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## „Add-on Effect of an Exercise Intervention on Cognitive-Behavioral Therapy for Depression: an fMRI Study of Emotion Regulation“


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Luise Dorothea Bergold, BSc


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**Abstract**

A significant proportion of patients with Major Depressive Disorder (MDD) do not benefit from Cognitive-Behavioral Therapy (CBT). To increase its efficacy, the underlying neurobiological mechanisms of MDD and CBT must be understood. Impairments in fronto-limbic loops during emotion regulation and cognitive functioning represent common characteristics of MDD. Adjunctive exercise therapy might target these dysfunctions and yield enhancing effects on CBT. This fMRI study investigates the neural correlates of cognitive emotion regulation after an exercise intervention (t2) and a subsequent CBT (t3) in MDD. The sample consisted of 75 MDD patients at t2 and 58 patients at t3 that had previously been randomized to a high-intensity exercise, low-intensity exercise, or wait-list control group. Subsequently, all patients received CBT. fMRI data during a cognitive emotion regulation paradigm were obtained at both measurement points. Regions-of-interest analyses were performed. MDD patients recruited a prefrontal control network comprising the dorsolateral prefrontal cortex (DLPFC) and inferior parietal cortex during cognitive emotion regulation. During passive viewing, higher activity in the amygdala and subgenual anterior cingulate cortex were observed. The exercise groups exhibited higher DLPFC and lower amygdala activity during regulation than the control group. No differences between the high- and low-intensity exercise groups were found. A CBT-related increase in DLPFC activity could be identified that was similar across groups. Taken together, MDD patients can recruit areas of the cognitive emotion regulation network and modulate amygdala activity. The exercise interventions led to an increase in cognitive control, but the dose-response relationship was not confirmed. Consequently, disentangling exercise-related effects from unspecific treat-effects remains impossible. The add-on of exercise on CBT efficacy was not found.

*Keywords*: Major depressive disorder, exercise therapy, cognitive-behavioral therapy, cognitive emotion regulation, functional magnetic resonance imaging

**Zusammenfassung**

Ein signifikanter Anteil Betroffener mit Major Depression profitiert nicht von einer kognitiven Verhaltenstherapie (KVT). Um die Wirksamkeit der KVT zu erhöhen, müssen die zugrundeliegenden neurobiologischen Mechanismen besser verstanden werden. Veränderungen in der Hirnaktivierung bei Emotionsregulation und Defizite in kognitiven Funktionen sind charakteristisch für depressive Störungen. Sporttherapie könnte einen positiven Effekt auf diese Beeinträchtigungen haben und die Wirksamkeit einer KVT verbessern. Diese Studie untersucht die neuronalen Korrelate von kognitiver Emotionsregulation nach einer Sportintervention (t2) und einer anschließenden KVT (t3) bei Depression. Die Stichprobe bestand aus 75 Patient*innen mit Depressionen zum Zeitpunkt t2 und 58 Patient*innen zum Zeitpunkt t3, die zuvor in eine hochintensive Trainingsgruppe, eine niedrigintensive Trainingsgruppe oder eine Wartegruppe randomisiert worden waren. Anschließend erhielten alle Patient*innen eine KVT. Zu beiden Messzeitpunkten wurden fMRT-Daten während eines Emotionsregulationsparadigmas erhoben. Regions-of-Interest-Analysen wurden durchgeführt. Die Patient*innen rekrutierten während der kognitiven Emotionsregulation ein präfrontales Kontrollnetzwerk, das den dorsolateralen präfrontalen Cortex (DLPFC) und den inferioren parietalen Cortex einschloss. Beim Betrachten negativer Bilder wurde eine höhere Aktivierung der Amygdala und des subgenualen anterioren zingulären Cortex beobachtet. Die Sportgruppen wiesen eine höhere DLPFC- und eine geringere Amygdala-Aktivierung auf als die Kontrollgruppe. Allerdings unterschied sich die hochintensive Sportgruppe nicht von der Niedrigintensiven. Die KVT führte zu einer Zunahme der Aktivierung im DLPFC, die in allen Gruppen ähnlich war. Die Studie zeigt, dass Patient*innen mit Depressionen Bereiche des kognitiven Emotionsregulationsnetzwerks rekrutieren und die Amygdala-Aktivierung modulieren können. Die Sportinterventionen führten zu einem Anstieg in kognitiver Kontrolle, aber die Dosis-Wirkungs-Beziehung konnte nicht bestätigt werden. Folglich ist es nicht möglich, sportbezogene Effekte von unspezifischen Interventionseffekten zu unterscheiden. Sport erhöhte die Wirksamkeit der KVT nicht.

*Schlüsselwörter*: Major Depression, Sporttherapie, kognitive Verhaltenstherapie, kognitive Emotionsregulation, funktionelle Magnetresonanztomografie

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| | |
|---|---|
| ACC | Anterior cingulate cortex |
| BDI-II | Beck Depression Inventory-II |
| CBT | Cognitive-behavioral therapy |
| DLPFC | Dorsolateral prefrontal cortex |
| IOG | Inferior occipital gyrus |
| IPL | Inferior parietal lobule |
| ITG | Inferior temporal gyrus |
| MDD | Major Depression Disorder |
| ROI | Regions-of-interest |
| SMA | Supplementary motor area |
| SVC | Small volume correction |
| VLPFC | Ventrolateral prefrontal cortex |
| VMPFC | Ventromedial prefrontal cortex |

# Add-on effect of an exercise intervention on CBT for depression: an fMRI study of emotion regulation

Major Depressive Disorder (MDD) is one of the most prevalent disorders in Germany and the second leading cause of disability worldwide (DGPPN et al., 2015; WHO, 2008). 16-20% of the general population will suffer from at least one depressive episode in a lifetime (Bijl et al., 1998; Ebmeier et al., 2006). Although cognitive-behavioral therapy (CBT) as a single intervention or combined with pharmacological treatment has proven to be highly effective in the treatment of MDD (Butler et al., 2006), response rates ranging from 51 to 87% indicate that a substantial part of MDD patients does not benefit from CBT (Hofmann et al., 2012).

Given the immense psychological strain of people affected by MDD and the societal and economic consequences (Ferrari et al., 2013; Greenberg et al., 2015), a more profound understanding of the mechanisms of CBT to develop more effective treatment interventions remains highly important. Recently, there has been a focus on the neurobiological mechanisms of depression and CBT (see Drevets, 2001, for a review). Depression is associated with altered activations in prefronto-limbic loops during emotion regulation, and CBT seems to have a normalizing effect on these alterations (Karch et al., 2012). Also, implementing additional interventions as an adjunct to psychotherapy seems promising. For instance, research on endurance exercise in the treatment of depression has gained attention.

## Exercise and depression

Recent meta-analyses of randomized controlled trials suggest that endurance exercise interventions yield moderate- to large-sized significant effects in the treatment of depressive symptoms compared to control interventions (Cooney et al., 2014; Kvam et al., 2016; Rethorst et al., 2012). However, these meta-analyses suffer from some severe methodological weaknesses. For instance, only 7 out of 23 (Kvam et al., 2016) and 6 out of 39 trials included (Cooney et al., 2014) lived up to high-quality study design standards (allocation concealment, intention-to-treat-analysis, blinded outcome-assessment) and most sample sizes were small. Analyzing only the trials fulfilling adequate methodological standards, no association was found between exercise and the reduction of depressive symptoms (Cooney et al., 2014). Consequently, the risk of bias in the findings is high, and the association might, in fact, be small. The optimal intervention characteristics (type, frequency, intensity, etc.) and sustained long-term effects remain unclear (Cooney et al., 2014, Rethorst et al., 2012). According to one meta-analysis, the effect was not significant at follow-up (Kvam et al., 2016). The alternate approach of implementing exercise as an adjunct to antidepressant and/or

psychotherapeutic treatment might be more promising. One meta-analysis investigated the combination treatment of exercise and antidepressant medication (Kvam et al., 2016) but less work examined the combination of exercise and psychotherapy. According to two studies, CBT and an additional physical exercise intervention led to a greater reduction of depressive symptoms (Abdollahi et al., 2017; Gary et al., 2010) and greater improvements in suicidal ideation and daily life activities (Abdollahi et al., 2017) than CBT only. This was also the case for patients on antidepressant medication (Gourgouvelis et al., 2018). However, the exact neurobiological mechanisms of the antidepressant effect of exercise are still not fully understood.

**Neurobiological mechanisms of exercise**

Endurance exercise leads to an increase in the brain-derived neurotrophic factor system (Seifert et al., 2010) that further leads to a decrease in cortisol (Taliaz et al., 2011), and a reduced physiological stress response (Sothmann et al., 1996). Additionally, exercise stimulates growth factors that facilitate neurogenesis and increase synaptic plasticity (Cotman et al., 2007). These structural and functional changes are linked to enhanced brain activity in prefrontal control regions during memory and cognitive control tasks, suggesting an exercise-related overall improvement in cognitive control (for a review, see Angevaren et al., 2008). This is especially valuable in the context of possible adjuncts to CBT in depression, since higher brain activation in cognitive control regions before CBT could be linked to better treatment success (Heller et al., 2013).

Before looking more into treatment considerations for depression, a more profound understanding of the underlying psychopathological mechanisms of depression is needed. As such, dysfunctional emotion regulation represents an inherent feature of affective disorders (Campbell-Sills et al., 2006). Emotion regulation skills at the beginning of treatment have been shown to be predictive of improving depressive symptoms (Fehlinger et al., 2013). To fully understand the neural correlates of emotion regulation and their alterations in depression, one has to understand the fundamental characteristics of emotion generation and modulation processes.

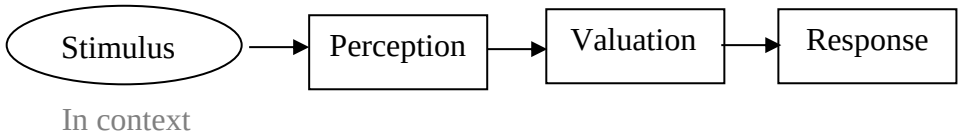
**Emotion and emotion regulation**

The generation of emotion can be viewed as a process that begins with the perception of an internal or external stimulus in a certain context that is evaluated as “good for me” or “bad for me” (see Figure 1). Thoughts, feelings, or sensations are internal cues, and facial expressions or gestures are external cues. The valuation describes the conscious or unconscious process of appraising the personal relevance of the stimulus in terms of one’s

needs and goals and is followed by sets of affective, physiological, cognitive, or behavioral responses. Importantly, emotions typically change the environment of the individual positively (by, for example, the avoidance of a fear-inducing stimulus; Etkin et al., 2015).

**Figure 1**

*Schematic illustration of the emotion generation process based on Etkin et al. (2015)*




Emotion regulation refers to the process by which individuals consciously or unconsciously modulate their emotions - "when they have them, and how they experience and express these emotions" (Gross, 1998). Different emotion regulation strategies can be classified based on what stage of the emotion generation process they impact. For instance, distraction as an attention-focused strategy occurs at the first stage of perception. It describes the process of shifting one's attention from a stimulus to secondary information. Suppression is a response-focused strategy as it modulates the emotional response (Ochsner et al., 2012).

An emotion regulation strategy is maladaptive if it is accompanied by costs that outweigh the short-term benefits brought by the reduction of acute emotions. An emotion regulation that successfully decreases subjective distress and supports one's ability to pursue short- and long-term goals is considered adaptive (Campbell-Sills et al., 2014). Expressive suppression is a maladaptive strategy due to the associated cognitive and physiological costs (Gross, 1998). Emotion regulation can be further divided into explicit and implicit emotion regulation. Explicit emotion regulation refers to the active modulation of emotions that requires voluntary effort, whereas implicit emotion regulation is evoked by a stimulus automatically and does not require voluntary effort (i.e., fear inhibition; Etkin et al., 2015).

Cognitive reappraisal is a well-studied explicit emotion regulation paradigm. It refers to the process of changing the meaning of a stimulus to alter one's emotional response to the stimulus and decrease its emotional impact (Gross, 1998). An example of cognitive reappraisal would be the reinterpretation of a picture showing a person covered in blood, thinking that the person is an actor and not really injured. Another reappraisal tactic involves detaching oneself from an emotionally disturbing scene by mentally adopting the perspective of an uninvolved observer (i.e., viewing a picture of a disturbing scene and imaging that it

was a long time ago and/or far away). Adaptive detachment is associated with a decrease in the personal relevance of the stimuli to oneself (Dörfel et al., 2014),

As such, cognitive reappraisal is an explicit emotion regulation strategy that targets the valuation stage of the emotion generation process. Cognitive reappraisal is considered an adaptive strategy as it effectively reduces negative feelings in response to aversive stimuli (John & Gross, 2004) and is associated with enhanced cognitive control of emotions, thereby leading to less negative affect, more positive affect, and increased well-being. Since it involves the reinterpretation of a stimulus, it yields longer-lasting effects than attention-focused strategies such as distraction (Gross, 1998; Webb et al., 2012). Another explanation for the immense research attention regarding reappraisal is that it is a core element of many forms of psychotherapy, for example, CBT (Beck, 2005).

Depression is associated with less frequent use of effective strategies such as reappraisal (Joormann & Gotlib, 2010). Instead, individuals with depression use ineffective emotion regulation strategies such as suppression and rumination in response to negative affect more frequently (Campbell-Sills et al., 2006; Nolen-Hoeksema, 1991).

**Neural correlates of cognitive emotion regulation**

Cognitive emotion regulation has been studied extensively in non-clinical populations. On a neural level, cognitive regulation of emotions recruits the same cognitive control networks as cognitive control tasks in non-emotional contexts (attention, memory, thoughts; Ochsner & Gross, 2008). As such, cognitive reappraisal is associated with increased activations in the prefronto-parietal network, including the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex, and ventrolateral prefrontal cortex (VLPFC). Also, the dorsal anterior cingulate cortex (ACC), inferior parietal lobule (IPL), the insula, supplementary motor area (SMA) and pre-SMA are involved (Buhle et al., 2014; Kohn et al., 2014). The medial and prefrontal cortex are associated with cognitive processes (conflict monitoring, working memory, etc.) and the regulation of inner states to achieve desired goals (Phillips et al., 2008). During cognitive emotion regulation, the DLPFC and parietal cortex are associated with selective attention and holding reappraisals in mind. The VLPFC is associated with the selection and inhibition of appraisals (Buhle et al., 2014). The DLPFC seems to yield a major regulatory influence on emotion processing systems (amygdala, VLPFC, insula; Ochsner & Gross, 2005). Anatomically, the DLPFC is in an ideal position to regulate a broad range of behavioral reactions but lacks a direct connection to the amygdala. The ACC seems to play this integratory role: Lying in an ideal position to regulate subcortical limbic systems involved in emotion generation and also connected to the control regions of the brain (i.e.,

DLPFC), it is expected mediate the influence from the DLPFC on the emotion generating system (Kohn et al., 2014). The ACC is a rather heterogenous region that fulfills different functions during emotion generation and regulation. The dorsal ACC and the IPL/superior parietal lobule are responsible for allocating resources during processes that require goal-oriented attention (Cole & Schneider, 2007). During cognitive emotion regulation, the dorsal ACC is involved in the generation, appraisal, and expression of emotions and monitoring the reappraisals to check whether upcoming emotional responses are changed in the intended way (Ochsner et al., 2012). The subgenual ACC is associated with regulating limbic regions involved in generating emotional responses (Etkin et al., 2011). The IPL is associated with spatial attention (Husain & Nachev, 2007), highlighting a relevant role during emotion regulation by the tactic of detachment.

Simultaneously to the activations in prefrontal control regions, cognitive emotion regulation is characterized by deactivations in the limbic subcortical network, including the amygdala, the ventral striatum, and the insula (Buhle et al., 2014; Etkin et al., 2015; Kohn et al., 2014). These regions are believed to be downregulated by the cognitive control systems described above. The amygdala is involved in the emotion generation process and modulation of cognition and behavior in reaction to emotional cues (Phelps, 2006). More precisely, it is involved in detecting arousing stimuli that yield goal-relevant information and the encoding and organization of adequate responses. Since stimuli that evoke negative feelings are naturally arousing, most reappraisal studies investigate negative/aversive stimuli. However, the amygdala seems especially sensitive to potentially threatening stimuli (Phelps & LeDoux, 2005).

**Altered activation patterns in brain regions involved in emotion regulation in MDD**

MDD patients show altered activation patterns in regions involved in cognitive emotion regulation. Neural models of depression highlight hyperactivations in regions associated with emotion processing and hypoactivations in areas of cognitive control and regulation of affect (Campbell-Sills et al., 2014; Disner et al., 2011; Hamilton et al., 2012; Ochsner & Gross, 2008). Depression is associated with elevated baseline activation in the amygdala (Drevets et al., 2003) and amygdala hyperreactivity in response to aversive stimuli (Hamilton et al., 2012). Also, a recent meta-analysis suggests that a reduced recruitment of the DLPFC and VLPFC during a cognitive reappraisal task is characteristic across different psychiatric disorders. In patients with mood disorders, this is accompanied by enhanced amygdala activation (Zilverstand et al., 2017).

In line with this, Erk and colleagues (2010) revealed that patients exhibit decreased activation in the DLPFC compared to healthy individuals during the regulation of negative stimuli (Erk et al., 2010). However, the ability to downregulate the amygdala in response to negative pictures did not differ between MDD patients and controls but was inversely correlated with symptom severity. This finding sugggests that group differences might be apparent in a more depressed sample. A psychophysiological interaction analysis revealed diminished functional coupling of the amygdala with the DLPFC and IPL in patients. Hence, the amygdala hyperactivation might at least be partly rooted in impaired top-down modulation (Erk et al., 2010). In another study, the relationship between the activation increase of the DLPFC and hyperactivation of the amygdala during the reappraisal of emotional pictures was mediated by the VLPFC in healthy individuals but not in MDD patients, indicating an impaired recruitment of top-down prefrontal-limbic circuits in depression (Johnstone et al., 2007). In a similar study setting, no group differences in neural activation between patients and controls were found. Still, depressive severity was inversely related to activation in the left DLPFC, suggesting group differences might be apparent in a larger sample (Dillon & Pizzagalli, 2013).

As described above, the ACC plays an important role in emotion generation and regulation (Etkin et al., 2015). MDD patients show increased activation during the control of aversive stimuli in the dorsal ACC (Beauregard et al., 2006) compared to healthy controls. In contrast, patients with borderline personality disorder exhibited less dorsal ACC activity and higher amygdala activity during reappraisal than healthy controls (Koenigsberg et al., 2009). In PTSD, higher dorsal ACC activity in patients was associated with better treatment outcome (Bryant et al., 2008). Increased activity in the rostral and pregenual ACC is associated with good pharmacological treatment response (Mayberg et al., 1997). The subgenual ACC plays a critical role in affective disorders and their treatments: as mentioned above, it is involved in the regulation of limbic regions (Etkin et al., 2011) and has been shown to be activated to a greater extent in patients with depression compared to healthy controls (Drevets, 2000). Also, high subgenual ACC activity is associated with enhanced emotional reactivity (Hamilton et al., 2011; Phillips et al., 2008) and hence, is counteracting with voluntary emotion regulation. This might disturb treatment success and is a possible explanation for non-response to CBT (Heinzel et al., 2018).

Summed up, the deficit in emotion regulation in depression seems to be at least partly a problem of an underlying deficit in cognitive control. As such, bias in memory, attention, and interpretation might account for the maladaptive use of emotion regulation strategies.

Reappraisal, for instance, requires more cognitive control than the inefficient suppression strategy. Given the deficit in cognitive control in depressed individuals, this might explain the more frequent use of maladaptive strategies (Joormann & Stanton, 2016).

**CBT-induced neurobiological changes**

CBT addresses the identification and alteration of dysfunctional negative thoughts and beliefs. With regard to emotion regulation, CBT leads to an increase in cognitive control and thereby dampens the emotional reactivity to aversive stimuli (Campbell-Sills & Barlow, 2007). Neurobiologically, psychotherapy seems to lead to the normalization of abnormal fronto-limbic activation patterns that are involved in emotion regulation (for reviews, see Barsaglini et al., 2014; Karch et al., 2012). More specifically, interventions seem to lead to a normalization of activations in the amygdala, ventromedial prefrontal cortex (VMPFC), ACC, and orbitofrontal cortex. In patients with depression, psychotherapy led to a decrease in the hyperactivation of the amygdala. Additionally, psychotherapy is associated with activation changes in the DLPFC, hippocampus, and subgenual ACC (Karch et al., 2012). More specifically, psychotherapy leads to a decrease of previous hyperactivations in the subgenual ACC, and low baseline activity in the subgenual ACC has been shown to lead to better treatment response (Siegle et al., 2012). One study that compared the neural underpinnings of the emotional processing of arousing stimuli before and after CBT found that the reduced activation of the VMPFC and amygdala before therapy showed more similarity to healthy controls after CBT – thus supporting the theory that altered brain activations normalize during CBT (Ritchey et al., 2011). In social anxiety disorder, an improvement in a cognitive reappraisal task was exhibited both neurobiologically and behaviorally after treatment with CBT (Goldin et al., 2013).

**Summary**

Taken together, cognitive emotion regulation is characterized by activations in prefrontal control regions that modulate subcortical areas, i.e., the amygdala (Buhle et al., 2014; Kohn et al., 2014; Ochsner et al., 2012). MDD is associated with impaired cognitive control (and corresponding brain activation) during emotion regulation and thus, less downregulation of the amygdala (Disner et al., 2011). Endurance exercise is expected to yield antidepressive effects (Cooney et al., 2014) by enhancing cognitive control during emotion regulation and corresponding brain activations in prefronto-parietal networks (Angevaren et al., 2008; Voelcker-Rehage & Niemann, 2013). Finally, CBT likely leads to a normalization of altered fronto-limbic loops during emotion regulation (Karch et al., 2012).

However, precise statements about neural correlates of emotion regulation in depression remain unsatisfactory to date. Although there seems to be general consent about the involved brain regions, many findings regarding the direction of activation and the exact mechanisms are inconsistent (Karch et al., 2012). This might be due to task characteristics, small sample sizes, and, consequently, a high risk of bias (Zilverstand et al., 2017).

Therefore, the aims of this study are 1) the identification of regions that are involved in emotion regulation in MDD, 2) to shed light on exercise effects on the cognitive emotion regulation network, 3) investigate potential normalization processes of altered neural activation patterns during CBT and 4) examine whether exercise yields a buffer effect adjunctive to CBT in the treatment of depression. Regions of particular interest in this study are the DLPFC, IPL, amygdala, and ACC. Neural underpinnings of cognitive reappraisal are, among others, located in the DLPFC and IPL, whereas the amygdala is expected to be modulated by reappraisal (Buhle et al., 2014). The ACC is expected to play a role in integrating both activity in prefrontal control regions and the amygdala (Kohn et al., 2014) and is anticipated to play an important role with respect to therapy outcome (Siegle et al., 2012).

The emotion regulation paradigm by Erk and colleagues (2010) will be used to study neural correlates of cognitive emotion regulation in patients with MDD before (t2) and after CBT (t3). In addition, the patients underwent either a high-intensity, low-intensity, or no exercise intervention before CBT. Both a high-intensity and low-intensity exercise group were included to be able to examine dose-response relationships between exercise and emotion regulation.

Based on these considerations, the following hypotheses are derived:

## Hypotheses

### *Hypotheses about t2*

Hypothesis 1: During the regulation of negative stimuli (“Detach”-condition), patients across all groups are expected to show higher activation in the prefronto-parietal network (including the DLPFC and IPL) and reduced activation in the amygdala and subgenual ACC compared to the control condition (“Permit”-condition).

Hypothesis 2: Patients in the high-intensity group compared to the low-intensity group and patients in the low-intensity group compared to the waiting list control group (dose-response relationship) are expected to show higher activation in the DLPFC and IPL and lower activations in the amygdala and subgenual ACC during the regulation of negative stimuli.

***Hypotheses about the change from t2 to t3:***

Hypothesis 3: The CBT leads to an activation increase in the DLPFC and IPL, and a reduction in subgenual ACC and amygdala activity across all groups during the regulation of negative stimuli.

Hypothesis 4: The exercise intervention yields a "booster" effect in the sense that patients in the high-intensity group compared to the low-intensity group and patients in the low-intensity group compared to the waiting list control group are expected to exhibit higher activation increases in the DLPFC and IPL and higher activation decreases in the amygdala and subgenual ACC during the regulation of negative stimuli.

## Methods

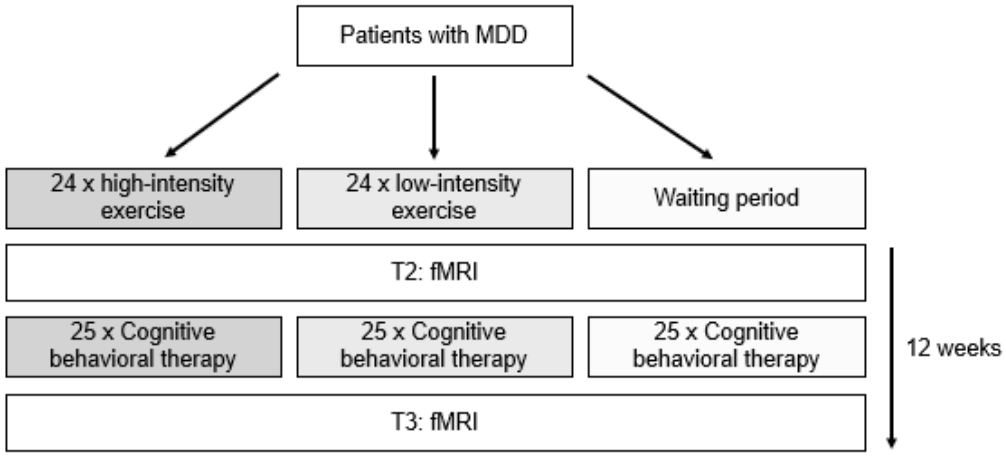
This study is part of a larger project on the treatment effects of CBT and endurance exercise: The SPeED study (Sport/Exercise Therapy and Psychotherapy—evaluating treatment Effects in Depressive patients; Heinzel et al., 2018).

### Study design

At baseline (t1), MDD patients were randomly allocated to 1) a high-intensity exercise intervention, 2) a low-intensity exercise intervention, or 3) a wait-list control group (no exercise intervention). After participants completed the exercise intervention/waiting period (t2), they received CBT (t3; see Figure 2). Functional MRI scans were performed at both measurement points, and t3 scan sessions took place approximately 12 weeks after t2. This study examines neural activation at t2 and changes in neural activation from t2 to t3.

**Figure 2**

*Study design: Sub-part of the SpeED-Study, adapted from Heinzel et al. (2018)*




*Note*. MDD patients were randomly allocated to a high-intensity, low-intensity exercise intervention or waiting period and then received CBT. Functional MRI data were obtained at both measurement points.

## Description of the interventions

### *Exercise interventions*

The endurance exercise interventions consisted of 24 sessions with two 60-minutes sessions per week. One session of the high-intensity exercise intervention consisted of 20 minutes training on a bicycle ergometer, 20 minutes running or nordic walking, and 20 minutes of aerobic body workout. The high-intensity group trained at 55-85% intensity measured by the individual heart rate reserve. A training session in the low-intensity exercise intervention included 20 minutes bicycle ergometer, 20 minutes walking, and 20 minutes stretching and relaxation. The low-intensity group trained at 20-30% intensity (for a detailed description of the exercise interventions, see Heinzel et al., 2018). Both groups were trained by the same sport-therapists.

### *CBT intervention*

A therapy manual for CBT was developed based on Hautzinger et al. (2008). The CBT intervention consisted of 25 sessions with two sessions per week covering five modules (1) psychoeducation, 2) positive activities, 3) cognitive therapy, 4) training in social competencies, and 5) relapse prevention. All psychotherapists received training for the therapy manual and were monitored by supervision. Psychotherapists were blinded to their patients' group allocation.

## Sample

Individuals with MDD were recruited via flyers and online advertisements through the Center for Psychotherapy at the Humboldt Universität zu Berlin, Germany. The final sample consisted of 75 MDD patients at timepoint 2 (35 female, 40.28 +- 10.53 years old) and 58 MDD patients at timepoint 3 (27 female, 40.23 +-11.12 years old). Sample demographics are depicted in Table 1. At baseline, patients were diagnosed using the German version of the Structural Clinical Interview (SCID-I; Wittchen et al., 1997) for DSM-IV (American Psychiatric Association, 1994). Inclusion criteria were a mild or moderate depressive episode and passing a sports medical examination. Physical fitness was assessed by an electrocardiogram during bicycle ergometry with increasing resistance until maximum physical exertion. Psychopathology was assessed by the self-report measure Beck Depression Inventory-II (BDI-II; Beck et al., 1996).

Patients who fulfilled one or more of the following criteria were excluded: current severe depressive episode, 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 seven 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.

At t2, data were available for 25 patients in the high-intensity exercise group (11 females, 39.32 ± 10.73 years old), 28 patients in the low-intensity group (9 females, 37.61 ± 9.02 years old), and 22 patients in the control group (15 females, 44.77 ± 11.08 years old). At t3, group size decreased further due to additional drop-out with remaining 18 patients in the high-intensity group (eight females., 38.67 ± 11.97 years old), 25 patients in the low-intensity group (seven females., 39.15 ± 10.47 years old) and 15 patients in the control group (11 females, 44.07 ± 11.05 years old).

Patients in the three groups significantly differed in their age, $F(2, 72) = 3.19$, $p = .05$ and gender, $\chi^2(2) = 6.54$, $p = .04$. Tukey post-hoc tests revealed a significant age difference between the control group and low-intensity sports group ($p = .04$) and gender ($p = .03$). The three groups did not differ in their physical fitness, $F(2, 72) = 2.00$, $p = .14$. Nine patients in the high-intensity group, nine patients in the low-intensity group, and 11 patients in the control group were on psychiatric medication.

At t2, the functional MRI data was available for 87 patients. One patient from the control group had to be excluded because of missing records of events and timing during the scan session. Ten patients had to be excluded during the quality check after HALFpipe preprocessing (five participants from the low-intensity group and five from the wait-list control group) due to a high amount of head movement indicated by the Framewise Displacement (FD) index. One patient had to be excluded due to suspected cerebral atrophy.

From t2 to t3, 18 patients dropped out (four from the high-intensity group, five from the low-intensity group, and nine from the control group). Another three patients from the high-intensity group were excluded because of missing data, and five patients due to head motion (one from the low-intensity group and four from the control group). BDI-II data was missing from one subject in the low-intensity group. The number of days between the fMRI scan session after the exercise intervention/waiting period (t2) and the fMRI scan session after CBT (t3) did not differ between groups, $F(1, 55) = 0.00$, $p = .97$ (see Table 2).

**Table 1**

*Demographics of MDD patients per group after the exercise intervention (t2)*

| Measure | High (N = 25) | Low (N = 28) | Control (N = 22) | Statistic |
|---|---|---|---|---|
| Age | 39.32 (10.73) | 37.61 (9.02) | 44.77 (11.08) | $F(2, 72) = 3.19$, ***p* = .05** |
| Gender | 11 f / 14 m | 9 f / 19 m | 15 f / 7 m | $\chi^2(2) = 6.54$, ***p* = .04** |
| Years in education | 15.02 (3.80) | 15.77 (2.41) | 16.48 (2.86) | $F(2, 67) = 1.25$, $p = .30$ |
| Physical fitness[1] (W/kg) | 2.40 (0.47) | 2.40 (0.47) | 2.15 (0.54) | $F(2, 72) = 2.00$, $p = .14$ |
| BDI-II (sum) | 21.52 (14.42) | 19.82 (9.86) | 20.68 (7.93) | $F(2, 72) = 0.15$, $p = .86$ |
| BDI-II category | | | | |
| None | N = 5 | N = 4 | N = 1 | n.a |
| Minimal depression | N = 4 | N = 3 | N = 4 | n.a |
| Mild depression | N = 4 | N = 8 | N = 5 | n.a |
| Moderate depression | N = 6 | N = 7 | N = 7 | n.a |
| Severe depression | N = 6 | N = 6 | N = 5 | n.a |
| Comorbid axis-I disorders[2] | N = 13 | N = 14 | N = 8 | n.a |
| Comorbid axis-II disorders[3] | N = 0 | N = 0 | N = 2 | n.a |
| Current medication[4] | N = 9 | N = 9 | N = 11 | $\chi^2(2) = 1.77$, $p = .41$ |

*Note.* Means and standard deviations (in parentheses) are shown. Significant values are indicated in bold.

[1] Physical fitness: measured by the maximum effort during a stress electrocardiogram in Watt adjusted by kg body weight. [2] Comorbid axis-I-disorders (registered at T1): High-intensity: 2 substance use disorder, 1 depressive disorders, 3 dysthymia, 1 agoraphobia, 3 social anxiety disorder, 1 generalized anxiety disorder, 1 specific phobia, 1 post-traumatic stress disorder. Low-intensity: 2 substance use disorder, 2 depressive disorders, 6 dysthymia, 1 agoraphobia, 2 social anxiety disorder, 1 mental and behavioural disorders due to multiple drug use and use of other psychoactive substances. Control: 4 dysthymia, 1 social anxiety disorder, 1 panic disorder, 1 obsessive-compulsive disorder, 1 other hyperkinetic disorders. [3] Comorbid axis-II disorders: Control: 1 schizophrenic personality disorder, 1 avoidant personality disorder.

[4] Current medication: High-intensity: 6 selective serotonin reuptake inhibitors, 2 tricyclic antidepressants, 2 selective noradrenaline/dopamine reuptake inhibitors. Low-intensity: 9 selective serotonin reuptake inhibitors. Control: 8 selective serotonin reuptake inhibitors, 3 selective noradrenaline/dopamine reuptake inhibitors.

**Table 2**

*Time difference between time points and depressive severity per group after the CBT (t3)*

| Measure | High (N = 18) | Low (N = 24) | Control (N = 15) | Statistic |
|---|---|---|---|---|
| Time difference (days) | 155.44 (26.96) | 170.20 (47.65) | 153.14 (40.98) | $F(1, 55) = 0.00$, $p = .97$ |
| BDI-II (sum) | 15.00 (14.84) | 10.62 (6.89) | 10.80 (8.68) | $F(2, 28.50) = 0.85$, $p = .44$[1] |
| BDI-II (category) | | | | |
| No | N = 8 | N = 11 | N = 7 | n.a |
| Mild | N = 2 | N = 6 | N = 4 | n.a |
| Minimal | N = 2 | N = 4 | N = 2 | n.a |
| Moderate | N = 2 | N = 3 | N = 1 | n.a |
| Severe | N = 4 | N = 0 | N = 1 | n.a |

*Note*. Means and standard deviations (in parentheses) are shown. Time difference = difference between scan sessions after the exercise intervention/waiting period (t2) and after CBT (t3) in days.

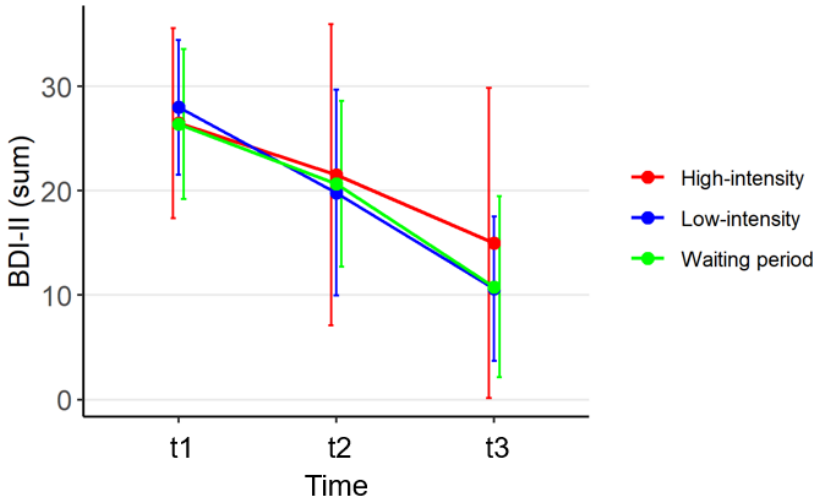
[1] Robust Welch's ANOVA.

The three groups did not differ in their BDI-II scores before CBT (t2), $F(2, 72) = 0.15$, $p = .86$. nor after CBT (t3), $F(2, 28.50) = 0.68$, $p = .52$. Interestingly, five patients in the high-intensity group, four patients in the low-intensity group, and one patient in the control group did not meet the diagnostic criteria of a mild depressive episode according to BDI-II already before CBT. BDI-II sum scores decreased from a mean of 20.64 ± 11.01 across all groups after the sports intervention/waiting period (t2) to 12.00 ± 10.36 after CBT (t3; see Figure 3). A linear mixed-effects model was set up with BDI-II sum score as the dependent variable, timepoint (before and after CBT) as a within-subject fixed effect, and group (high-intensity, low-intensity, and waiting period) as fixed between-subject effect, and patient as random effect. Depressive severity decreased significantly from t2 to t3 across all groups (main effect of time: $\chi^2$ (1) = 43.25, $p < .001$) while group allocation did not have an effect on BDI-II sum

scores, $\chi^2$ (2) = 0.68, p = .71. Also, the decrease of depressive severity did not differ in the three groups (interaction effect: $\chi^2$ (2) = 0.92, $p$ = .63). The high-intensity group exhibited a higher mean of BDI-II sum score than the low-intensity and control group at t3 (see Table 2), but this difference did not reach significance.

**Figure 3**

*Depressive symptoms per group and time point*




*Note.* Means and standard deviations indicated by error bars are depicted. Depressive symptoms were measured by Beck-Depression Inventory-II. Scores from baseline measurement are depicted for better illustration. t1 = baseline; t2 = after the exercise intervention/waiting period; t3 = after CBT.

**Experimental procedure**

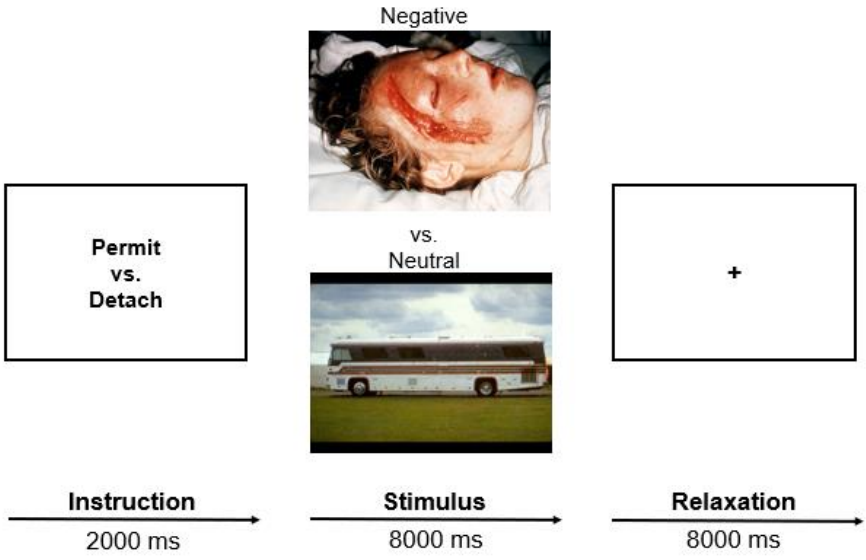
An adapted version of the explicit emotion regulation paradigm by Erk et al. (2010) was used in this study. During the scan, sixty images from the International Affective Picture System (Lang et al., 2008) were presented. The photos depicted negative or neutral content, and participants were instructed to allow all upcoming emotions ("Permit") or to detach themselves from the content by taking the perspective of an uninvolved observer ("Detach"). The instruction was displayed for two seconds, followed by the picture presentation for eight seconds and a relaxation period of eight seconds (see Figure 4). This setup resulted in four task conditions (not regulated negative, not regulated neutral, regulated negative, and regulated neutral) that were presented in a pseudo-randomized order.

Each scanning session consisted of two runs with a duration of 10 minutes each. After each scanning session, participants were asked to rate the affective valence they experienced for each stimulus ("how strong are the negative emotions you are experiencing?"). Ratings

were given on a 9-point Likert scale, with 1 indicating no negative emotions and 9 indicating very strong negative emotions. The scanning procedure was repeated for each measurement point. Different stimulus sets were used for each measurement point but counterbalanced across subjects.

**Figure 4**

*Illustration of the task design adapted from Erk et al. (2010)*




**Scanning parameters**

The functional MRI scans were conducted at Charité Campus Mitte, Berlin, with a 3TMagnetom Trio TimMRsystem (Siemens) and a 32-Channel-Headcoil (Siemens, Erlangen, Germany). At the beginning of each session, a T1-weighted 3D pulse sequence was obtained with 192 sagittal slices of 0.91 mm thickness (repetition time (TR)=2440 ms, echo time (TE)=4.81 ms, flip angle=8°, matrix size=256×258, voxel size=0.91×0.91×0.91 mm3). Functional images were acquired using a gradient echo-planar imaging (GE-EPI) pulse sequence with 33 slices descending parallel to the bicommissural plane (TR=2000 ms, TE=30 ms, flip angle=78°, matrix size=64×64, voxel size=3.0×3.0×3.75 mm).

**Data analysis**

***Preprocessing***

The preprocessing of the obtained fMRI data was performed using the HALFpipe tool version 1.2.1 (Harmonized Analysis of Functional MRI pipeline; Waller et al., 2022) on a high-performance cluster. The authors aim to provide an open-source software based on fMRIPrep (Esteban et al., 2019) for standardized state-of-the-art preprocessing and basic data analysis of fMRI data to address replication issues within the field of neuroimaging. The data

was available in Brain Imaging Data Structure (BIDS) format. The anatomical T1-weighted image was skull-stripped and spatially normalized to the ICBM 152 Nonlinear Asymmetrical template (Fonov et al., 2011) version 2009c ("MNI152NLin2009cAsym"), and brain tissue segmentation of grey matter, white matter, and cerebrospinal fluid was performed. The preprocessing of the functional data was conducted in the following order: Based on the first image as a reference volume, six head motion parameters (three translation and three rotation parameters) for each image of the time series were created. This was done by setting up a regression model for each voxel time series using the motion parameters as regressors and the time series as the dependent variable. The resulting motion parameters were later included in the first-level model as regressors-of-no-interest. After that, field maps were used for susceptibility distortion correction. Slice-time correction and co-registration of the functional EPIs to the T1-weighted structural image were performed, and the BOLD time series was resampled to MNI152NLin2009cAsym standard space. The data were spatially smoothed using the implemented AFNI's 3dBlurInMask (Cox, 1996) with an isotropic Gaussian kernel of FWHM = 6mm. This describes the process of averaging each voxel's signal by the neighboring voxels' signal.

Quality assessment of the preprocessed images was conducted manually using the interactive web interface provided by HALFPipe. Exclusion criteria during preprocessing was a large amount of head movement as indicated by the Framewise Displacement (FD) index. Patients with a maximum FD > 3mm or mean FD > 0.5mm were excluded.

***Analysis of hypotheses 1 and 2***

The first-level analysis on the subject level was performed within the general linear model (GLM) using MATLAB R2020b version 9.9.0 (The Math Works, Inc., 2020) and Statistical Parametric Mapping (SPM12; Penny et al., 2011).

For the analysis of t2 data, the first-level model comprised the two runs and consisted of four task regressors each (not regulated negative, not regulated neutral, regulated negative, and regulated neutral) that were modeled as an event with a duration of eight seconds and convolved with the hemodynamic response function (hrf) to model neural activation. Additionally, the instruction was modeled as an event with a duration of two seconds, and six motion parameters were included as regressors-of-no-interest. A high-pass filter cutoff of 128 seconds was chosen to eliminate slow signal drifts. The autoregressive AR(1) model accounted for serial correlations due to aliased biorhythms and unmodelled neural activity. Contrast images were calculated for the four task conditions 1) not regulated negative, 2) not regulated neutral, 3) regulated negative, and 4) regulated neutral, versus baseline assigning

each condition weights of one for each contrast, respectively. These four contrast images were further analyzed on a group level in the second-level analysis.

The second-level analysis was conducted with the Sandwich Estimator Toolbox (SwE version 2.2.2; Guillaume et al., 2014) for SPM. The modified SwE was selected because it can be assumed that subjects in the same three groups share a common covariance matrix. A marginal model was fit, including the combinations of the within-subject factors (the four task conditions) and the between-subject factor (group) as covariates.

Two contrasts were set up to test the first hypothesis: 1) Negative regulation > no regulation, and 2) negative no regulation > regulation. Hypothesis 2 was tested via two orthogonal contrasts accounting for the testing of three groups: 1) negative regulation > no regulation – sports group (high-intensity and low-intensity) > control group and 2) negative regulation > no regulation – high-intensity > low-intensity group.

***Analysis of hypothesis 3 and 4***

To investigate hypothesis 3 and 4, a new first-level model was set up. The model comprised both time points t2 and t3 consisting of two runs each. The four task regressors and six motion parameters remained the same. Two contrast images were calculated for 1) negative regulation > negative no regulation – post > pre and 2) negative regulation > negative no regulation – pre > post. On the second level, a one-sample t-Test was computed over the contrast images from the first-level analysis to examine overall changes from before CBT (t2) to after CBT (t3) across all groups (hypothesis 3). Second, a one-way ANOVA was set up to investigate differences in the activation changes between the high-intensity exercise, low-intensity exercise, and control group (hypothesis 4). The contrasts were set up the same way as for testing group differences at t2.

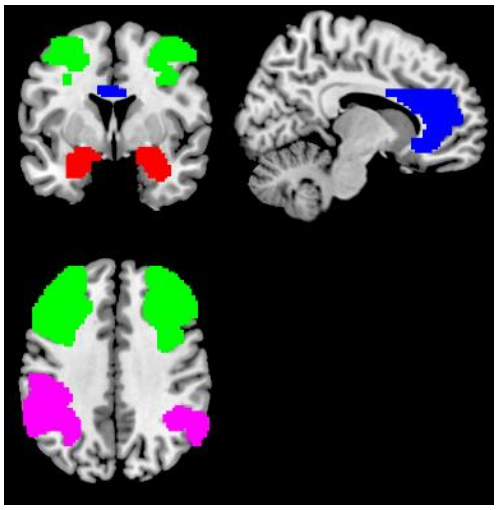
Supplemental analyses were performed with RStudio version 4.2.1 (RSstudio Team, 2020) and visualized with the ggplot2 package (Wickham, 2016). Functional MRI results images were created in MRIcron (Rorden, 2019).

***Regions-of-interest (ROI) mask***

Based on the theoretical considerations stated above, a bilateral regions-of-interest (ROI) mask was created using the automatic anatomical labelling (AAL) atlas parameters (Tzourio-Mazoyer et al., 2002) implemented in the toolbox WFU-Pickatlas 3.0.5 (Maldjian et al., 2003). The ROI mask was designed to cover the middle frontal gyrus, the inferior parietal gyrus, the amygdala, and the anterior cingulate cortex. It was dilated by one voxel in three dimensions (see Figure 5). This ROI mask was used to perform small volume correction (SVC) analyses.

**Figure 5**

*Regions-of-interest mask*



*Note*. Regions-of-interest mask covering the bilateral amygdala (red), the anterior cingulate cortex (blue), the middle frontal gyrus (green), and the inferior parietal lobule (pink).

## Results

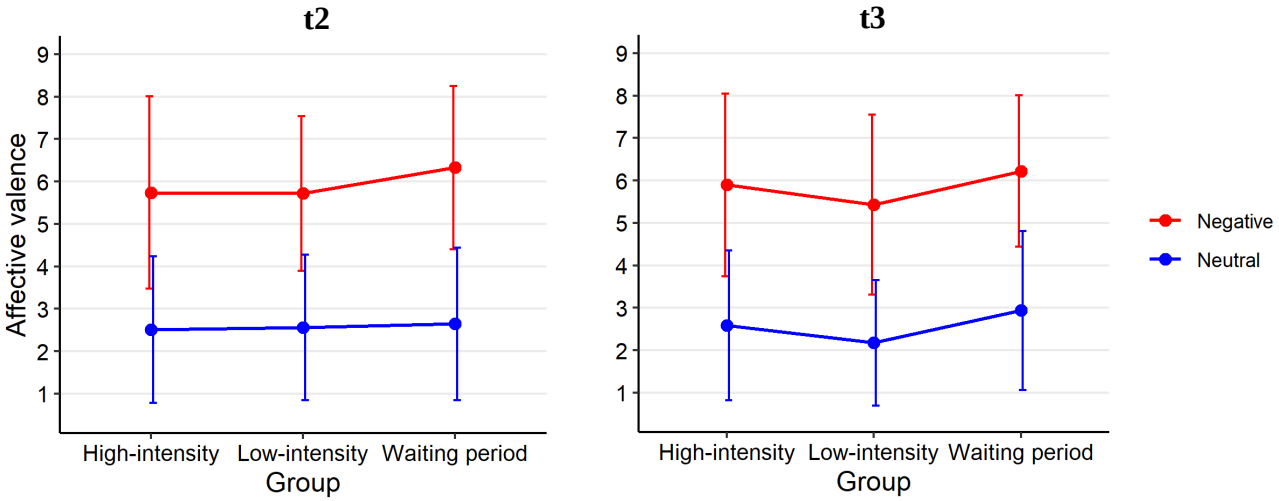
### Behavioral results

Affective valence ratings were available for all subjects but one after CBT (t3). Kruskal-Wallis tests as a non-parametric ANOVA equivalent were used to investigate group differences in the ratings of negative and neutral stimuli between the three groups due to variance homogeneity and normality violations. After the exercise intervention (t2), the three groups showed significant differences in their ratings of negative stimuli, $H(2) = 12.55$, $p = .002$. Pairwise comparisons using Wilcoxon-Tests corrected for multiple comparisons after Benjamini & Hochberg (1995) revealed that patients in the control group experienced negative stimuli more negative compared to both the high-intensity sports group ($p = .02$) and the low-intensity sports group ($p = .001$).

After CBT (t3), the three groups significantly differed in their ratings of negative, $H(2) = 13.93$, $p < .001$ and neutral stimuli, $H(2) = 15.72$, $p < .001$. Post-hoc tests revealed that patients in the low-intensity group rated negative stimuli significantly less negatively than both patients in the high-intensity group ($p = .04$) and the control group ($p < .001$). Patients in the low-intensity group also rated neutral images less negative than patients in the control group ($p < .001$; see Figure 6).

**Figure 6**

*Affective valence ratings per stimulus valence, time point, and group.*




*Note*: Means and standard deviations indicated by error bars are depicted. Ratings were given on a scale from 1 (no negative emotions) to 9 (strong negative emotions. t2 = after the exercise intervention/waiting period; t3 = after CBT.

## Functional MRI results

### *Hypothesis 1*

**Brain activation during cognitive emotion regulation.** During the regulation of negative stimuli (negative regulation > no regulation), patients across all groups exhibited higher activations in a right hemispheric prefronto-parietal network comprising one large cluster in the DLPFC (middle frontal gyrus, cluster size = 1104, peak coordinates = [38, 38, 42], peak Z-value = 5.32, *pFDR* = .001), one cluster in the right inferior parietal gyrus (cluster size = 665, peak coordinates = [56, -55, 38], peak Z-value = 5.21, *pFDR* = .001) and two smaller clusters in the superior frontal gyrus and middle frontal gyrus (see Table 3 and Figure 7).

During the processing of negative stimuli without downregulating the emotional response (negative no regulation > regulation), patients showed bilateral amygdala activations (right: cluster size = 172, peak coordinates = [34, -1, -21], peak Z-value = 4.20, *pFDR* = .012), activity in the left hippocampus (cluster size = 31, peak coordinates = [-29, -11, -13], peak Z-value = 4.42, pFDR = .008), in the left subgenual ACC (cluster size = 24, peak coordinates = [-7, 32, -7], peak Z-value = 3.68, *pFDR* = .018) and left supracallosal ACC (cluster size = 25, peak coordinates = [-3, 26, 26], peak Z-value = 3.31, *pFDR* = .029). The activation patterns are illustrated in Figure 7.

**Table 3**

*Brain activation during the regulation and no regulation of negative stimuli after the exercise intervention/waiting period (t2)*

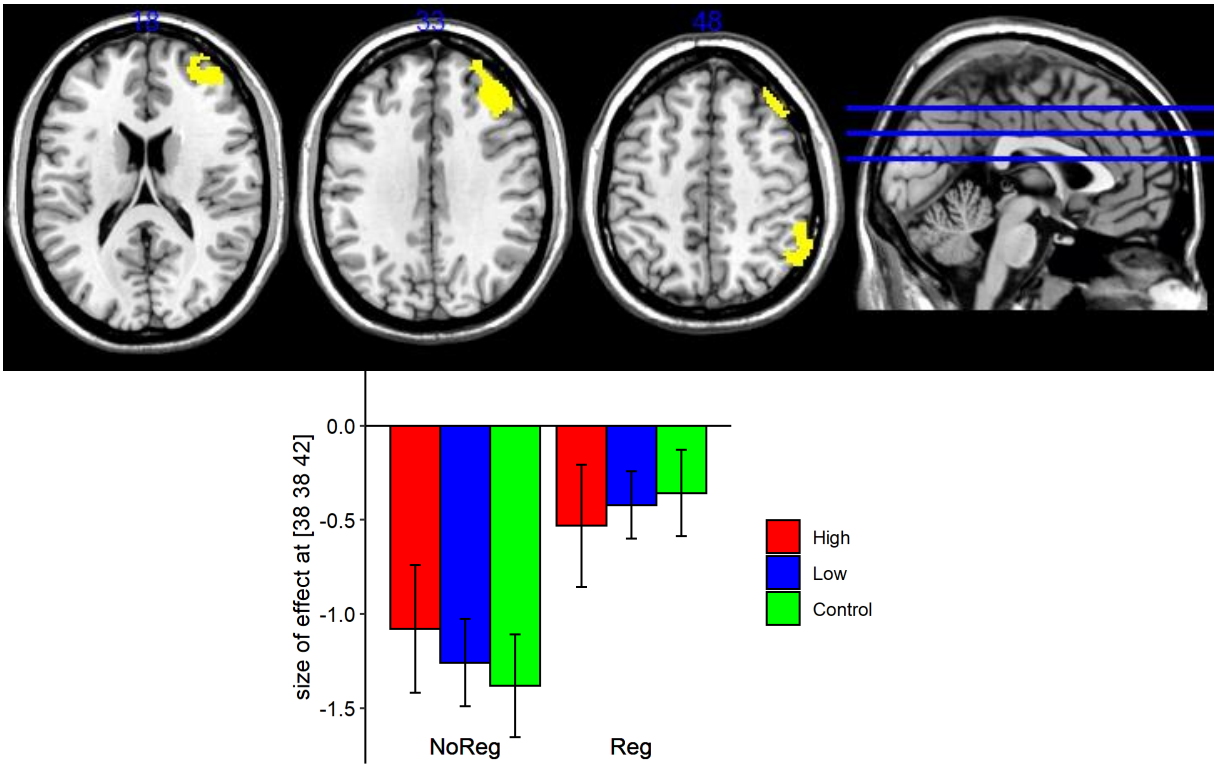
| Region | Hemisphere | MNI-coordinates | | | Peak Z - value | Cluster - size |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| **Negative regulation > no regulation** (*pFDR* < .05) | | | | | | |
| Middle frontal gyrus | R | 38 | 38 | 42 | 5.32 | 1104 |
| Inferior parietal gyrus | R | 56 | -55 | 38 | 5.21 | 642 |
| Superior frontal gyrus | R | 26 | 12 | 60 | 4.83 | 28 |
| Middle frontal gyrus | R | 42 | 52 | 6 | 3.82 | 24 |
| **Negative no regulation > regulation** (*pFDR* < .05) | | | | | | |
| Amygdala | L | -33 | -3 | -21 | 4.76 | 89 |
| Hippocampus | L | -29 | -11 | -13 | 4.42 | 31 |
| Amygdala | R | 34 | -1 | -21 | 4.20 | 172 |
| Subgenual ACC | L | -7 | 32 | -7 | 3.68 | 24 |
| Supracallosal ACC | L | -3 | 26 | 26 | 3.31 | 25 |
| **Negative regulation > no regulation** | | | | | | |
| **Sports > control** (*pFDR* < .05) | | | | | | |
| Middle frontal gyrus | R | 44 | 52 | 18 | 5.52 | 360 |
| **High > control** ($p_{uncorr}$ < .001) | | | | | | |
| Middle frontal gyrus | R | 36 | 42 | 18 | 4.01 | 103 |
| Middle frontal gyrus | R | 40 | 50 | 8 | 3.90 | 40 |
| **Low > control** ($p_{uncorr}$ < .001) | | | | | | |
| Middle frontal gyrus | R | 46 | 54 | 16 | 3.91 | 43 |
| Middle frontal gyrus | R | 44 | 44 | 18 | 3.65 | 24 |
| **No sports > sports** ($p_{uncorr}$ <.001) | | | | | | |
| Amygdala | R | 32 | -3 | -15 | 3.90 | 33 |

*Note.* All analyses were performed with small volume correction using the a-priori defined ROI-mask and cluster-size ≥ 20. R = right; L = left; FDR = false-discovery rate; high = high-intensity exercise group; low = low-intensity exercise group; control = wait-list control group; ACC = anterior cingulate cortex.

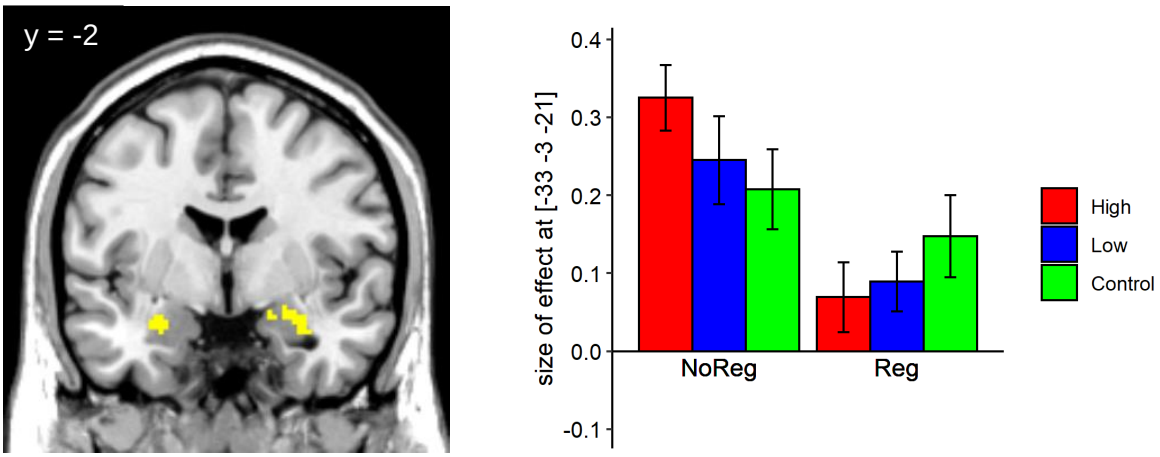
**Figure 7**

*Task effects: brain activation during A) regulation and B) no regulation of negative stimuli*

A) Significant activations in the DLPFC and IPL during negative regulation > no regulation




B) Significant activations in the amygdala during negative no regulation > regulation




*Note*. Brain activation during the two task conditions ($p < .05$, cluster size ≥ 20, false-discovery rate, and small volume correction for ROI). A) Regulation condition. Effect sizes and standard errors at the peak voxel in the right DLPFC [38 38 42] are displayed for each group and condition. B) Viewing condition. Effect sizes and standard errors at the peak voxel in the left amygdala [-33, -3, -21] are displayed for each group and condition. NoReg = no regulation; Reg = regulation; High = high-intensity exercise; Low = low-intensity exercise Control = waiting period.

***Hypothesis 2***

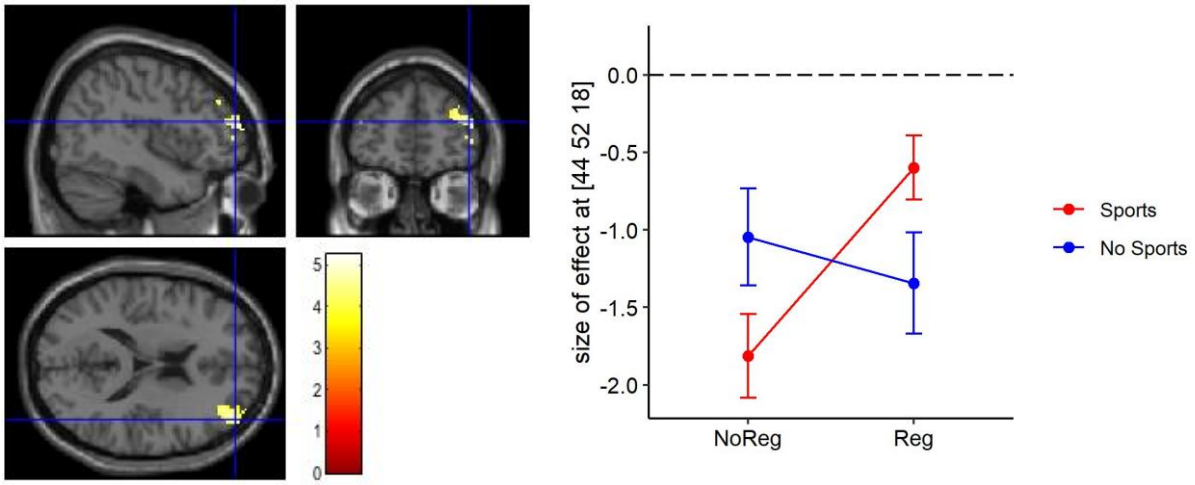
**Group differences after the exercise intervention/waiting period (t2)**. During the regulation of negative stimuli (negative regulation > no regulation – sports > control), patients who participated in a sports intervention (high- or low-intensity) exhibited higher activation in a cluster in the DLPFC than patients who were in the control group (middle frontal gyrus, cluster size = 360, peak coordinates = [44, 52, 18], peak Z-value = 5.52, *pFDR* = .001). This interaction effect is illustrated in Figure 8. Due to small sample sizes and, thus, a lack of power, the following analyses examining group differences were conducted under a significance threshold of p < .001. As depicted in Figure 9, patients in the control group exhibited higher activation in the right amygdala during the regulation of negative images than patients in the sports group (negative regulation > no regulation – control > sports; cluster size = 33, peak coordinate = [32, -3, -15], peak Z-value = 3.90, $p_{uncorr} < .001$). Activations in the amygdala and ACC while viewing negative images did not differ between groups (negative no regulation > regulation – control > sports).

Patients in the high-intensity group compared to the low-intensity group did not differ in their recruitment of the DLPFC and IPL during downregulating negative emotions (negative regulation > no regulation – high-intensity > low-intensity) nor in their activation patterns in the amygdala and ACC during no-regulation (negative no regulation > regulation – low-intensity > high-intensity).

Post-hoc tests were conducted to shed light on activation differences during the regulation between the high-intensity and control group, and the low-intensity and control group, respectively. Both patients in the high-intensity and low-intensity group recruited two clusters in the DLPFC during regulation compared to the control group (see Table 3). The high-intensity group recruited two clusters in the middle frontal gyrus (first: cluster size = 103, peak coordinates = [36, 42, 18], peak Z-value = 4.01, $p_{uncorr} = < .001$; second: cluster size = 40, peak coordinates = [40, 50, 8], peak Z-value = 3.90, $p_{uncorr} = < .001$). The same pattern was observed in the low-intensity group compared to the control group (first: cluster size = 43, peak coordinates = [46, 54, 16], peak Z-value = 3.91, $p_{uncorr} = < .001$; second: cluster size = 24, peak coordinates = [44, 44, 18], peak Z-value = 3.65, $p_{uncorr} = < .001$). There were no significant group differences in the activation during viewing negative images without downregulating (negative no regulation > regulation).

**Figure 8**

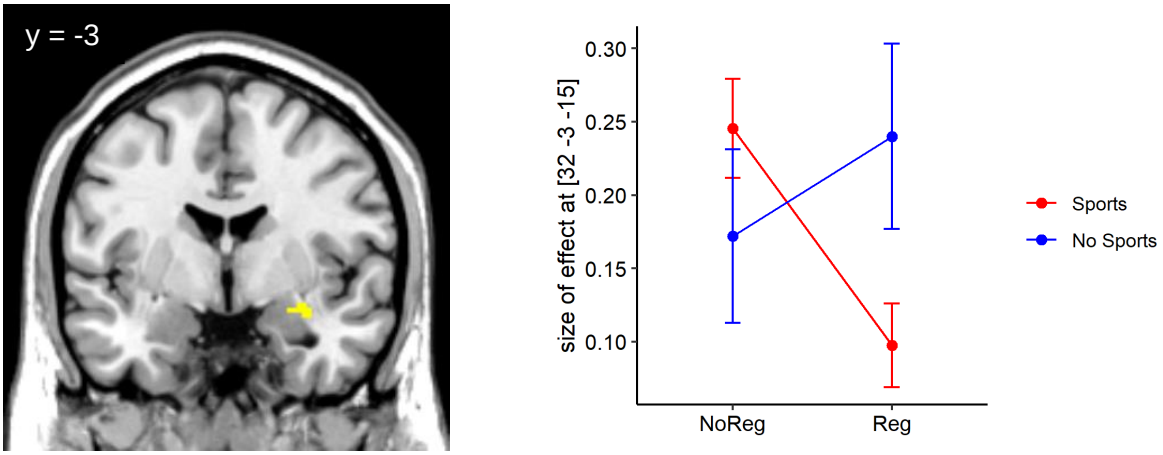
*Significant activations in the DLPFC in the sports groups compared to the control group (negative regulation > no regulation – sports > control)*




*Note*. Brain activation during the regulation of negative images ($p < .05$, cluster size ≥ 20, false-discovery rate, and small volume correction for ROI). Right: Effect sizes and standard errors at the peak voxel in the right dorsolateral prefrontal cortex [44 52 18]. NoReg = No regulation; Reg = Regulation; Sports = high-intensity and low-intensity exercise; No sports = waiting period.

**Figure 9**

*Amygdala activity during the regulation of negative images in the control group compared to the sports group (negative regulation > no regulation – control > sports)*




*Note*. Brain activation during the regulation of negative images ($p_{uncorr} < .001$, cluster size ≥ 20, small volume correction for ROI). Right: Effect sizes and standard errors at the peak voxel in the right the right amygdala [32 -3 -15]. NoReg = No regulation; Reg = Regulation; Sports = high-intensity and low-intensity exercise; No sports = waiting period.

***Hypothesis 3***

**CBT-associated change in activation across groups.** A one-sample t-Test over the contrast images depicting the change in regulation activation through CBT (regulation > no regulation – post > pre) in the regions of interest was computed. This analysis revealed an increase in activation in the right precentral gyrus during the regulation condition (cluster size = 28, peak coordinates = [42, 6, 50], peak Z-value = 3.70, $p_{\text{uncorr}}$ (cluster-level) = .014). No changes in activation in the amygdala and ACC associated with the CBT were found.

***Hypothesis 4***

**Buffer effect of exercise intervention**. To determine whether patients in the exercise groups would benefit more from the CBT than patients who did not receive the exercise intervention, a one-way ANOVA with group as a between-subject factor was conducted on the regulation contrast images (negative regulation > no regulation – post > pre). However, no group differences in changes from t2 to t3 in the predefined regions were found.

***Exploratory analysis***

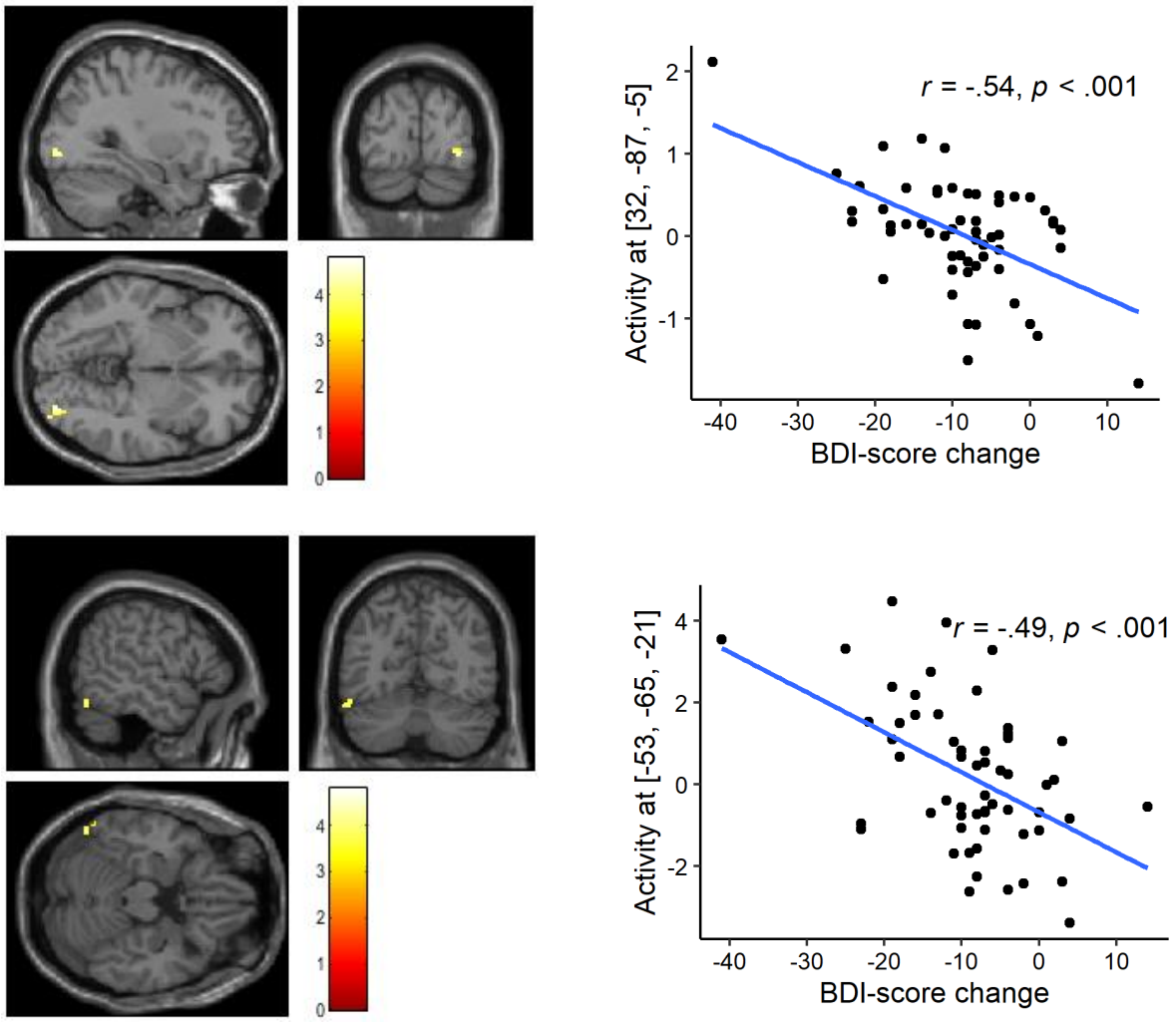
An exploratory whole-brain analysis was performed to locate possible group differences in activation changes associated with CBT outside the a-priori-defined regions of interest. This analysis revealed a higher activation increase in the left inferior frontal gyrus in the control group compared to the high-intensity group (negative regulation > no regulation – post > pre – control > high-intensity; cluster size = 39, peak coordinates = [-37, 42, -5], peak Z-value = 3.38, $p_{uncorr} < .001$) and a higher increase in the left superior parietal gyrus activation in the low-intensity group compared to the high-intensity group (negative regulation > no regulation – post > pre – low-intensity > high-intensity; cluster size = 55, peak coordinates = [-15, -71, 50], peak Z-value = 3.93, $p_{uncorr} < .001$).

Additionally, an exploratory whole-brain regression analysis was performed to identify regions associated with CBT efficacy measured by the change in BDI-II scores from before (t2) to after CBT (t3). The regression model was set up in SPM12 using the contrast images depicting the change in activation during regulation of negative images from t2 to t3 (negative regulation > no regulation – Post > Pre) and adding the mean-centered BDI-II-score change from t2 to t3 as a covariate. One subject of the low-intensity group had to be excluded due to missing BDI-II data from t3. The results are illustrated in Figure 10. Two clusters survived thresholding and minimum cluster size: one cluster was located in the right inferior occipital gyrus (IOG; cluster size = 32, peak coordinates = [32, -87, -5], peak Z-value = 4.37, $p_{\text{uncorr}} < .001$, $r = -.54$) and one in the left inferior temporal gyrus (ITG; cluster size = 26, peak coordinates = [-53, -65, -21], peak Z-value = 3.85, $p_{\text{uncorr}} < .001$, $r = -.49$) indicating a

negative correlation between the change in BDI-II-scores and activity in these clusters. Inversely, no regions were positively related to activation increases during regulation (i.e., the higher the activation increase, the smaller the decrease in depressive severity).

**Figure 10**

*Activity changes in the right inferior occipital gyrus and left inferior temporal gyrus related to depression improvement*




*Note*. Negative correlations between the change in BDI-II scores from t2 to t3 and the change in brain activation during the regulation of negative images ($p_{uncorr} < .001$, cluster size ≥ 20, whole-brain analysis). Top: cluster in the right inferior occipital gyrus (peak coordinates = [32, -87, -5]). Bottom: cluster in the left inferior temporal gyrus (peak coordinates = [-53, -65, -21]).

## Discussion

This study aimed to investigate neural correlates of a cognitive emotion regulation network and identify its functionality in depression. Also, the influence of exercise on depression and corresponding brain activation during emotion regulation in predefined regions of interest was examined using three groups with differing exercise intensities (high-intensity, low-intensity, waiting period). Finally, this study aimed to look into potential normalization mechanisms of altered fronto-limbic loops during cognitive emotion regulation and if the preceding exercise would augment this normalization effect, thereby increasing the efficacy of CBT. The regions of interest were chosen based on a-priori hypotheses. The DLPFC and IPL, as part of the prefronto-parietal network, were expected to be involved in the cognitive regulation of emotions (Buhle et al, 2014). The amygdala and subgenual ACC have been shown to be implicated in emotion generation (Etkin et al., 2011; Phelps, 2006). Finally, the subgenual ACC seems to be altered in MDD and is a relevant determinant of treatment response (Drevets, 2000; Siegle et al., 2012).

### Neural correlates of cognitive emotion regulation in MDD

First, the ROI analysis revealed that all patients recruited a right-lateralized prefronto-parietal network during cognitive emotion regulation. Patients showed increased activations in the right DLPFC and IPL when instructed to detach themselves from negative images, as opposed to allowing all upcoming emotions (passive viewing). During passive viewing, patients exhibited activity in the bilateral amygdala, the left subgenual ACC, supracallosal ACC, and the left hippocampus. These findings extend a broad body of research highlighting the hyperactivity of the DLPFC during cognitive reappraisal (Erk et al., 2010; Greening et al., 2014; Koenigsberg et al., 2010; McRae et al., 2010; Ochsner et al., 2002; Ochsner et al., 2004). This pattern illustrates part of a top-down emotion regulation network as described by Ochsner & Gross (2005), in which the DLPFC is believed to be implicated in executive control and holding reappraisals in mind (Phillips et al., 2008). The hyperactivation of the IPL is also consistent with the hypothesis, given its expected role in spatial processing and sustaining attention (Cole & Schneider, 2007; Husain & Nachev, 2007). The patients were asked to mentally detach themselves from the scene by obtaining the perspective of a third-person observer, thereby the task required spatial components. The right-lateralization of the activations in the DLPFC and IPL is in line with previous findings (Buhle et al., 2014; Dörfel et al., 2014; Erk et al., 2010). The right DLPFC and VLPFC (as opposed to the left) are associated with the inhibition and the selection of different responses (Aron et al., 2004). This mental process is required during reappraisal since it involves inhibiting an automatic

response instead of choosing an alternative valuation. Studies investigating the neural correlates of reappraising in the sense of increasing emotions (rather than decreasing) found that prefrontal activations were more strongly left-lateralized (Aron et al., 2004). This seems plausible since no response inhibition is required in this scenario. Additionally, studies have demonstrated greater right hemisphere recruitment in visual processing and the processing of negative stimuli as opposed to positive stimuli (Craig, 2005).

The hyperactivation of the bilateral amygdala during the passive viewing condition reflects part of the emotion generation system that is downregulated during cognitive reappraisal. As mentioned above, the amygdala plays a central role in emotional processing. It encodes stimuli considering their relevance concerning one's current goals and needs and triggers appropriate responses. As such, it is sensitive to affective salient stimuli and exhibits particular sensitivity towards aversive stimuli that might potentially be threatening (Phelps, 2006; Phelps & LeDoux, 2005; Shin & Liberzon, 2010).

The hyperactivation of the hippocampus during passive looking at negative pictures is consistent with previous work on the interactions between the amygdala and hippocampal area (for a review, see Engen & Anderson, 2018). The generation of emotion in a particular context is affected by recalling emotionally charged memories and experiences. Consequently, the control of memory recalls plays a central part in emotion regulation (Engen & Anderson, 2018). On a neural basis, the amygdala and hippocampal area interact reciprocally during encoding emotional situations (Richardson et al., 2004). On the one hand, the amygdala can modulate the encoding and storage of certain events. On the other hand, the hippocampus forms representations of emotional significance and the interpretation of certain events, thereby affecting later emotional responses when emotional stimuli are encountered (Phelps, 2004). Being able to control the emotional impact of upcoming memories reduces their emotional impact and modulates amygdala activity. This demonstrates the potential role of the hippocampal area in cognitive emotion regulation. Additionally, observed deficits in memory control in depression suggest that affect and memory are intertwined processes and that memory control may contribute to successful emotion regulation (Engen & Anderson, 2018).

The activation of the subgenual ACC likely reflects its involvement in the regulation of limbic regions (i.e., the amygdala) associated with the generation of emotional responses (Etkin et al., 2011) and represents a brain region that is altered in terms of structure and functionality in depression. In patients with mood disorders, the metabolism in the subgenual ACC is generally increased (Drevets et al., 2008). Also, low subgenual ACC activity before

treatment has been linked to better treatment success (Siegle et al., 2012). However, since there was no healthy control group in this study, no conclusions about the altered metabolism of the subgenual ACC compared to healthy controls can be drawn.

Taken together, hypothesis 1 could be confirmed in this sample. The present findings support previous evidence that patients with MDD can cognitively modulate negative emotions to some extent when explicitly instructed to do so. By changing the affective salience in the context of one's personal goals and needs, the experience of negative emotions can be diminished also in depression (Ochsner & Gross, 2005). However, this study did not analyze data from a healthy control group, so conclusions about emotion regulation capacities are solely based on activation patterns between task conditions. They cannot be compared to healthy controls' brain activation during cognitive emotion regulation.

**Group differences after the exercise intervention/waiting period (t2)**

Second, group differences in brain activation in the regions of interest after the exercise intervention/waiting period were examined. The preceding exercise intervention was expected to yield antidepressive effects by supporting cognitive control mechanisms. This was anticipated to be reflected in higher DLPFC and IPL activity and lower amygdala and ACC activity during emotion regulation. Also, high-intensity exercise was expected to have greater effects than low-intensity exercise (hypothesis 2). Consistent with the hypothesis, comparing patients who received an exercise intervention (high- or low-intensity) with patients who did not (waiting period) revealed a higher activation of the right DLPFC during regulation in the exercise groups. No difference was found between the amygdala and ACC activity during the look-condition, indicating that both groups showed similar amygdala sensitivity to the negative stimuli.

Interestingly, the patients in the control group showed higher right amygdala activation during negative regulation than patients in the exercise groups. However, it must be noted that this and all the following analyses were performed under uncorrected significance thresholds. Consequently, inferences must be drawn with caution, and the analyses must be repeated in a larger sample. Given the increase in DLPFC activation related to the exercise intervention, it seems likely that the amygdala hyperactivity in the control group can be explained by a lack of cognitive control. In line with this assumption, previous work has highlighted the positive effect of endurance exercise on cardiovascular function and, in turn, cognitive control (for reviews, see Angevaren et al., 2008; Voelcker-Rehage & Niemann, 2013). Additionally, the found effects could be explained by an increase in fronto-limbic coupling. Evidence suggests that depression is characterized by diminished coupling between

the amygdala and the right DLPFC (Erk et al., 2010). Through exercise, the functional connectivity between the amygdala and the orbitofrontal cortex can be increased (Chen et al., 2019; Ge et al., 2021). In a recent study, anxiety-prone individuals exhibited increased functional connectivity of the amygdala with the orbitofrontal cortex during exposure to positive faces after a running intervention (Chen et al., 2019). Potentially, the exercise intervention led to an increase in coupling between the DLPFC and amygdala, that was not apparent in the control group, explaining the increased amygdala activity during regulation in the control group. However, since no functional connectivity analyses were performed in this study, I can only speculate about the potential interaction effects during cognitive emotion regulation and how these are affected by exercise.

Against expectations, the high-intensity and low-intensity exercise group did not differ in their activity during the cognitive emotion regulation task or the processing of emotional stimuli without regulation. Thus, higher training intensity did not yield more substantial effects than lower training intensity, and the expected dose-response relationship was not observed.

It must be noted that patients in the control group rated the negative stimuli more negatively than those in the high-intensity and low-intensity exercise groups. Thus, the difference between the control and exercise groups in their ability to downregulate amygdala activity might not be entirely attributable to the cognitive emotion regulation mechanisms. Instead, patients in the control group possibly experienced more negative affect during the exposure to the negative images and consequently were less successful in modulating the amygdala activation during regulation. From this point of view, the lower DLPFC activity in the control group compared to the exercise groups during regulation could also be explained by the control group being more “overwhelmed” by the stimuli since they experienced them as more aversive (Campbell-Sills et al., 2011). However, no increased amygdala reactivity was observed in the control group in the passive viewing condition, so the valence ratings' impact on subsequent regulation activity seems negligible.

Since only differences between patients having received an intervention (high- or low-intensity) and no differences between the high-intensity and low-intensity group were found, it is not possible to determine whether physical exercise or secondary factors led to the observed effects. Because exercise was done in a group setting, social interaction, support and attention might have yielded antidepressive effects. Supporting the latter, evidence suggests that high intensity is required for exercise interventions to be effective (Dunn et al., 2005). Other work in the “SpeED-Project” revealed that only patients in the high-intensity group

significantly increased their physical fitness level from baseline to t2 measurement (Heinzel et al., 2022). In a similar study, a high-intensity exercise intervention decreased depressive symptoms more than a low-intensity exercise intervention. The low-intensity intervention yielded effects equivalent to a control intervention (flexibility class). Interestingly, patients in the low-intensity and control group still experienced a significant improvement that can be explained by unspecific intervention effects such as social interaction, support, and engagement (Dunn et al., 2005). In line with this, another study found that the association between leisure-time exercise and improvement in depressive symptoms could be better explained by secondary factors such as context, social interactions, and engagement than biological changes (Harvey et al., 2010).

Taken together, hypothesis 2 was partly confirmed. Consistent with the hypothesis, the observed differences between patients having participated in an exercise intervention versus patients who did not presumably reflect an exercise-related increase in cognitive control, as demonstrated in previous reviews (Angevaren et al., 2008; Voelcker-Rehage & Niemann, 2013). Consequently, patients in the exercise groups were more successful in downregulating the amygdala. On a clinical level, the groups did not differ in their depressive symptoms. Thus, the hypothesized antidepressive effect of exercise (Cooney et al., 2014) could not be confirmed in this sample. Contrary to the hypothesis, high-intensity did not yield more significant effects than low-intensity exercise, and thus, the influence of unspecific effects of the interventions cannot be ruled out.

**Changes from pre- to post-CBT across groups**

Third, pre-post analyses were performed to investigate whether CBT led to an increase in DLPFC and IPL activation with a simultaneous decrease of subgenual ACC and amygdala activity across all groups during cognitive emotion regulation (hypothesis 3). On a clinical level, patients were significantly less severely depressed after CBT (t3) than before CBT (t2). This finding suggests that CBT effectively reduces depressive symptoms, thereby extending a large body of evidence (Butler et al., 2006).

As expected, an increase in the right precentral gyrus during cognitive emotion regulation through CBT could be identified. The precentral gyrus can be interpreted as an extension of the middle frontal gyrus, depicting the functional region of the DLPFC (Kohn et al., 2014). Kohn and colleagues (2014) identified the precentral gyrus as part of the cognitive reappraisal network. Also, it is involved in response inhibition (Bush et al., 1998). Hence, the observed activation increase might reflect an increased ability to inhibit automatic emotional responses. This illustrates the hypothesized increase in cognitive control through CBT on a

neural level. However, compared to healthy individuals, studies indicate that individuals with depressive disorders show higher recruitment of the precentral gyrus during cognitive emotion regulation (Picó-Pérez et al., 2017). The found increase in activation after the CBT seems surprising since it does not depict a normalization pattern in this sense. One could hypothesize that depressed individuals require more effort to down-regulate negative information (Campbell-Sills et al., 2011).

CBT did not affect amygdala or ACC activity during cognitive emotion regulation or the processing of negative images. Hence, previous findings suggesting a CBT-related decrease in activation in the subgenual ACC could not be replicated (Karch et al., 2012). However, the study comprised a relatively small sample and hence, a lack of statistical power. Additional changes in activation patterns through CBT might be apparent in a larger sample. Taken together, hypothesis 3 was partly confirmed. The increased activation in the precentral gyrus presumably reflects an improvement in cognitive control. However, no changes in the amygdala or subgenual ACC were found.

Subsequently, an exploratory whole-brain regression analysis was performed to locate affected regions outside the a-priori-defined regions of interest. Interestingly, the right IOG and the left ITG were negatively related to the CBT-related decrease in clinical symptoms (i.e., the more depressive symptoms decreased, the more the activity in the IOG and ITG increased). The ITG is associated with object recognition and visual memory and conveys information about stimuli. Additionally, it connects stimuli with a reward outcome facilitated by its direct connection to the amygdala (Kobayashi et al., 2009). A meta-analysis on the neural correlates of emotion regulation revealed a co-activation pattern of the bilateral ITG and (pre)-SMA, a region that has been linked to regulation success by changing mental representations of stimuli (Kohn et al., 2014), and embodied cognition (Niedenthal, 2007). Additionally, the recruitment of middle temporal regions during cognitive emotion regulation extends previous findings (Buhle et al., 2014; Kohn et al., 2014). Reappraisal alters the semantic and perceptual representations stored in the middle temporal gyrus (MTG). The MTG is associated with changing semantic and perceptual representations of stimuli, extracting semantic meanings, and reflecting on intentions. These representations and interpretations further affect the emotional impact of stimuli (Ochsner et al., 2012). However, since patients were instructed to use distancing rather than reinterpreting strategies, the described mechanisms do not seem quite applicable. Additionally, temporal regions seem to play a mediatory role between the DLPFC and amygdala (Ochsner et al., 2012). Another role assigned to the middle and superior temporal cortex is self-directed inner speech (Geva et al.,

2011). Inner speech might play a role in reflecting on the significance of stimuli by verbal labeling. In this way, it could facilitate appraising a stimulus (Burns & Engdahl, 1998). Verbal labeling is considered an emotion regulation process (Lieberman et al., 2011). However, whether these proposed mechanisms apply to inferior temporal cortex regions remains unclear.

The IOG is implicated in object recognition, the perception, and processing of faces, and is connected to the amygdala (Sato et al., 2017). The role of the IOG in cognitive emotion regulation is less consistent. One study found a higher IOG activation during watching negative pictures compared to neutral in healthy participants (Walter et al., 2009). Others found that patients with MDD recruited the left IOG more during cognitive reappraisals than healthy controls (Picó-Pérez et al., 2017). Altered activity in the occipital lobe seems characteristic of depression (Guan et al., 2021). Patients exhibited weaker activation when looking at negative pictures than controls (Li et al., 2013). Occipital lobe activity has been linked to visual cognitive function (Li et al., 2018). It must be noted that the identified activations in the IOG and ITG stem from an exploratory analysis. Their role in the neurobiological mechanisms of CBT must be tested in an independent sample in future studies to draw valid inferences.

**Augmentation effect of exercise on CBT**

Fourth, I investigated whether the high-intensity group experienced a higher increase in prefrontal activation (DLPFC and IPL) and a higher decrease in subcortical activation (amygdala and subgenual ACC) from t2 to t3 than the low-intensity group and the control group (hypothesis 4). Against expectations, no group differences in the activation changes from pre- to post-CBT were found in the regions of interest. In line with this, the hypothesized add-on effect of exercise was not reflected in the BDI-II score change from t2 to t3 either: the high-intensity exercise, low-intensity exercise, and wait-list control group exhibited a similar decrease in depressive symptoms from t2 to t3. Also, depressive symptoms after CBT were not lower in the high-intensity group compared to the low-intensity group or lower in the low-intensity group compared to the wait-list control group.

Subsequent whole-brain exploratory analyses revealed effects contrary to the expectations. For instance, patients in the control group exhibited an activation increase in the left IFG, whereas IFG activation in the high-intensity exercise group decreased. The IFG reflects a brain region that has consistently been associated with cognitive emotion regulation (Buhle et al., 2014; Frank et al., 2014; Kohn et al., 2014). Additionally, patients who received low-intensity exercise showed higher increases in left superior parietal gyrus recruitment

through CBT than those who received precedent high-intensity training. The parietal cortex is involved in cognitive control processes (such as selective attention and working memory; Miller & Cohen, 2001), and the superior parietal cortex is believed to be part of the cognitive emotion regulation network (Buhle et al., 2014; Kohn et al., 2014).

These findings suggest that control subjects and subjects in the low-intensity exercise group recruited cognitive control regions more strongly during the regulation of negative information than patients who received high-intensity exercise. The fact that patients in the high-intensity group were more depressed after CBT (even though it did not reach a significant effect) could partly explain this counterintuitive finding. However, due to the analysis's lack of power and exploratory nature, the findings must be interpreted with caution.

Summed up, hypothesis 4 could not be confirmed in this sample. Both on a clinical and neural level, a preceding exercise intervention did not lead to a better CBT outcome than CBT only. This finding is consistent with previous studies (Imboden et al., 2020; Kerling et al., 2015) and a recent meta-analysis (Bernard et al., 2018). In contrast, Abdollahi and colleagues (2017) suggest that an exercise intervention improves the efficacy of CBT in moderately depressed patients. However, in their study, patients trained at a higher frequency (three times a week), and the exercise intervention was implemented simultaneously with the CBT. These opposite findings highlight the possible moderating effects of exercise characteristics, such as intensity, frequency, and exercise type. For instance, a longer intervention duration is associated with greater effect sizes (Bernard et al., 2018). The most benefitting intervention characteristics and knowledge about the underlying mechanisms remain unknown. It is possible that the parallel application of both interventions would counteract a loss of motivation and subsequent drop-out, leading to better effects. Additionally, according to a meta-analysis, the antidepressive effects of exercise were not significant at follow-up measurements that took place about 11 months later (Kvam et al. 2016). It may be hypothesized that the “boosting” effect of the exercise intervention on cognitive control capacities that was present at t2 diminished through time and, consequently, could not be observed at t3, being on average five months after t2. According to this finding, the effects of exercise interventions might be relatively short-lived.

Again, it must be noted that after CBT (t3), patients in the low-intensity group rated negative stimuli significantly less negative than both patients in the high-intensity group and the control group. Thus, whether differences in activation patterns during emotion regulation between the low- and high-intensity exercise group are attributable to differences in emotion

regulation or the perception of stimuli remains unanswered. However, as discussed above, the influence of the image ratings is regarded as negligible.

In the present study, 29 out of 75 patients were on antidepressant medication**.** A meta-analysis revealed that amygdala reactivity to negative stimuli decreased in patients with mood disorders on antidepressant medication. Additionally, DLPFC activity increased with antidepressants when processing negative stimuli. In this way, antidepressants might normalize alterations in emotional processing in depression (Ma, 2015). In the present study, the percentage of patients receiving antidepressant medication was the same for all groups. However, the overall ability to cognitively downregulate negative emotions reflected in neural activation might be less apparent in an unmedicated sample. A recent study found that unmedicated MDD patients were able to recruit prefrontal control areas (including the DLPFC) during cognitive emotion to the same extent as healthy controls. In contrast, only controls could downregulate amygdala activity (Greening et al., 2014).

Interestingly, DeRubeis et al. (2008) suggest that antidepressant and therapeutic treatment share some properties and are distinctive in others. More specifically, CBT is aimed at changing dysfunctional cognitions and increasing inhibitory control in prefrontal control areas that further dampen emotional responses located in the amygdala. As such, foci of CBT are directing attention, voluntary emotion regulation, and reappraisal. Consequently, CBT leads to enhanced cognitive control that further dampens the emotional reactivity to negative information. Conversely, antidepressant therapy might target the limbic regions directly by affecting synaptic serotonin levels. With regard to this study, the CBT-related increase in DLPFC activity mentioned above may reflect an increase in limbo-cortical inhibition (DeRubeis et al., 2008). Further analyses should shed light on the role of antidepressants on amygdala reactivity during cognitive emotion regulation.

Deficits in cognitive control are a characteristic feature of depression (Beck, 1967) and impaired emotion regulation seems to be rooted in diminished cognitive control (Joormann & Gotlib, 2010). Patients with MDD use maladaptive emotion regulation strategies requiring less cognitive control effort more frequently. Correspondingly, depression is associated with diminished activation in prefrontal brain regions during working memory, cognitive control, and cognitive emotion regulation tasks (for a review, see Joormann & Stanton, 2016). This is in line with the cognitive model of depression (Beck, 1967), which states that depressive symptoms are related to maladaptive cognitions (biases in attention, processing, thoughts and rumination, memory, and about the environment). Neural correlates of biased attention are decreased DLPFC, VLPFC, and superior parietal lobule (SPL) activations that reflect the

inability to disengage from negative information. Biased processing of negative stimuli is related to amygdala hyperreactivity and dorsomedial PFC hypoactivity (Disner et al., 2011). Hence, cognitive control plays a significant role in the development and maintenance of MDD. Cognitive control at the beginning of psychotherapy is predictive of treatment success (Heller et al., 2013). Consequently, addressing cognitive control in treating MDD seems crucial. Even though the expected add-on effect of the exercise intervention on CBT outcome was not found in this study, the present findings demonstrated that exercise might yield a significant impact on cognitive control.

**Strengths and limitations**

To my knowledge, this is the first study examining the cognitive emotion regulation ability in MDD patients in response to an exercise intervention adjunctive to CBT. A primary strength of the present study is the inclusion of both a high- and low-intensity exercise group that share all properties except the training intensity. Participants were blinded regarding their allocation to the high- or low-intensity exercise intervention. This way, differences between the two groups can be traced back to the intensity, and secondary factors can be ruled out (effects of group interventions, attention, etc.).

Some methodological weaknesses must be considered. First, 37.5% of the initially randomized 120 patients dropped out, indicating an above-average attrition rate (Heinzel et al., 2022; Stubbs et al., 2016). Thirty-five patients already dropped out during the sports intervention/waiting period due to numerous reasons (i.e., lack of motivation, time constraints, symptom-related reasons). Especially in depression, exercise might be perceived as challenging since patients often lack energy and motivation (Kvam et al., 2016). As such, drop-out was higher in the exercise groups. This dampens the validity of the findings, and future studies should target the patients' individual preferences to increase motivation. During CBT, another 18 patients dropped out. Additionally, 15 patients had to be excluded due to insufficient quality of the fMRI data or missing record data/documentation. Thus, the relatively small sample size in this study is a consequence of lack of motivation, time constraints, and clinical factors on the part of the patients, and partly poor quality of the fMRI data. Importantly, small sample sizes in task-based fMRI affect the statistical power and, consequently, the replicability of findings. Recent findings suggest that a sample size of 36 results in a replicability of below 0.5 (meaning 50 percent of cluster peak voxels will not reach suprathreshold significance in an exact replication), and even findings from large datasets with 100 participants did not replicate (Turner et al., 2018). Consequently, the present

results obtained with a sample size of partly less than 20 must be interpreted cautiously, and replication in a larger sample is crucial.

Second, the depressive severity of the sample must be considered. The criteria for depression by BDI-II were not met in 10 subjects already after the exercise intervention/waiting period (t2). Possibly, more severely depressed patients would have been less successful in cognitively regulating emotions than the present sample. A potential explanation is that blinding regarding the allocation to an exercise group or the control group was not possible and might have led to expectancy effects. Additionally, the patients already received five probationary therapy sessions before t2, which might have led to therapeutic and expectancy effects on depressive symptoms. Further, unspecific effects such as attention, the social interaction within a group might have decreased depressive symptoms.

Third, patients in the control group were, on average, 5.45 and 7.16 years older than patients in the high-intensity and low-intensity group, respectively. Even though cognitive control and working memory decrease with age, some evidence suggests that older adults experience less negative affect than younger adults (Gross et al., 1997). This might be due to diminished processing of negative stimuli (Charles et al., 2003), decreased amygdala reactivity to negative stimuli (Mather et al., 2004), and increased prefrontal activity during the processing of negative stimuli (Nashiro et al., 2012). Additionally, the percentage of women was significantly higher in the control group than in the high-intensity and low-intensity group. Evidence suggests that men recruit prefrontal regions to a lesser extent and show greater decreases in the amygdala during reappraisal than women (McRae et al., 2008). In contrast, women exhibit higher activation in the ventral striatum, a region that is responsible for reward processing. Potentially, men might require less cognitive effort during cognitive regulation, and women might emphasize more on using positive emotions during reappraisal (McRae et al., 2008). Regarding the present study, differences between the exercise and control group might have been more significant in even-aged groups with similar gender ratios. However, research on age-related changes in emotion regulation typically focuses on distinctly older adults (over 70). Thus, the described effects of age might not be relevant in the present sample.

Finally, even though depressed individuals can improve cardiorespiratory fitness through exercise (Stubbs, Rosenbaum, et al., 2016), the differences in physical fitness after the exercise intervention/waiting period (t2) between groups did not reach significance (i.e., the high-intensity group exhibited only marginally higher fitness than the other groups).

Possibly, group differences would have been more apparent in subjects differing in their physical fitness substantially.

**Future directions**

Future studies should test the present study's findings in a larger sample and compare the activation changes during the course of the study to a healthy control group. This way, statements about potential alterations from "normal" activation patterns and normalization processes can be made. CBT and exercise could be applied simultaneously, and training programs should be more individualized to meet each person's individual needs and expectations to prevent high attrition rates. Future studies should investigate the interactions between prefrontal control regions and subcortical emotion generation regions during emotion regulation by functional connectivity analyses, as well as how these are affected by exercise. Also, the biological processes by which exercise unfolds its antidepressive and cognitively enhancing have to be examined. The lack of knowledge regarding the optimal intervention characteristics (intensity, duration, type) might contribute to the mixed evidence regarding its efficacy and have to be investigated in the future. Effects of a longer and more intense exercise intervention tailored to the patients' preferences leading to significant differences in physical fitness between groups should be investigated. In addition to exercise groups of differing intensities, a control intervention that shares the intervention setting but lacks the physical activity component should be included to control for social support and other unspecific effects. Neural alterations yield promising potential in the research field of predicting therapy outcomes. Precise predictions provide the possibility to tailor interventions to individual needs and increase response rates of CBT (Cohen & DeRubeis, 2018).

**Conclusion**

This study revealed that patients with MDD can actively regulate brain activity in fronto-limbic circuits during the exposure to negative information by recruiting a cognitive emotion regulation network. After an exercise intervention, individuals with MDD recruited prefrontal control regions more strongly than patients in the control group and were more successful in downregulating amygdala activity. However, high-intensity exercise did not lead to better effects than low-intensity exercise. Hence, it is impossible to disentangle exercise-related effects from unspecific effects of the interventions, such as social interaction and support. CBT resulted in increased recruitment of prefrontal control regions during cognitive emotion regulation across all groups, but exercise did not have the expected add-on effect on the efficacy of CBT. Future studies should repeat the analysis in a larger sample, implement

individualized exercise programs to increase motivation and prevent high attrition rates, and control for unspecific group intervention effects.

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