment outcomes.

Study I further explored the potential added benefit of physical exercise training to CBT, particularly expecting greater benefits in the HEX group compared to LEX and the WL group. However, the anticipated advantage was not observed, as the CBT outcomes did not differ among the three groups, and no augmentation effect was evident. Despite physiological improvements in physical fitness within the HEX group, this did not translate into the anticipated *boosting effect* on CBT, i.e., a reduction in depressive symptoms post-CBT. Other studies that integrated physical exercise training, CBT, and medication also did not demonstrate significant improvements in depression outcomes (Imboden et al., 2020; Kerling et al., 2015). The authors attributed this lack of improvement to the fact that the exercise interventions did not provide any significant additional benefit over and above the already effective control conditions (intensive CBT, medication, and low-intensity physical activity). Supporting this concept, a meta-analysis conducted by (Lindheimer et al., 2015) on exercise studies involving depressed patients revealed an overall effect size of d = 0.20 for control interventions, encompassing relaxation, very low intensity exercise, social contact, and acupuncture.

In contrast to our findings, Abdollahi et al. (2017) reported enhanced CBT outcomes when exercise was added to the treatment regimen. Notably, their study differed from ours in that they conducted exercise sessions three times a week, in conjunction with CBT. The combination of a simultaneous approach and a higher physical exercise session frequency likely contributed to the significant improvement in relieving depressive symptoms observed in their study. This suggests a non-linear dose-response relationship between physical activity and

depressive symptom improvement, implying that reaching a certain threshold of physical activity may be necessary to achieve positive effects.

Although we didn't observe a general enhancement or *boosting effect* from a vigorous physical exercise intervention on the overall results of CBT, our regression analyses in Study I did reveal a noteworthy correlation: the extent of improvement in physical fitness predicted the response to CBT. Even through the amount of variation explained by this relationship was relatively modest, it's a compelling discovery that hints at the importance of individual differences within the groups, which could help explain variations in subsequent CBT responses. The response to CBT and physical activity/exercise training can vary greatly from person to person. The effectiveness of interventions may depend on individual differences, including genetic, biological and psychosocial factors. This finding may hold significance for shaping an ideal training regime. It appears that personalized training programs aimed at optimizing an individual's fitness level may prove to be more effective within the context of a comprehensive treatment plan. Such tailored approaches could potentially yield greater improvements in depressive symptoms. Patient preferences should also be taken into account, as well as adaptation to the patient's individual capabilities. An individualized approach seems to be important.

6.1.2. Working memory in MDD and Effects of physical exercise

The results found in Study II and III on WM in MDD in relation to physical fitness and exercise confirm previous findings found in the literature (see chapter 1.2.). Study II found that MDD patients generally showed higher RTs when performing an n-back task as well as WM performance decrements specifically at high WM loads. These findings are largely consistent with previous results from a recent meta-analysis by (Nikolin et al., 2021) indicating a WM deficit in MDD patients. Increased reaction times observed across all n-back task conditions point to a slowdown in psychomotor functioning among individuals with MDD while engaging

in the n-back task, regardless of WM load. These findings align with prior research studies (Bennabi et al., 2013; Buyukdura et al., 2011; Nikolin et al., 2021) which have been interpreted as indicative of psychomotor retardation associated with depression. Performance deficits noted specifically under high WM load during the n-back task suggest that individuals with MDD encounter challenges, especially when higher-level executive functions such as updating (Owen et al., 2005) are engaged. This could indicate deficits in executive control functions, possibly affecting the coordination of different WM subprocesses (Nikolin et al., 2021).

The higher performance and shorter reaction times after physical exercise training seen in Study III (especially in exercise groups at higher WM loads) is also consistent with the current state of research. Imboden et al. (2020) found a significant positive effect of a 6-week exercise program on WM, suggesting a general procognitive effect of physical exercise in depression treatment. Also, the results from a recent meta-analysis by Contreras-Osorio and colleagues (2022) have illuminated a noteworthy finding: physical exercise training can enhance WM in MDD with a small yet statistically significant positive effect, denoted by an effect size of 0.33 ($p= 0.026$), when comparing the intervention group to the control group. While our effect may not appear as a significant interaction in the group x time analysis, it is evident in both reaction times and performance at t-test level, even reaching higher effect sizes than those reported by Contreras-Osorio et al. (2022). Consequently, it appears that physical exercise training could particularly bolster WM, especially at high demands.

6.1.3. Neuroplasticity in working memory processes in MDD and physical fitness/exercise training

FMRI analyses were used to investigate WM processes in MDD in general and in the context of physical fitness (Study II) and after physical exercise training (Study III).

6.1.3.1. Frontoparietal Activity

The results of Study II, in which we examined the specificity of WM load in MDD (see chapter 1.2.) revealed six frontoparietal clusters indicating reduced neural activity during high WM load tasks in individuals with MDD. These findings are in line with previous meta-analyses, which have investigated neural activations associated with the n-back task (Mencarelli et al., 2019; Owen et al., 2005). Thus, these clusters are part of the frontoparietal WM network, suggesting that the neuronal activity changes associated with MDD in WM tasks are due to network dysfunction rather than a specific brain region.

The most prominent cluster was situated in the left parietal cortex (superior parietal lobule (SPL) and inferior parietal lobule (IPL)), aligning with prior findings by Wang et al. (2015). The SPL plays a crucial role in manipulating and rearranging information in WM, as well as shielding against external distractions and updating WM content (Koenigs et al., 2009). When performing WM tasks, the IPL is linked to adjusting attentional focus within activated WM content (Nee et al., 2013). Additional clusters were identified in frontal areas, including the middle frontal gyrus and the inferior frontal gyrus, suggesting potential impairments in executive WM components in MDD. These could involve mental refreshing of recently presented stimuli and updating WM content by continuously removing and adding information (Nee et al., 2013). Our findings align with previous studies (Garrett et al., 2011; Meusel et al., 2013; Vasic et al., 2009; Wang et al., 2021; Xia et al., 2019; Zhu et al., 2018). Divergent from (Wang et al., 2015) meta-analysis, no frontal hyperactivations were detected in our MDD sample, which are frequently described also in this field of research (see chapter 1.2.). Our results show a reduced WM-dependent modulation of neural activity in MDD that is driven by reduced activation at medium and high WM load.

In previous research within the framework of models like the CRUNCH model (Reuter-Lorenz & Cappell, 2008), frontal hyperactivations have been interpreted as compensatory

efforts to maintain normal performance levels. However, when these compensatory attempts fail, and capacity limits are exceeded, performance decrements and reduced neural activity are expected at high task demand (Barulli & Stern, 2013; Heinzel et al., 2015; Reuter-Lorenz & Cappell, 2008; Schneider-Garces et al., 2010). Our findings suggest a reduced neural capacity within the WM network in MDD, particularly evident during high WM load. This aligns well with other research in the field. Reduced frontoparietal activity observed in MDD is often interpreted as a manifestation of network dysfunction (Tan et al., 2021). Additionally, previous research has identified links between the effectiveness of the frontoparietal network and cognitive function (Sheffield et al., 2015). WM, which is vital for various cognitive tasks, relies on a distributed network of brain regions, including the frontal and parietal areas (see chapter 1.2.). The observed decrease in global efficiency of frontoparietal network in individuals with MDD may suggest the breakdown of some distal connections (Tan et al., 2021). This observation is in line with earlier research that has documented the hypoconnectivity of distant regions within the frontoparietal network, such as the inferior parietal cortex and superior prefrontal areas, in individuals with MDD during WM tasks (Vasic et al., 2009). The hypoconnectivity in these distant regions may result from a failure of coordinated activity among them. Notably, the abnormal activation patterns of neural components within the frontoparietal network during WM tasks are characterized by considerable heterogeneity (Wang et al., 2015). In simpler terms, while some frontal regions may exhibit excessive activity (frontal hyperactivation), other parietal areas may show reduced activity (parietal hypoactivation). These complex patterns collectively provide evidence of altered activation, connectivity, and connectomic properties related to WM within the frontoparietal network in individuals with MDD.

In Study II, we introduced physical fitness as an additional regressor in our analysis to investigate the connection between physical fitness and brain function during WM tasks in

patients with MDD. Our findings demonstrated a strong and positive link between physical fitness and the activation of the SPL in both hemispheres in MDD patients. Our finding can be attributed to the dorsal attention network, which is involved in internal and external attention processes and appears to be associated with reduced connectivity with the frontoparietal network in patients with MDD (Kaiser et al., 2015). This suggest that physical fitness may be a crucial factor in preventing WM impairments in depression, possibly by influencing SPL activation. These results are consistent with a meta-analysis that integrated findings from 20 neuroimaging studies in healthy individuals, suggesting that physical exercise can enhance the functional integration of the frontoparietal control network, particularly in the precuneus, which is part of the SPL (Yu et al., 2021).

Furthermore, ROI analysis in Study II revealed a positive association between parietal activity, specifically in the left SPL and IPL, during WM tasks and physical fitness in MDD patients. These regions are essential components of the dorsal attentional and frontoparietal networks, supporting our findings (Yu et al., 2021). Additional support for our observed positive correlation between physical fitness and parietal activation comes from studies involving healthy older adults. These studies indicate that higher physical fitness levels are associated with increased brain activation in areas involved in demanding cognitive functions, such as the prefrontal and parietal cortex (Colcombe et al., 2004; Prakash et al., 2011). These findings align with our similar discovery in patients with MDD, suggesting that higher physical fitness levels are linked to better cognitive performance and increased activation of fronto-parietal areas.

From a theoretical standpoint, considering the neuroplasticity hypothesis regarding the mechanisms of action of physical activity in MDD, the finding could be elucidated as follows (see chapter 1.3.1.1.): In physically fitter individuals, blood flow is increased, delivering more oxygen and nutrients to the brain. This promotes the growth of new blood vessels

(angiogenesis). Additionally, higher physical fitness stimulates the release of neurotrophic factors such as BDNF, which promote the survival and growth of neurons (neurogenesis), fostering neuroplasticity. All of these processes could occur in frontoparietal regions associated with learning and memory, leading to these regions becoming more efficient at transmitting signals and resulting in better cognitive performance. Future research is needed at this point to investigate and confirm the correlates of these processes in more detail.

6.1.3.2. Hippocampus

Our main finding in Study III was that after exercise training, the hippocampus showed increased activity during the n-back task in the group that exercised (HEX) compared to control group (WL). This finding aligns with other studies, although those studies did not involve individuals with depression. In one study with healthy adults, researchers examined the effects of intensive aerobic training on memory recall (Wagner et al., 2017). They found significant differences in the activation pattern of the left anterior hippocampus after the exercise intervention. They believed this could be due to increased blood flow and responsiveness in the hippocampus caused by physical exercise, a view supported by research in animals and humans. It has been consistently shown in rodents that aerobic exercise leads to beneficial effects in the hippocampal memory system (Snyder et al., 2009; van Praag et al., 2005). Moreover, studies involving young and physically fit individuals have shown that engaging in aerobic exercise for three months results in improvements in the relative cerebral blood volume in the dentate gyrus of the hippocampus, along with enhanced memory performance (Pereira et al., 2007). In older adults, a three-month exercise program led to increased hippocampal blood flow and improved recognition memory (Maass et al., 2015). Another study involving middle-aged individuals found that individual fitness levels influenced brain activity during a spatial learning task, including in the hippocampus (Holzschneider et al., 2012). Based on current research in healthy individuals, the results of Study III suggest that in the high exercise group, there was an increase

in hippocampal activation compared to no sport group (WL). This increase was noticeable regardless of whether the WM load was high or low. This suggests that physical exercise can boost blood flow in the hippocampus and make neurons more responsive during WM processing in individuals with MDD. These improvements in the vascular system, which help transport neurotrophic factors and oxygen more efficiently through blood vessels, may play a critical role in the brain's ability to change and adapt due to physical exercise, as proposed by Stimpson et al. (2018). Support for this neuroplasticity hypothesis can be found in a study by Brüchle et al. (2021), which revealed after the moderate-intensity exercise program the largest effect size within the WM dimension (ES = 1.51). They reported that improvements in cognitive symptoms were accompanied by a significant increase in neuroplasticity (BDNF increase). This strongly supports the assumption that physical exercise indeed has beneficial effects on cognition by enhancing neuroplasticity and preventing diseases associated with cognitive decline (Augusto-Oliveira et al., 2023; Hötting & Röder, 2013).

Considering the structural findings, we did not observe an increase in overall brain volume or specifically in hippocampal volume in individuals with MDD after three months of aerobic training, which is consistent with the findings of Krogh et al. (2014). Despite a significant improvement in maximal oxygen uptake following physical exercise intervention, Krogh and colleagues did not find an increase in hippocampal volume in MDD patients. However, through post-hoc analysis, they were able to demonstrate a positive association between changes in hippocampal volume and verbal memory (Rho=0.27; p=0.05) as well as changes in hippocampal volume and depressive symptoms (Rho=0.30; p=0.03). Research on changes in hippocampal volume due to aerobic exercise in healthy individuals (e.g., Erickson et al., 2011; Maass et al., 2015; Wagner et al., 2015; Wilckens et al., 2021) and other patient groups, like those with schizophrenia (Pajonk et al., 2010), has shown positive correlations. However, a systematic review by Hvid et al. (2021) argued that the effects of physical exercise on grey

matter volume, including the hippocampus, are generally inconclusive and limited, even in healthy individuals. Consequently, the current knowledge regarding the relationship between exercise and hippocampal growth remains uncertain, and our study does not provide evidence to suggest that exercise can stimulate hippocampal growth in individuals with depression.

The discrepancy between the changes in functional activation observed in the hippocampus and improvements in behavior following physical exercise training, and the absence of significant findings in structural brain measures and symptom levels, can be attributed to several factors. The length of exercise training is a crucial factor in providing antidepressant advantages to people with MDD, as suggested by research conducted after our intervention began in 2015 (Dishman et al., 2021; Pearce et al., 2022). Also, Wilckens et al. (2021) have found that exercise interventions lasting longer than 24 weeks are more likely to show training effects, implying that a three-month increase in physical fitness might not be sufficient to induce volumetric changes in certain populations. Furthermore, research on neuroplasticity confirms our finding that functional changes in the brain occur more frequently and faster than changes at the structural level (e.g., Bruel-Jungerman et al., 2007). Conversely, this is the case in individuals with memory loss, where brain markers first register a decline in functional neuroimaging followed by structural brain changes and finally by cognitive decline (Clark et al., 2012). Therefore, our 12-week intervention, consisting of only two sessions per week, may not have been long enough to induce structural changes, even though we adhered to the American Heart Association's endurance training guidelines outlined by Fletcher et al. (2013).

Another factor is that physical exercise is often just one aspect of a healthier lifestyle, which can enhance the effects of physical activity on brain structure. Lifestyle factors like obesity, smoking and alcohol consumption have been associated with reduced gray matter volume, which can influence the results (Fernández-Andújar et al., 2021; Herrmann et al., 2019; Vňuková et al., 2017; Wilson et al., 2017; Yang et al., 2020). Furthermore, research in rodents

has indicated that a combination of voluntary physical exercise and enriched environments can promote neurogenesis in the hippocampus more effectively than either condition alone (Fabel et al., 2009; Olson et al., 2006). This suggests that physical activity alone may not be enough to produce measurable changes in brain volume. Therefore, the cumulative effects of physical activity over a lifetime, along with other environmental factors and longer intervention periods, may contribute to significant changes in brain structure.

6.2. General strengths and limitations

The major strength of the overall SPeED study is that it is a randomized controlled trial that was subject to strict inclusion and exclusion criteria. This allows numerous systematic biases to be controlled and more internally valid conclusions to be derived (Jacobi, 2020). Another strength of the longitudinal studies (I and III) is the type of intervention (aerobic exercise) and the fact, hat exercise interventions were comparable in all parameters but the training intensity. Patients adapted well to the program, improving their physical fitness, both training sessions were held at the same site, and participants were randomly assigned while blinded to their involvement in LEX and HEX.

The following limitations must be considered: First, in the longitudinal studies (I, III) the dropout rate was relatively high and follow-up data at t2 and t3 were available only in a minority of dropouts, thus, unfortunately, the longitudinal analyses have lost some of their power. Second, due to ethical reasons, probationary sessions for CBT with MDD patients were already conducted before t2 assessment. It is possible that this may have influenced depressive symptoms (as discussed in 6.1.1.). Third, we ensured that all participants in our practice groups attended at least 18 of the 24 sessions offered (75%). However, for some participants, this resulted in a longer duration of participation in the training program and actual weekly attendance was on average lower than the intended 2 sessions per week (HEX: 1.71; LEX: 1.60). This lower training frequency may not have been sufficient to achieve the desired

enhancement in depressive symptom relief, as it falls below the recommended minimum of 3 weekly sessions, as suggested by recent research (Piercy et al., 2018; Rethorst & Trivedi, 2013; Schuch et al., 2016; Stubbs et al., 2018). Fourth, a high number of dropouts was recorded, of which a particularly large number were female. For further discussion of the high dropout rates please see discussion Study I (chapter 3). Fifth, all studies utilized a physical fitness index measured through power output during an exercise ECG on a bicycle ergometer. In the future, researchers could expand this index to incorporate additional fitness indicators for a more comprehensive assessment of individual physical fitness. Sixth, the study did not systematically assess the duration of the disorder in patients. Future research should gather and include this information in statistical analyses because the length of illness may influence WM performance, physical fitness, and related brain functioning. Seventh and final important point: approximately half of the individuals in our study with MDD were taking medication, which could have potentially influenced the results. However, it's worth emphasizing that this reflects the typical patient population encountered in real-world clinical settings. In most practical clinical interventions involving exercise, participants are likely to be on similar medication regimens.

6.3. Clinical Implications: Physical Exercise as treatment for working memory impairment in MDD

Previous research in physical training in MDD has already led to clinical implications. There are now clear treatment recommendations for physical training in depression, which are implemented in the S3 guidelines/national care guidelines for depression treatment (DGPPN & ÄZQ, 2017). To put this in a broader context with cognitive deficits in depression and their underlying patho- and mechanisms of action, this section will outline the clinical implications from the studies of this dissertation project.

First, our results suggest that testing more personalized training programs, designed to optimize individual training success, seems like a promising consideration for the design of a

therapy regime for patients with MDD. According to training research, it appears that extensively customized training programs yield greater effectiveness in improving fitness compared to standardized training protocols (Byrd et al., 2019; Weatherwax et al., 2019). Consequently, it is reasonable to anticipate more substantial improvements in fitness when training sessions are personalized to align with an individual's unique requirements and capabilities concerning factors such as intensity, frequency, duration, and content. This seems particularly important in the context of MDD, where the motivation to actively participate in training sessions can diminish if the training fails to align with one's personal expectations, goals, and abilities (Callaghan et al., 2011).

Second, the finding that physical exercise training led to changes at behavioral and functional levels (hippocampal activations) of WM processing, but not at symptom and structural levels, could imply that physical trainings should be done more often per week to achieve changes also at structural neuronal level and also the symptom level. In practice, this means that physical exercise training should take place at least 3 times a week, as is now often recommended (Piercy et al., 2018; Rethorst & Trivedi, 2013; Schuch et al., 2016; Stubbs et al., 2018).

Third: Regular attendance should be ensured. This is very important, as we also can assume that patients with MDD seem to have low motivation for physical exercise (visible in attendance rates). As proposed by Kruisdijk et al. (2019) it appears reasonable to highlight the positive health benefits when conducting psychoeducation during patient recruitment to encourage exercise, rather than making promises of immediate reduction in depressive symptoms. This approach may help prevent further feelings of failure among clinical patients who are already burdened by their MDD. Prescribing physical exercise to MDD patients presents many challenges for the physician, as many patients lack the motivation to start and maintain an exercise program precisely because of the disease.

Fourth, the findings on pathomechanisms in MDD that there is capacity-limited WM processing especially during high demands and that physical exercise training leads to improvements therein suggest a general procognitive effect of physical exercise in depression treatment. Furthermore, the finding of a significant positive correlation between physical fitness and cognition-related functional activation of the superior parietal lobe on both sides in patients with MDD may inform the development and investigation of physical fitness interventions that prevent or counteract WM impairments in MDD. Thus, it is conceivable that physical fitness could be used preventively as a safeguard against memory deficits. In terms of the under activation of some (frontoparietal) brain areas identified here in MDD patients, physical exercise can help to reduce the functional impairments of these regions. For example, prevention programs could be developed in healthy individuals, including, for example, in the workplace, because memory deficits are particularly relevant there. This could be clinically meaningful since only a few other treatment options show procognitive effects in depression. Physical exercise might thus be a feasible way to enhance neurocognitive symptoms of depression during acute treatment which could have important implications for work-related rehabilitation (Imboden et al., 2020).

Fifth, WM is not only an important cognitive impairment in MDD, but also a target for intervention focused on improving the quality of life of MDD patients (Ponsoni et al., 2021). Based on studies examining functional impairments in WM of people with depression, researchers have investigated different training methods, e.g., cognitive control training and WM training, in addition to physical exercise, to alleviate depressive symptoms and address cognitive deficits (for review, see Chen et al., 2023). Similar to Study I, it is conceivable that psychotherapy, cognitive training and physical exercise can be used as complementary approaches for cognitive impairment in MDD patients in clinical practice. Cognitive training and physical therapy have the potential to rehabilitate neurological functioning and enhance cognitive capabilities, including executive functions and WM, thus helping to alleviate

depressive symptoms. However, there is a shortage of studies examining the effects of cognitive training and physical therapy on cognitive efficiency in individuals with depression, and further research is necessary to validate the effectiveness of these training programs in a clinical setting as well (Chen et al., 2023).

6.4. Outlook and Future Directions

The findings of this thesis underscore the significance of the design and intensity of a physical exercise intervention. It can be assumed that individualized training improves the attendance rate which would increase the training intensity and the benefit of physical exercise in MDD. Also, a simultaneous application of motivational psychological interventions would be suitable to improve the attendance rate and the success of physical exercise interventions, as has recently been suggested (Wolf et al., 2020). Overall, there is still a lot of research needed in the field of exercise therapy to find out the optimal exercise design to reduce symptoms in patients with MDD. Although much research has been done, exercise interventions conducted in randomized controlled trials currently do not regularly meet recommended public health thresholds (Ross et al., 2023). In addition, the parameters of exercise prescriptions (i.e., frequency, intensity, time, type) are not consistently reported in the studies, making accurate replication of the studies or clinical application difficult (Yu et al., 2021). A more standardized prescription of physical exercise intensity would be greatly beneficial for enabling meta-analytical data analysis and simplify the reproducibility of studies (Gronwald et al., 2019; Herold, Aye et al., 2020). However, it's worth noting that the optimal method for describing physical exercise intensity is still a subject of debate (Herold, Müller et al., 2019; Herold, Törpel et al., 2020; Jamnick et al., 2020).

As Studies II and III are among the first to explore the neural connections between cognitive task performance and physical fitness/exercise training in MDD, they serve as a foundational step for future investigations. Future research could involve different cognitive tasks,

examining various WM subprocesses separately, or exploring other executive tasks like planning or inhibition. While the n-back task is commonly used to measure WM in depression (e.g., Nikolin et al., 2021), especially at higher workloads (e.g., 2- and 3-back), it is a complex task that also taps into higher executive functions such as updating. Therefore, it may not solely represent pure WM (e.g., Miller et al., 2009). Some studies have suggested that the n-back task might be less sensitive than other tasks, like the Digit Span or Spatial Span tasks (Redick & Lindsey, 2013), in detecting WM deficits in depression. Consequently, further research is needed to determine the n-back task's sensitivity and specificity in this population. It's crucial to note that when interpreting the results of the n-back task performance in individuals with depression, researchers should consider using it in conjunction with other measures.

As WM deficits are recognized as a severe cognitive impairment in patients with MDD, there is a need to clarify the impact of impaired WM function and brain areas in the future. The results from this work on the pathophysiology of MDD in WM processing have provided starting points, particularly at the neuronal level, but many questions remain. Chen et al. (2023) recently found that the CE components, updating, shifting and inhibition, influence WM processing, and that this may be one of the factors influencing cognitive distortions as it relates to repetitive negative thinking and rumination. The authors state that future research endeavors may consider adopting a neural systems perspective to explore the interplay among neural networks in MDD. They could aim to formulate a therapeutic training program that incorporates psychotherapy, cognitive training, exercise, and physiotherapy as complementary interventions to enhance deficits in WM function with the ultimate goal of alleviating depressive symptoms. It is essential that future studies investigate whether the brain regions identified in this dissertation could be neurobiological markers for depression. In particular our finding in Study II that there is a physical fitness correlate in the SPL can serve as a target for the (preventive) treatment of depression through physical exercise.

Further, it's important to highlight that physical exercise exerts a significant influence on learning, neurogenesis and angiogenesis by initiating various growth factor processes (Cotman et al., 2007). The impact of exercise on memory, learning, and synaptic plasticity primarily appears to be regulated by a growth factor called BDNF (Leal et al., 2015). The present work has illustrated potential neural connections to neuroplasticity, a mechanism of action of physical exercise in MDD. It would been intriguing to explore associations with growth factors like BDNF. This consideration should be taken into account for future analysis.

Finally, by focusing primarily on neural processing in the context of WM in this thesis, other factors that play a role in beneficial effects of physical exercise have been left out. (Kandola et al., 2019) provided an overview of significant psychological and biological factors in this context. These factors include changes in neuroplasticity, inflammatory processes, the endocrine system, and oxidative stress. They also involve psychosocial elements like self-esteem, social support, and self-efficacy. This illustrates the highly interdisciplinary nature of this field, necessitating a nuanced collaboration across various scientific disciplines. However, moderators should be examined in future well-designed exercise-cognition studies using neuroimaging-techniques. Consequently, the observed positive changes could potentially be attributed to several other factors that interact with physical exercise interventions. For example, individuals who start an exercise program might change their dietary habits and/or have increased social interactions, which are closely associated with improved cognitive function (Bailey et al., 2019; Hardman et al., 2020; Yu et al., 2021).

The current state of research on the effects of exercise on depression highlights two key findings: physical exercise has positive impacts on depression, but the underlying mechanisms are not well understood. This knowledge gap hinders efforts to optimize exercise as a treatment for depression. To address this Ross et al. (2023) postulate that there are two major challenges that need to be overcome in the field of exercise science: the lack of integrated multidisciplinary

collaboration and limitations in public funding. By undertaking these comprehensive efforts, the field can move beyond fragmented research findings and provide a more robust understanding of exercise's role in combating depression and its cognitive impairments.

6.5. Conclusions

The main aim of this dissertation project was to shed further light on the effects of physical activity/exercise training on WM functions in major depression disorder patients and their neural underpinnings. To bring these areas together, this thesis first described the clinical, cognitive and neurobiological characteristics of MDD, WM dysfunction in depression and the mechanisms of action of physical activity/exercise training in MDD with a focus on neuroplasticity (chapter 1). Subsequently, I examined the following research questions.

> *Does a previous exercise intervention increase the success of as subsequent CBT in the treatment of MDD and is this augmentation effect associated with specific physiological change?*

The results showed that physical fitness increased significantly in the HEX group compared to the LEX and WL groups. Depressive symptoms improved significantly after physical exercise treatment in all groups surprisingly. Also, after subsequent CBT, no mean differences in depressive symptoms were found between the groups. Thus, the high intensity of training did not lead to an overall *boosting effect* for CBT. However, regression analyses showed that the extent of individual fitness improvement predicted the subsequent response to CBT (chapter 3).

> *Can a WM load-dependent specificity be observed in individuals with MDD compared to healthy individuals in both behavioral and neural measures and is there a relationship between physical fitness and brain functioning during WM task performance in MDD?*

Patients with MDD showed generally higher RTs during the performance of a n-back task as well as WM performance decrements specifically at high WM demands. FMRI analyses revealed significant group x WM-load interaction effects in six frontoparietal clusters, indicating reduced BOLD response at medium and high WM load in MDD. Moreover, a distinct positive correlation of physical fitness with cognition-related functional activation of the superior parietal lobe bilaterally in patients with MDD was identified (chapter 4).

Are there neuronal changes in activation during a WM task or changes in brain volume evident in MDD patients after 12 weeks of exercise training, particularly in hippocampal function/volume?

Especially in the exercise groups, higher performance and shorter reaction times were observed at higher WM loads after the exercise intervention. At the functional level, there was an increase in activation in the left hippocampus in the HEX > WL contrast after training at high and low demands. Structural volume changes in grey matter or the hippocampus after the physical exercise training were not found (chapter 5).

The three studies have highlighted different aspects of beneficial effects of physical exercise training in MDD, resulting in several conclusions. Our results suggest that testing more personalized training programs to optimize individual training success could be a promising approach for future studies. Regarding the relationship between functional brain activity in a WM task, the results indicate frontoparietal hypoactivity in MDD at high demands, signifying a reduction in WM capacity. The neuronal results provide fundamental insights into the pathomechanism of MDD. The discovery of a correlation between physical fitness and the SPL may inform the development and investigation of physical exercise interventions aimed at preventing or mitigating WM deficits in MDD. Furthermore, our results lend support to the hypothesis that physical exercise can positively impact WM functions by enhancing neuroplasticity in hippocampal regions at a neurofunctional level, even though structural

changes are not observed. Future studies should delve into physical exercise adaptations, such as duration and intensity, as well as the modulating effects of various environmental and individual factors on neuroplasticity. Physical exercise training seems to be a promising treatment for MDD patients to enhance WM functioning. Further research is needed to corroborate the neurobiological findings and gain a better understanding of the mechanisms of physical exercise. The intricate biological underpinnings of depression make it challenging to fully comprehend the neural mechanisms through which physical exercise training influences cognitive processes in MDD. Nonetheless, these present findings can guide future research on the effects of physical fitness and exercise on mental health and cognition, ultimately lead to optimized physical exercise therapies as valuable complementary options for the treatment of MDD.

7. References

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Appendix

A Supplementary Material for Article I

Supplementary Material

for

Physical exercise training as preceding treatment to cognitive behavioral therapy in mild to moderate major depressive disorder: A randomized controlled trial

Stephan Heinzel[1], Melanie Schwefel[1], Alba Sanchez[2], Darlene Heinen[2], Lydia Fehm[3], Romy Henze[3], Christina Terán[2], Gunnar Kallies[4], Michael A. Rapp[2], Thomas Fydrich[3], Andreas Ströhle[4], & Andreas Heissel[2]*

[1] Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany;

[2] Social and Preventive Medicine, University of Potsdam, Potsdam, Germany;

[3] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany;

[4] Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitäts-medizin Berlin, Berlin, Germany

Supplementary Methods:

Exclusion criteria: The following exclusion criteria were applied to all patients: Current severe depressive episode with or without psychotic symptoms, current borderline or antisocial personality disorder, current suicidality, lifetime schizophrenia spectrum disorder, delusional disorder, or bipolar disorder, current alcohol or drug addiction, current severe neurological diseases of the central nervous system, severe chronic obstructive pulmonary disease, coronary heart disease and heart failure, body mass index of > 35 or < 18, insufficient language abilities in German, uncorrectable visual or hearing impairments, Magnetic Resonance Imaging

unsuitability, use of benzodiazepines or beta-blockers within the last 7 days, tricyclic antidepressants and neuroleptic drugs with a dose of > 40% of the cumulated maximum recommended daily dose, more than 2 x 45min vigorous physical exercise per week.

Sample size estimation: A target sample size of 105 participants starting the exercise treatments / waiting period (or 72 completers) was estimated using the software G*Power, version 3.1.7 (Faul et al., 2007) to ensure sufficient power of at least 80% of a 2-sided test with level of significance of 5% to detect effect sizes of .60 or greater (Cooney et al., 2013; Morres et al., 2019; Rethorst et al., 2009).

Psychotherapy intervention: There are five consecutive modules: Module 1: psychoeducation (information on depression, session 1-3), Module 2: Positive activities (session 4-8), Module 3: Cognitive Therapy (session 9-16); Module 4: Training in social competences (session 17-22), Module 5: relapse prevention (session 23-25).

Assessment of physical fitness

For the graded exercise test, we used the WHO-exercise protocol as recommended by the German Society of Cardiology (Trappe and Löllgen, 2000) and reported in the guidelines of the American Heart Association (Fletcher et al., 2013). The test was constantly monitored by electrocardiogram, measurements of blood pressure, lactate and Borg's rating scale of perceived exertion (Borg, 1982) before starting the test, at the end of each level, at maximum exhaustion, as well as three and five minutes post exercise. The test was supervised by an experienced sports physician.

Supplementary results:

Effects of sex on intervention effects in primary outcomes

Including sex as an additional factor in the ANOVAs of the primary outcomes to compare intervention effects between male and female patients with MDD showed no significant interactions involving the factor sex. Interactions for HAMD: Time by sex ($F(2, 138) = .19$, $p = .825$); group by sex ($F(2, 69) = 1.26$, $p = .290$); time by group by sex ($F(4, 138) = .84$, $p = .501$). Interactions for BDI-2: Time by sex ($F(2, 138) = .88$, $p = .418$); group by sex ($F(2, 69) = .80$, $p = .454$); time by group by sex ($F(4, 138) = 1.19$, $p = .320$). Thus, the intervention effects did not differ between men and women.

Dysfunctional Attitude Scale (DAS) sumscore

A 3 (group) by 3 (time) ANOVA with DAS as outcome revealed a significant interaction ($F(4, 138) = 2.57$, $p = .041$, partial $\eta^2 = .069$). There was a significant main effect of time, indicating a general improvement from t1 to t3 ($F(2,138) = 26.88$, $p < .001$, partial $\eta^2 = .280$). No main effect of group was found ($F(2, 69) = .37$, $p = .690$, partial $\eta^2 = .011$).

Longitudinal follow-up t-tests showed that DAS did not change significantly in HEX ($t(21) = 1.49$, $p = .150$, $d = .32$) or WL ($t(22) = -.20$, $p = .847$, $d = -.04$), but in LEX ($t(27) = .048$, $d = .39$) from t1 to t2. A significant improvement from t2 to t3 was found in HEX ($t(21) = 3.84$, $p = .001$, $d = .82$) and WL ($t(21) = 4.87$, $p < .001$, $d = 1.04$), but not in LEX ($t(28) = 1.33$, $p = .195$, $d = .25$).

Brief Symptom Inventory (BSI)

A 3 (group) by 3 (time) ANOVA with BSI as outcome did not reveal a significant interaction ($F(4, 140) = .67$, $p = .614$, partial $\eta^2 = .019$). There was a significant main effect of time, indicating a general improvement from t1 to t3 ($F(2,140) = 47.45$, $p < .001$, partial $\eta^2 = .404$). No main effect of group was found ($F(2, 70) = .78$, $p = .462$, partial $\eta^2 = .022$).

Table S1. ITT-Analyses of primary and secondary clinical outcomes. Reported means are pooled means derived from 5 imputations using a multiple imputation approach.

Variable	HEX (n=41)	LEX(n=42)	WL (n=30)
HAMD			
T1	13.34	12.83	12.80
T2	10.51	10.31	10.47
T3	8.58	7.67	7.23
BDI-2			
T1	27.29	27.33	27.33
T2	20.16	20.52	21.30
T3	15.63	13.13	12.39
DAS			
T1	146.58	147.72	147.70
T2	146.36	138.04	151.33
T3	123.36	125.94	129.69
BSI			
T1	1.10	1.07	1.01
T2	0.96	0.80	0.89
T3	0.68	0.50	0.58

Table S2: Results of the 3 (group) by 3 (time) ANOVAs in the ITT-sample for the 5 imputations. F and p-values for the interaction effects are reported.

Variable	Imputation 1 (F, p)	Imputation 2 (F, p)	Imputation 3 (F, p)	Imputation 4 (F, p)	Imputation 5 (F, p)
HAMD	.33, .857	1.39, .238	.45, .774	.71, .584	.19, .946
BDI-2	.86, .487	1.30, .273	.24, .917	.50, .736	.19, .943
DAS	.77, .547	1.03, .392	1.70, .150	2.14, .078	2.05, .089
BSI	1.26, .289	.89, .468	.58, .681	1.21, .309	1.13, .345

B Supplementary Material for Article II

Supplemental Material for

Physical fitness is associated with neural activity during working memory performance in major depressive disorder

Schwefel, M.K. [1*], *Kaufmann, C.* [2], *Gutmann, G.* [1], *Henze, R.* [1,2], *Fydrich, T.* [2], *Rapp, M.A.* [3], *Ströhle, A.* [4], *Heissel, A.* [3], *& Heinzel, S.* [1]

[1] Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany;

[2] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany;

[3] Social and Preventive Medicine, University of Potsdam, Potsdam, Germany;

[4] Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitätsmedizin Berlin, Berlin, Germany

*** Corresponding author:**

Melanie Schwefel

Clinical Psychology and Psychotherapy, Freie Universität Berlin,

Habelschwerdter Allee 45, 14195 Berlin, Germany

E-mail: melanie.schwefel@fu-berlin.de

Supplementary Methods:

Inclusion and exclusion criteria SPeED-Study

The SPeED-study includes outpatients (age 18–65 years) with a diagnosis of a mild or moderate depressive episode (a single episode or an episode within a recurrent depressive disorder) who passed the sport medical examination. The following exclusion criteria were applied to all patients: current severe depressive episode with or without psychotic symptoms, current borderline or antisocial personality disorder, current suicidality, lifetime schizophrenia spectrum disorder, delusional disorder, bipolar disorder, current alcohol or drug addiction, current severe neurological diseases of the central nervous system, severe chronic obstructive pulmonary disease, coronary heart disease and heart failure, body mass index of >35 or <18, insufficient language abilities in German, uncorrectable visual or hearing impairments, magnetic resonance imaging unsuitability, use of benzodiazepines or beta-blockers within the last 7 days, tricyclic antidepressants and neuroleptic drugs with a dose of >40% of the cumulated maximum recommended daily dose, and more than 2 x 45-min physical exercise per week.

N-back paradigm

As described in Heinzel (1), the WM load condition of each block was indicated by a cue displayed 2 sec before the block started. WM load (0-, 1-, 2-, and 3-back) was varied between blocks. In each block, 16 randomly generated digits from 0 to 9 were presented in the center of a black screen one at a time for 500ms with an interstimulus interval of 900ms. The occurrence of 5 target stimuli was pseudo-randomized. Targets were defined as re-occurrence of a number previously presented 1, 2, or 3 trials before (1-, 2-, or 3-back condition). In the 0-back condition, the target was defined as the digit ‘0’. The participants were instructed to press a button with their right thumb when they recognized a target. After each block, a white fixation cross was presented in the center of a black screen for 4 seconds. Every fourth block, the fixation cross was presented for 14 seconds. In total, 16 blocks were presented, resulting in a total task duration of 9 minutes. Before the fMRI session, two practice sessions of the n-back task were

performed outside the scanner to familiarize participants with the task. The n-back task was presented using the software Presentation (version 19; Neurobehavioral Systems Inc., Albany, CA, USA).

MR image processing and analysis

All fMRI data were analyzed using Matlab 9.3.0 (The Math Works, Inc., 2020) and SPM12 (2). To correct for head motion, the functional images were first spatially adjusted. None of the participants had to be excluded due to excessive head movements. Then, using the middle layer as a reference, corrections were made for the different measurement times of the layers. The two field maps with opposite phase encoding were used to estimate sensitivity-related biases following the method of Andersson et al. (2003) (3) using FSL 6.0 (4) and then correcting the functional EPI sequences for these influences. Based on the cleaned EPI sequences, an average EPI image was calculated, against which the T1-weighted signal was coregistered. Subsequently, the T1-weighted image was segmented and normalized using the tissue probability maps included in SPM12. This processing step also integrated the information from the T2-weighted signal that was previously coregistered with the T1-weighted images. The estimated spatial transformations of the T1-weighted image into the standard space were then used to normalize the EPI data. The resolution of the EPI images was thereby converted to an isotropic voxel size of 2 mm and then spatially smoothed with an isotropic Gaussian kernel of 6 mm full width at half maximum.

Supplementary Tables:

Table S1: Inner subject and between subject effects of two (group) by four (WM load) ANCOVA (age as covariate) of n-back performance and reaction time with the unmedicated MDD patients sample (MDD=66) and HC (N=55)

	df	*F*	*p*	η^2
		reaction time		
load	3	15.38	.000	0.115
group	1	11.95	.001	0.092
load x group	3	1.82	.142	0.015
		performance		
load	3	2.17	.091	0.018
group	1	4.41	.038	0.036
load x group	3	5.54	.001	0.045

Table S2: T-tests of the n-back performance and reaction time with the unmedicated MDD patients sample (MDD=66) and HC (N=55)

	MDD	*HC*	*T*	*df*	*p*
			reaction time		
0-back	436 (69)	397 (74)	2.99	119	.003
1-back	512 (83)	461 (88)	3.27	119	.001
2-back	614 (111)	564 (96)	2.64	119	.010
3-back	633 (111)	553 (119)	3.82	119	.000
			performance		
0-back	98.8 (3.1)	99.5 (1.5)	-1.56	98	.121
1-back	97.1 (4.4)	96.5 (5.8)	0.61	119	.543
2-back	78.9 (15.1)	82.7 (16.7)	-1.30	119	.195
3-back	69.0 (20.7)	81.2 (20.4)	-3.25	119	.001

Note: Means and standard deviations (in parentheses) are shown. Units: Performance [% correct]; Reaction time [ms]

Table S3: Correlations physical fitness and BOLD-activity in Peak2 (MNI -30 -48 44) and Peak4 (MNI -40 -48 42) in single WM-loads.

		Peak2 1back	Peak2 2back	Peak2 3back	Peak4 1-back	Peak4 2-back	Peak4 3-back
fitness W/kg	r	0.241	**0.281**	**0.262**	0.138	0.249	**0.310**
	p	0.013	**0.003**	**0.007**	0.157	0.010	**0.001**

Note: r = pearson's correlation, p = significance, bold = sig. correlations after bonferroni correction

Supplementary Figures:

Figure S1: WM-mask (including 12.010 voxels) created with *Neurosynth* (5) based on an automated meta-analysis of 1091 studies.

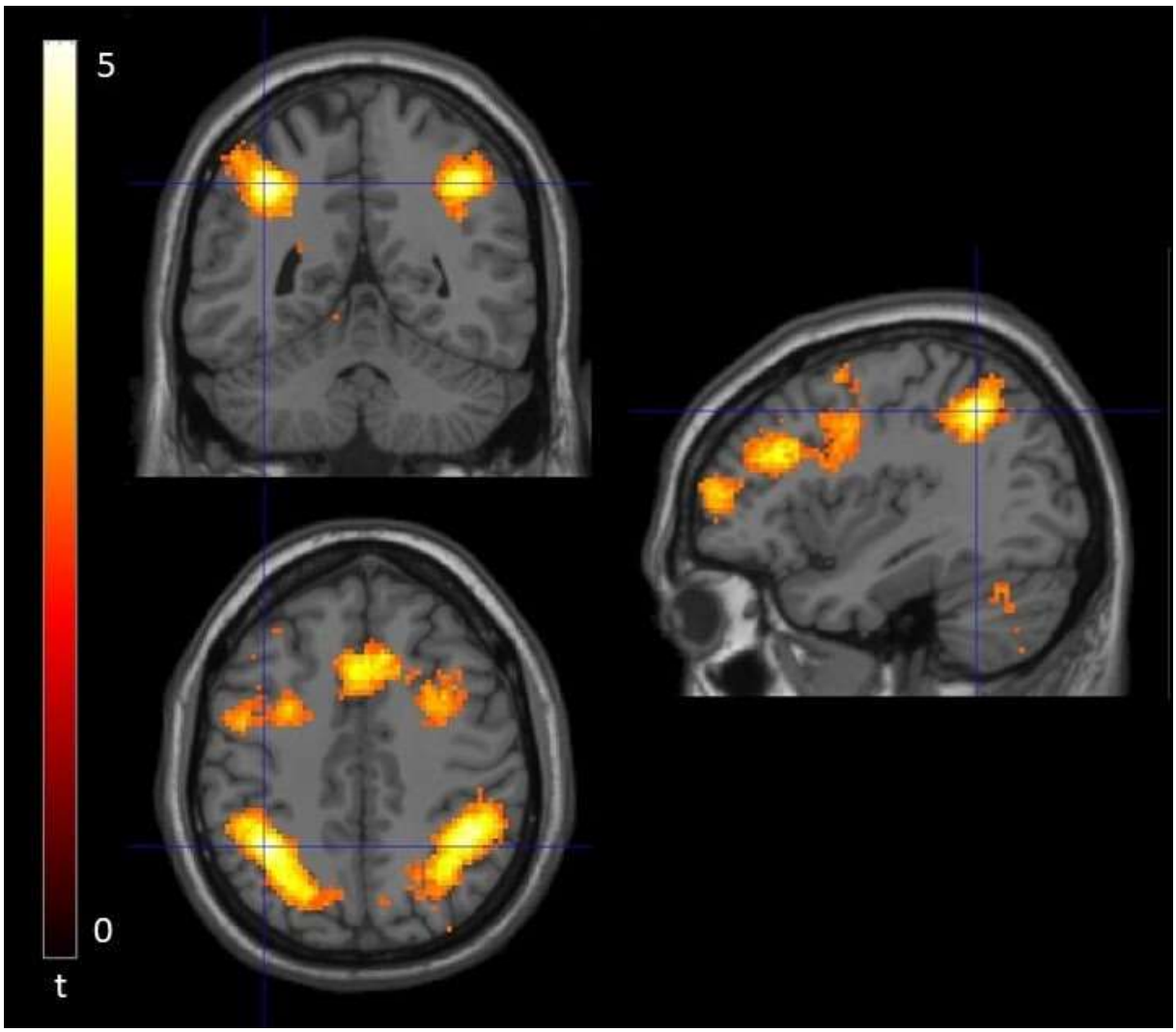
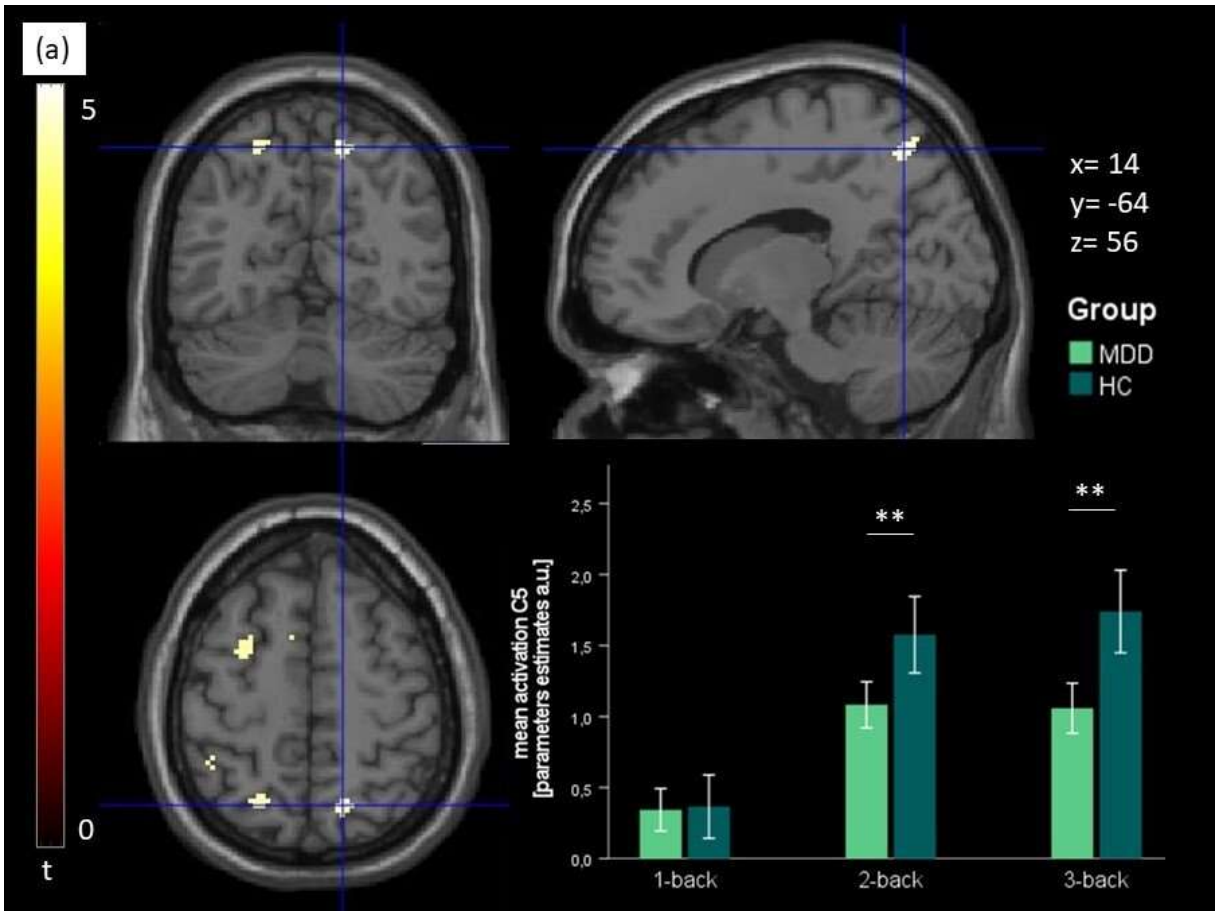
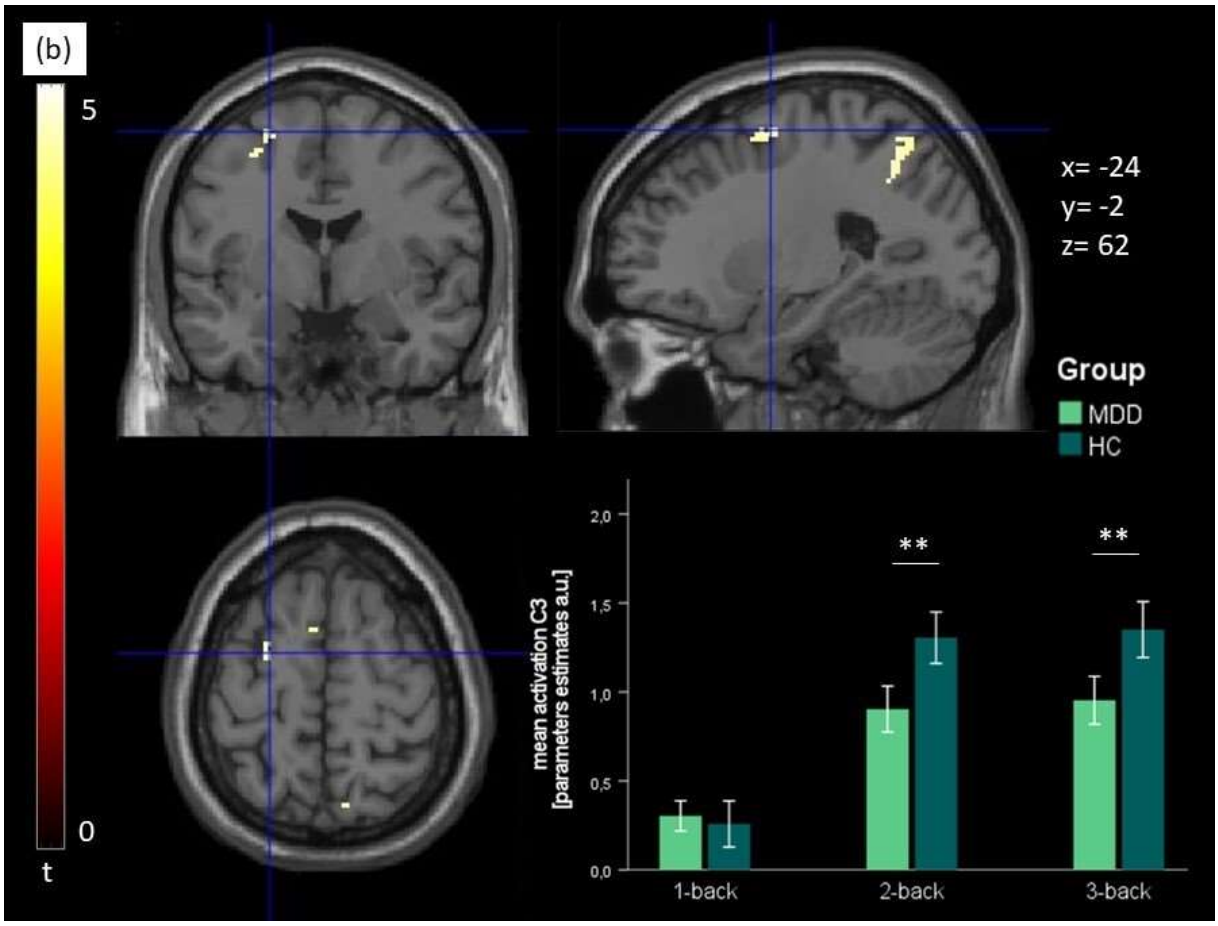
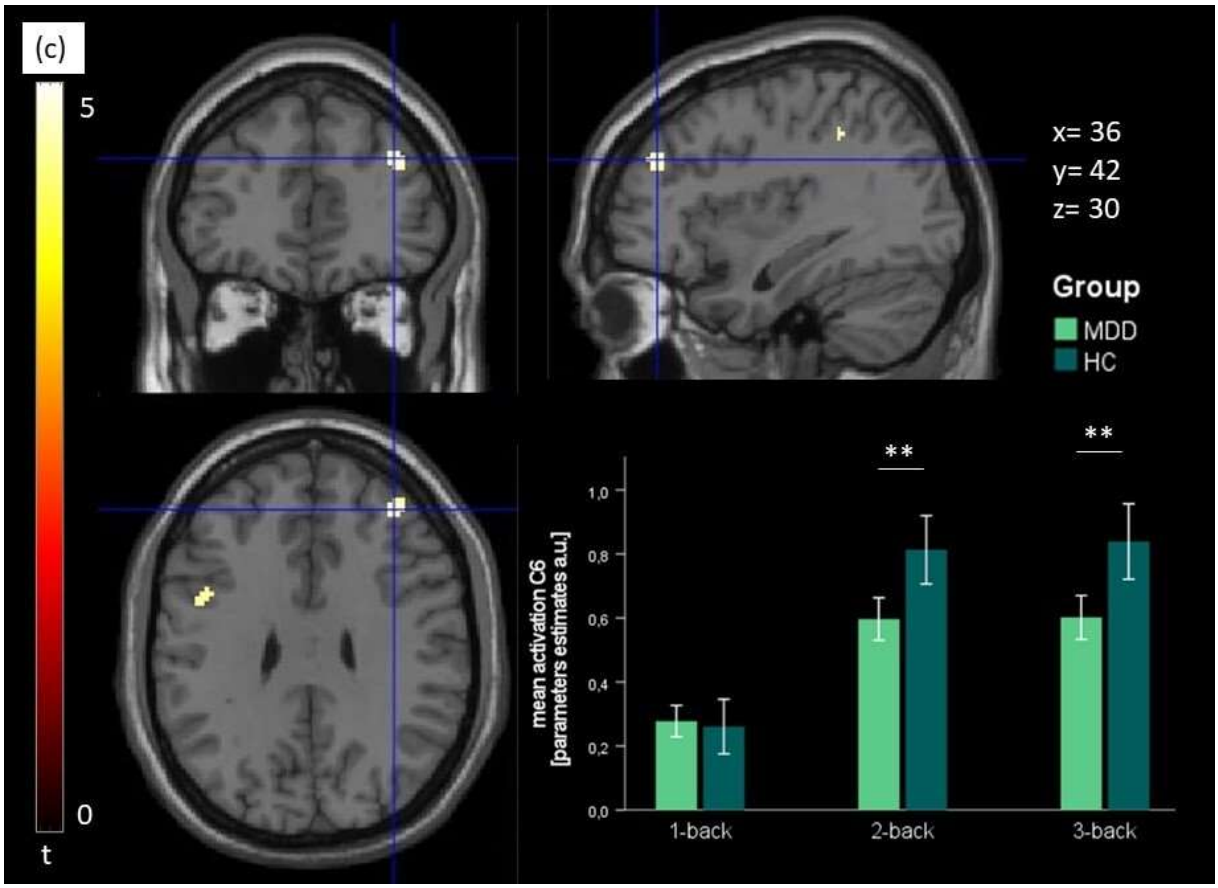
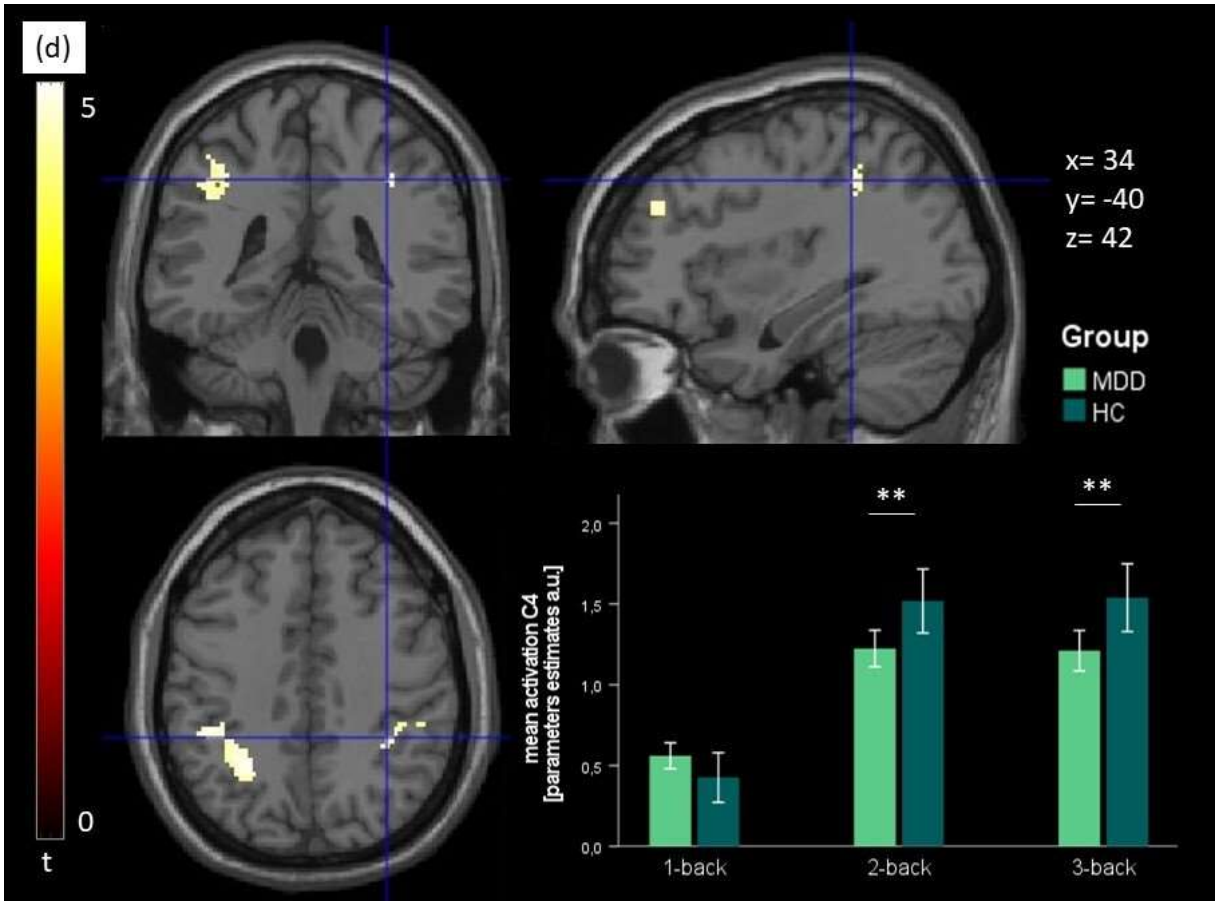


Figure S2: Cluster 3 to 6 of the significant interaction clusters (pTFCE and peak-level FWE p<0.05 corrected, cluster ≥ 10 voxel) and their activation patterns in the n-back task. Mean and standard error of the mean for the average activation divided by group and working memory load for each cluster. a) C3: Lateral Occipital Cortex / Superior Parietal Lobule, b) C4: Superior Frontal Gyrus/ Middle Frontal Gyrus, c) C5: Frontal Lobe /Middle Frontal Gyrus; d) C6: Superior Parietal Lobule / Supramarginal Gyrus; **p < .01.




(b)
5
0
t
x= -24
y= -2
z= 62
Group
MDD
HC
mean activation C3
[parameters estimates a.u.]
2,0
1,5
1,0
0,5
0,0
**
**
1-back
2-back
3-back


(c)
5
0
t
x= 36
y= 42
z= 30
Group
MDD
HC
**
**
mean activation C6
[parameters estimates a.u.]
1,0
0,8
0,6
0,4
0,2
0,0
1-back
2-back
3-back


(d)
5
0
t
x= 34
y= -40
z= 42
Group
MDD
HC
**
**
mean activation C4
[parameters estimates a.u.]
2,0
1,5
1,0
0,5
0,0
1-back
2-back
3-back

References

(1) Heinzel S, Kaufmann C, Grützmann R, Hummel R, Klawohn J, Riesel A, et al. (2018): Neural correlates of working memory deficits and associations to response inhibition in obsessive compulsive disorder. *NeuroImage: Clinical 17:* 426–434.

(2) Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE, & Penny WD (2007*): Statistical parametric mapping: The analysis of functional brain images.* Oxford: Elsevier.

(3) Andersson JL, Skare S, & Ashburner J (2003): How to correct susceptibility distortions in spin-echo echo-planar images: Application to diffusion tensor imaging. *NeuroImage* 20: 870-888.

(4) Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg, *et al.* (2004): Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 23: 208-219.

(5) Yarkoni T, Poldrack RA, Nichols TE, van Essen DC, & Wager TD (2011): Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods 8*: 665–670. Retrieved December 10, 2021 from https://neurosynth.org/.

C Supplementary Material for Article III

Supplemental Material for

Effect of physical exercise training on neural activity during working memory in major depressive disorder

Schwefel, M.K. [1*], *Kaufmann, C.* [2], *Gutmann, G.* [1], *Henze, R.* [1,2], *Fydrich, T.* [2], *Rapp, M.A.* [3], *Ströhle, A.* [4], *Heissel, A.* [3], *& Heinzel, S.* [1,5]

[1] Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany;

[2] Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany;

[3] Social and Preventive Medicine, University of Potsdam, Potsdam, Germany;

[4] Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitäts-medizin Berlin, Berlin, Germany;

[5] Institute of Psychology, Department of Educational Sciences and Psychology, TU Dortmund University, Dortmund, Germany.

*** Corresponding author:**

Melanie Schwefel

Clinical Psychology and Psychotherapy, Freie Universität Berlin,

Habelschwerdter Allee 45, 14195 Berlin, Germany

E-mail: melanie.schwefel@fu-berlin.de

Supplementary Methods:

Inclusion and exclusion criteria SPeED-Study

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As described in Heinzel (1), the WM load condition of each block was indicated by a cue displayed 2 sec before the block started. WM load (0-, 1-, 2-, and 3-back) was varied between blocks. In each block, 16 randomly generated digits from 0 to 9 were presented in the center of a black screen one at a time for 500ms with an interstimulus interval of 900ms. The occurrence of 5 target stimuli was pseudo-randomized. Targets were defined as re-occurrence of a number previously presented 1, 2, or 3 trials before (1-, 2-, or 3-back condition). In the 0-back condition, the target was defined as the digit ‘0’. The participants were instructed to press a button with their right thumb when they recognized a target. After each block, a white fixation cross was presented in the center of a black screen for 4 seconds. Every fourth block, the fixation cross was presented for 14 seconds. In total, 16 blocks were presented, resulting in a total task

duration of 9 minutes. Before the fMRI session, two practice sessions of the n-back task were performed outside the scanner to familiarize participants with the task. The n-back task was presented using the software Presentation (version 19; Neurobehavioral Systems Inc., Albany, CA, USA).

MR image processing and analysis

All fMRI data were analyzed using Matlab 9.3.0 (The Math Works, Inc., 2020) and SPM12 (2). To correct for head motion, the functional images were first spatially adjusted. None of the participants had to be excluded due to excessive head movements. Then, using the middle layer as a reference, corrections were made for the different measurement times of the layers. The two field maps with opposite phase encoding were used to estimate sensitivity-related biases following the method of Andersson et al. (2003) (3) using FSL 6.0 (4) and then correcting the functional EPI sequences for these influences. Based on the cleaned EPI sequences, an average EPI image was calculated, against which the T1-weighted signal was coregistered. Subsequently, the T1-weighted image was segmented and normalized using the tissue probability maps included in SPM12. This processing step also integrated the information from the T2-weighted signal that was previously coregistered with the T1-weighted images. The estimated spatial transformations of the T1-weighted image into the standard space were then used to normalize the EPI data. The resolution of the EPI images was thereby converted to an isotropic voxel size of 2 mm and then spatially smoothed with an isotropic Gaussian kernel of 6 mm full width at half maximum.

Supplementary Tables:

Table S1: Main effect of group and interaction effects of 3 (group) × 4 (load) × 2 (time) ANOVA of n-back performance in MDD patient sample (HEX=26, LEX=32, WL=28).

	df	*F*	*p*	η^2
		reaction time		
group	2	1.49	.230	.035
time × group	2	1.31	.275	.031
load × group	6	0.89	.502	.021
time × load × group	6	0.27	.951	.006

Table S2: Main effect of group and interaction effects of 3 (group) × 4 (load) × 2 (time) ANOVA of n-back reaction time in MDD patient sample (HEX=26, LEX=32, WL=28).

	df	*F*	*p*	η^2
		reaction time		
group	2	1.99	.144	.046
time × group	2	.746	.477	.018
load × group	6	.537	.780	.013
time × load × group	6	.531	.784	.013

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(1) Heinzel S, Kaufmann C, Grützmann R, Hummel R, Klawohn J, Riesel A, et al. (2018): Neural correlates of working memory deficits and associations to response inhibition in obsessive compulsive disorder. *NeuroImage: Clinical 17:* 426–434.

(2) Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE, & Penny WD (2007*): Statistical parametric mapping: The analysis of functional brain images.* Oxford: Elsevier.

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D List of Abbreviations

ACC	Anterior Cingulate Cortex
BDNF	Brain-Derived Neurotrophic Factor
CBT/KVT	Cognitive-Behavioral Therapy/ kognitive Verhaltenstherapie
CE	Central Executive
VLPFC	Ventrolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
(f)MRI	(functional) Magnetic Resonance Imaging
HEX	High-intensity Exercise
HPA axis	Hypothalamic-Pituitary-Adrenal axis
IPL	Inferior Parietal Lobule
LEX	Low-intensity Exercise
MDD	Major Depression Disorder
ROI	Region-of-Interest
SPeED	Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effect Depressive patients
SPL	Superior Parietal Lobule
TR	Repetition Time
TE	Echo Time
VBM	Voxel-based morphometry
WL	Waiting List
WM	Working Memory

E List of Figures

F List of Publications

Schwefel, M. K., Kaufmann, C., Gutmann, G., Henze, R., Fydrich, T., Rapp, M.A., Ströhle, A., Heissel, A., & Heinzel, S. (2023). Effect of physical exercise training on neural activity during working memory in major depressive disorder. Manuscript submitted for publication in *Biological Psychiatry*.

Schwefel, M. K., Kaufmann, C., Gutmann, G., Henze, R., Fydrich, T., Rapp, M. A., Ströhle, A., Heissel, A., Heinzel, S. (2023). Physical fitness is associated with neural activity during working memory performance in major depressive disorder. *NeuroImage. Clinical 38,* 103-401. https://doi.org/10.1016/j.nicl.2023.103401

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Kallies, G., Rapp, M.A., Fydrich, T., Fehm, L., Tschorn, M., Terán, C., **Schwefel,** M., Pietrek, A., Henze, R., Hellweg, R., Ströhle, A.*, Heinzel, S.*, & Heissel, A.* (2019). Serum brain-derived neurotrophic factor (BDNF) at rest and after acute aerobic

exercise in major depressive disorder. *Psychoneuroendocrinology 102,* 212-215. *equal contribution. https://doi.org/10.1016/j.psyneuen.2018.12.015

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Congress contributions - Poster

Schwefel, M. K., Rapp, M., Fydrich, T., Kaufmann, C., Ströhle, A., Henze, R., Terán, C., Kallies, G., Heissel, A., Heinzel, S. (2018). Effects of exercise on cognitive functions in depression. *International Conference on Learning and Memory 2018,* Huntington Beach, USA.

Schwefel, M., Schmicker, M., Müller, N. (2013). Near and far trasfer effects of attentional filtering taining. *Society for Neuroscience 2013,* San Diego, USA.

Schmicker, M., **Schwefel, M.,** Müller, N. (2013). Improving working memory capacity by training attentional filtering. *Aging & Cognition 2013,* Dortmund, Germany.

G Curriculum Vitae

Education and research experience

09/19 – 06/22	**Scientific Associate** COPE - "Cognitive Training in Obsessive-Compulsive Disorder Patients and Effects on Neural Processing" *Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany*
04/18 - 06/19	**Scientific Associate** STEP.De - Sports Therapy for Depression *Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany*
02/14 - 09/18	**Degree in Psychotherapy** *Institute of Psychotherapy (ZPHU)* *Humboldt University of Berlin, Germany*
Since 02/18	**PhD Candidate in Psychology** (Dr. rer. nat.) "Physical exercise training as treatment for working memory impairment in major depressive disorder - Understanding of the underlying mechanisms" *Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Germany*
12/15 – 02/18	**Research Assistant** SPeED – "Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients" *Universität Potsdam, Humboldt-Universität Berlin, Freie Universität Berlin, Germany*
07/14 – 12/15	**Research Assistant** Research group "Structural plasticity" (Prof. Simone Kühn) *Max Planck Institute for Human Development, Berlin, Germany*
10/11 – 03/14	**Research Assistant** Research group "Neuroprotection" (Prof. Notger Müller) *German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany*
09/11 - 10/13	**Master of Science, Psychology** Focus: Clinical Neuroscience Thesis: "Near and far transfer effects of a cognitive attention training" *Otto-von-Guericke University, Magdeburg, Germany*

10/08 - 09/11	**Bachelor of Science, Psychology** Thesis: "The influence of Anxiety on Cognitive Control Functions" *Otto-von-Guericke University, Magdeburg, Germany*
03/10 – 04/10	**Student Internship** Research project "Self-regulation after prostatectomy" *Institute for Medical Psychology Collaboration, Charité Berlin, Germany*

Clinical experience

Since 10/20	**Self-employed in own private Psychotherapeutic Practice** For self-payers, privately insured and via reimbursement *Berlin-Kreuzberg, Germany*
Since 02/19	**Honorary therapist** Focus: Trauma, Social Phobia and Depression *University Outpatient Clinic for Psychotherapy, Diagnostics and Health Promotion, Freie Universität Berlin, Germany*
02/14 - 09/18	**Trainee in the Postgraduate Cognitive Behaviour Therapy Program for Psychological Psychotherapists** *Centre for Psychotherapy at the Institute of Psychology of the Humboldt University Berlin (ZPHU), Germany*
Since 02/19	**Further training as a group therapist** *Centre for Psychotherapy at the Institute of Psychology of Humboldt University Berlin (ZPHU), Germany*
06/14 – 12/15	**Psychotherapist Trainee** Affective, acute geriatric ward & day clinic *Vivantes Spandau - Clinic for Psychiatry, Psychotherapy and Psychosomatics Berlin, Germany*
02/11 – 04/11	**Student Internship** Neuropsychiatric ward *Charité Berlin - Clinic for Psychiatry and Psychotherapy, Berlin, Germany*
07/10 – 08/10	**Student Internship** Psychosomatic medicine and psychotherapy *Theodor-Wenzel-Werk, Berlin, Germany*

Scholarships and Awards

07/2021 – 07/2022	**PhD Scholarship** Elsa-Neumann-Scholarship *From the state of Berlin*
04/2013	**1st poster prize winner** Aging & Cognition 2013 *Dortmund, Germany*
04/2018	**Travel Grant** awarded by Glaxo-Smith-Kline Foundation *International Conference on Learning and Memory 2018,* Huntington Beach, USA

H Selbstständigkeitserklärung

Hiermit erkläre ich, die vorliegende Dissertation selbstständig verfasst und ohne unerlaubte Hilfe angefertigt habe.

Alle Hilfsmittel, die verwendet wurden, habe ich angegeben. Die Dissertation ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

Ort, Datum

Melanie Schwefel