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

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ABSTRACT

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

1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders, affecting approximately 322 million people worldwide (World Health Organization, 2017), and is characterized by affective, cognitive, and somatic symptoms. MDD patients frequently exhibit cognitive deficits, such as impaired attentional processes, executive functions (Shenal et al., 2003) and working memory (Semkovska et al., 2019; Snyder, 2013). WM is a cognitive system that is essential to the performance of cognitive tasks and everyday activities (Wager and Smith, 2003). It is defined as a limited capacity processing system that serves to retain and process information (Baddeley et al., 2012; Rottschy et al., 2012), e.g., content manipulation and updating (Engle et al.,

1999). A commonly reported measure of WM is the n-back-task which allows to manipulate WM load. Studies using this measure in MDD showed that performance is impaired in the form of reduced accuracy and slowed response times (Harvey et al., 2004; Nikolin et al., 2021; Rose and Ebmeier, 2006). Such WM impairments are mediated by frontoparietal circuitry abnormalities (Wang et al., 2015) by virtue of hyper- and hypoactivity in frontoparietal regions. Some authors found hyperactivations in frontal areas (Harvey et al., 2005; Matsuo et al., 2007; Wagner et al., 2006; Walter et al., 2007) which might compensate for reduced neural efficiency (Barulli and Stern, 2013; Heinzel et al., 2014). Other studies found frontoparietal hypoactivations in MDD (Garrett et al., 2011; Meusel et al., 2013; Xia et al., 2019; Zhu et al., 2018), suggesting capacity-limited activity (Garrett et al., 2011; Meusel

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

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

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

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

We hypothesized that

1) Compared to healthy controls, patients with MDD show both lower performance and higher reaction times in an n-back task specifically at high WM load,
2) Patients with MDD show increased activation at low and decreased activation at high WM load in frontoparietal WM regions indicating reduced WM load-dependent modulation of neural activity compared to healthy controls,

3) Whole Brain-Analyses within the MDD group show a fitness correlate in parietal regions.
4) ROI-Analyses within the MDD group that performed a graded exercise test show a
   a. positive relationship between behavioral n-back performance and physical fitness,
   b. positive relationship between parietal n-back-activity and physical fitness.

2. Methods and materials

2.1. Participants and behavioral data

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

Table 1

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

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

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

[a] Number of recurrent depressive patients.

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

[c] data available for 106 MDD patients.

2.2. N-back Paradigm during fMRI

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

2.3. MR image acquisition

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

2.4. Estimation of BOLD effects in n-back

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

On the second level, a random effects model as implemented in the GLM_Flex_Fast4 toolbox (https://mrtools.mgh.harvard.edu/index.php?title=GLM_Flex) was applied to test a repeated measures ANOVA with the between-subjects factor group (MDD vs. HC) and the within-subjects factor WM load (1-, 2-, and 3-back respectively contrasted to 0-back). Because age differed significantly between groups, age was included as a control variable. For the whole-brain-effect of the analyses we used probabilistic threshold-free cluster enhancement (pTFCE) as implemented according to Spisák et al. (Spisák et al., 2019) in addition to whole brain peak-level (voxel-wise) FWE correction with p < 0.05 and a minimum cluster size threshold of k > 10. Because we were specifically interested in WM activations for the WM load-dependent hypothesis in MDD, we chose a more restrictive approach. For this, a WM-mask was created with the tool *Neurosynth* (Yarkoni et al., 2011) which is a platform for automatically synthesizing the results of different neuroimaging studies. Using the term *working memory*, the tool summarized

data from 1091 studies and created a tissue probability map (including 12,010 voxels) at a probability threshold of 0.1 to filter out the most common WM activations (see supplementary figures S1). For the physical fitness specific hypothesis, we used physical fitness as an additional regressor in our ANCOVA. As we had no specific expectations for the activation pattern for this analysis, a binary whole-brain mask was created using the gray matter tissue probability map (including 150,571 voxel) available in SPM at a probability threshold of 0.3.

2.5. ROI-analyses

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

2.6. Assessment of physical fitness

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

2.7. Statistical analysis

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

Table 2

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

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

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

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

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

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

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

3. Results

3.1. Behavioral results during n-back

A two (group) by four (WM load) ANCOVA of the n-back performance showed a significant interaction (F(1.9,486) = 6.74, p = 0.002, partial n^2 = 0.04) as well as a significant main effect of group (F(1,162) = 6.23, p = 0.014, partial n^2 = 0.037). There was a main effect of the covariate age (F(1,162) = 12.23, p = 0.001, partial n^2 = 0.07). The Greenhouse–Geisser adjustment was used to correct for violations of sphericity. Follow-up two-sample t-tests indicated that compared to patients with MDD, healthy control participants revealed better performance at 0-back (t(160,6) = -2.19, p = 0.03), 3-back (t(163) = -4.28, p = 0.00) and by trend also 2- back (t(163) = -1.89, p = 0.06) but not at

1-back (see Fig. 1, Panel A).

Compared with the results of the n-back performance, reaction time analyses showed a tendency of a two (group) by four (WM load) interaction (F(2.4, 486) = 2.59, p = 0.066, partial η2 = 0.016), a significant main effect of WM load (F(2.4, 486) = 21.15, p < 0.001, partial η2 = 0.115) and also a main effect of group (F(1, 162) = 20.01, p < 0.001, partial η2 = 0.110). There was also a main effect of the covariate age (F (1, 162) = 5.93, p = 0.016, partial η2 = 0.035). The Huynh-Feldt adjustment was used to correct for violations of sphericity. Follow-up two-sample t-tests indicated that compared to patients with MDD, healthy control participants had faster RTs in all conditions (0-back: t (163) = 4.37, p < 0.001; 1-back: t(163) = 4.63, p < 0.001; 2-back: t (163) = 3.72, p < 0.001; 3-back: t(163) = 5.36, p < 0.001; see Fig. 1, Panel B).

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

3.2. FMRI results during n-back

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

3.3. FMRI results of physical fitness

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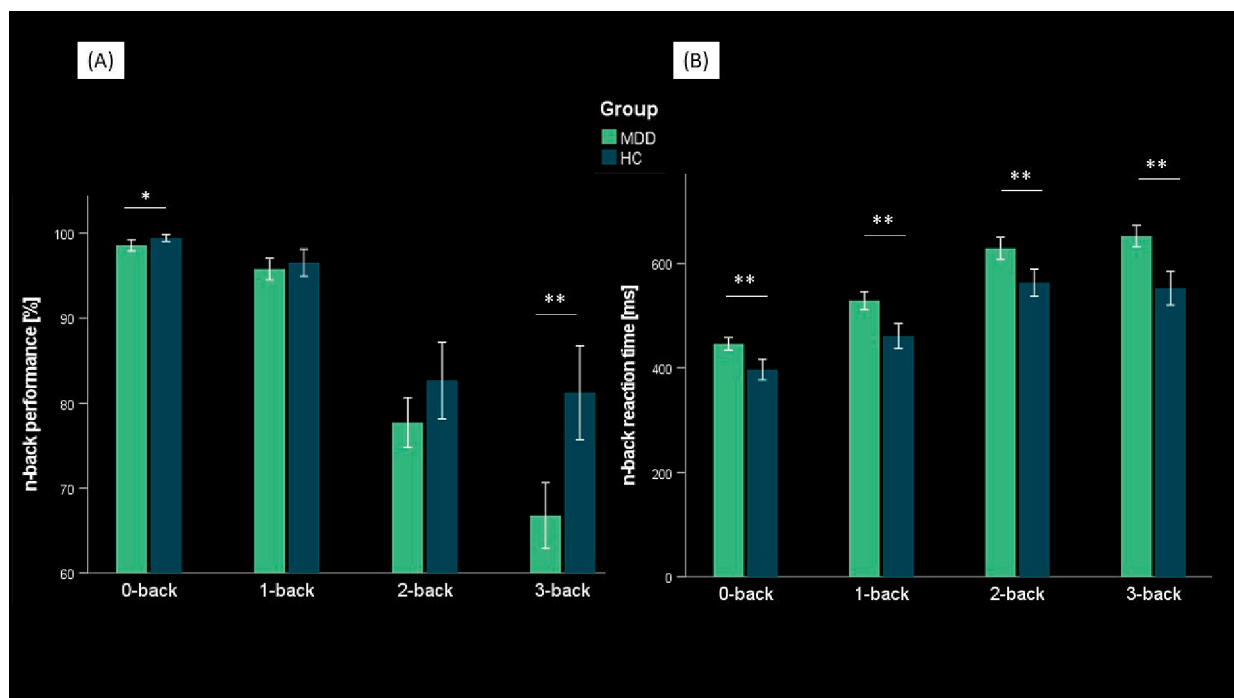

Fig. 1. Behavioral n-back data in healthy controls (HC) and major depressive disorder (MDD). Means and standard errors are reported for A) performance and B) reaction time. *p < 0.05; **p < 0.01.
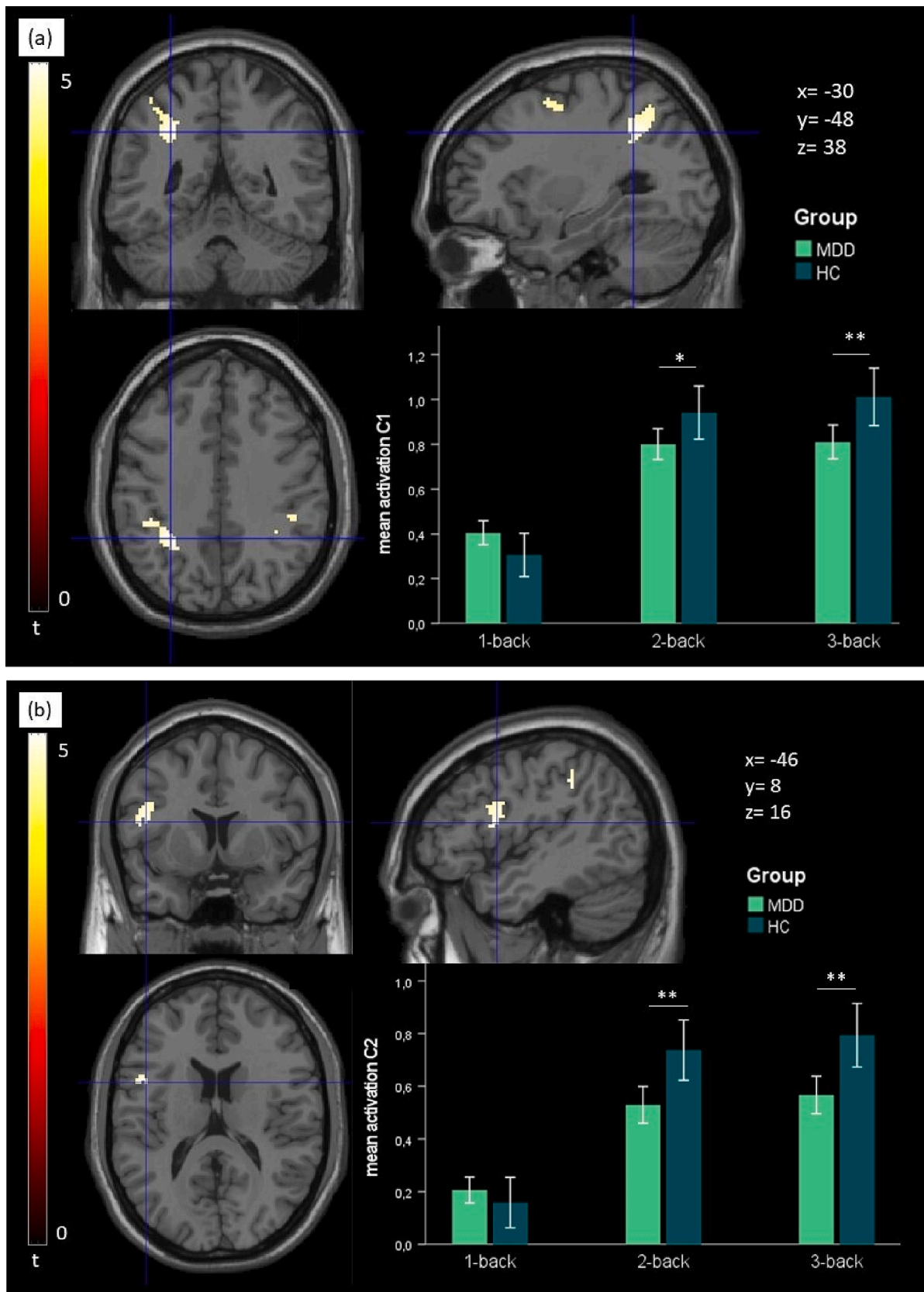
Fig. 2. Significant interaction clusters (pTFCE and peak-level FWE corrected, $p < 0.05$, cluster > 10 voxel) and their activation patterns in the n-back task. Mean and standard error of the mean for the average activation divided by group and WM load for each cluster. a) C1: Superior Parietal Lobule / Inferior Parietal Lobule, b) C2: Inferior Frontal Gyrus / Precentral Gyrus. *$p < 0.05$, *$p < 0.01$.
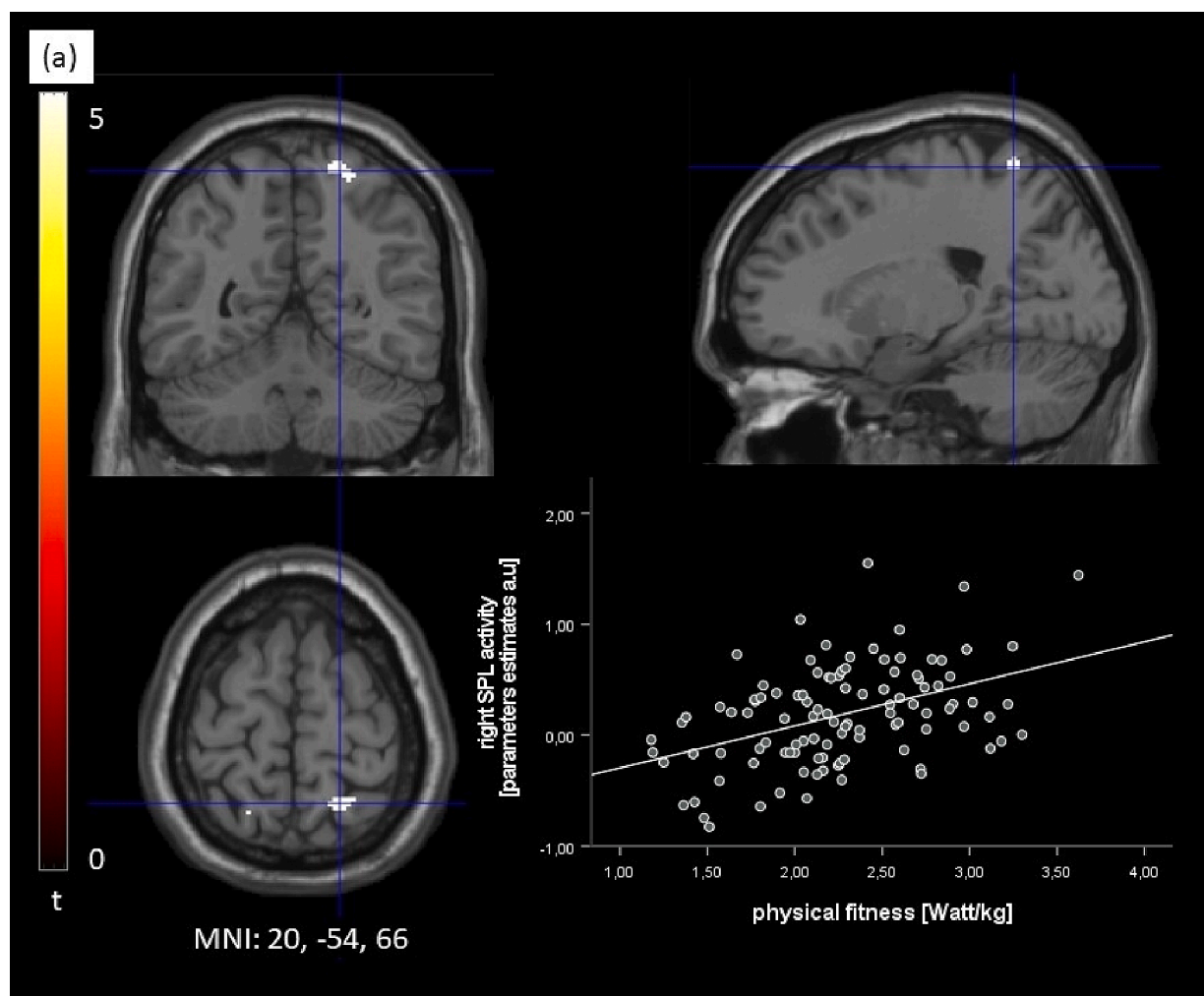
Fig. 3. Significant clusters of fitness (pTFCE and peak-level FWE corrected, $p < 0.05$, cluster ≥ 10 voxel) and their activation patterns in the n-back task. a) Right Superior Parietal Lobule / Lateral Occipital Cortex, $t = 4.84$, 37 voxels. Fitness and right SPL-activity in n-back in the MDD sample, R^2 linear = 0.19, b) Left Superior Parietal Lobule / Lateral Occipital Cortex, $t = 4.5$, 16 voxels. Fitness and left SPL-activity in n-back in the MDD sample, R^2 linear = 0.167.

the activation in the right and left superior parietal lobule.

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

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

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

4. Discussion

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

The behavioural results confirmed our hypotheses and are largely in line with previous findings of a current meta-analysis by Nikolin et al. (Nikolin et al., 2021), suggesting a WM deficit in patients with MDD. Higher RTs in all n-back conditions reflect a psychomotor slowing in MDD during the performance of the n-back task regardless of WM load and are consistent with previous findings (Nikolin et al., 2021; Bennabi et al., 2013; Buyukdura et al., 2011) and have been interpreted in terms of psychomotor retardation in depression. Performance decrements at high WM load during n-back indicate that patients with MDD have difficulties especially when higher-order executive functions such as
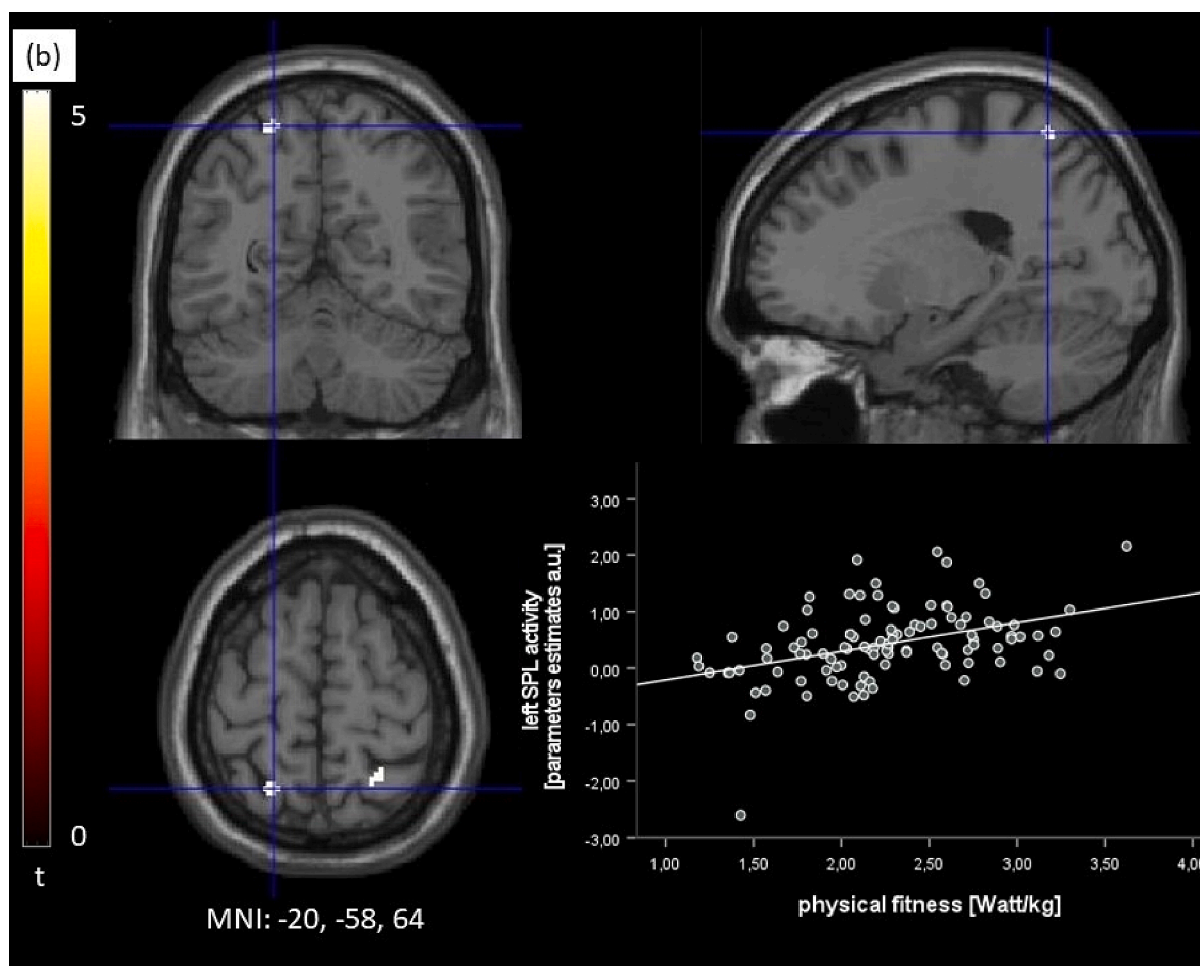
Fig. 3. (*continued*).

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

To test the WM load-dependent hypothesis in MDD compared with HC, we computed a whole-brain analysis with a brain mask of regions that are involved in working memory task. Results of the group by WM load interaction, showed significant interaction effects in six frontoparietal clusters, indicating reduced activity at high WM load in MDD. Consistent with previous (Owen et al., 2005) and current meta-analyses (Mencarelli et al., 2019) on neural activations related to the n-back task, the identified clusters belong to a frontoparietal WM network. Thus, MDD-related alterations in neural activity during WM performance point towards a malfunctioning network instead of a specific region. The largest cluster was located in left parietal cortex (SPL and inferior parietal lobule (IPL)) supporting previous results reported in Wang et al. (Wang et al., 2015). The SPL is critically important for the manipulation and rearrangement of information in WM (Koenigs et al., 2009)) and is associated with shielding external distractors and updating WM content, whereas the IPL is associated with shifting attentional focus within activated WM content during WM tasks (Nee et al., 2013). Additional clusters were located in frontal areas (middle frontal gyrus and inferior frontal gyrus) and may indicate MDD-associated impairments in executive components of WM, such as mental refreshing of recently presented triggers and updating (continuous removal and addition of information to WM) (Nee et al., 2013). These findings are in line with previous studies (Garrett et al., 2011; Meusel et al., 2013; Xia et al., 2019; Zhu et al., 2018; Wang et al., 2021; Vasic et al., 2009). Divergent

from Wang's et al. (Wang et al., 2015) meta-analysis, no frontal hyperactivations were detected in our MDD sample. While neural activity in MDD is slightly higher at low WM load compared to HC in our study, these differences were not significant in the regions that showed significant group by WM load interaction effects. It must be noted that our analyses were set up to identify MDD-related alterations in WM load-dependent activation patterns and we did not investigate group differences for individual n-back loads separately. Thus, our results show a reduced WM-dependent modulation of neural activity in MDD that is driven by reduced activation at medium and high WM load. Most studies in Wang's et al. (Wang et al., 2015) meta-analysis used WM tasks with relatively lower task demand that did not reveal any performance deficits in MDD (8 out of 10 studies). Studies that have reported frontal hyperactivations (Harvey et al., 2005; Matsuo et al., 2007; Wagner et al., 2006; Walter et al., 2007) interpreted these findings in terms of compensatory activations to maintain a normal level of performance. As described within models of compensatory activity in relation to task demand (e.g., the *CRUNCH*-model, (Reuter-Lorenz and Cappell, 2008)), performance decrements and associated reduced neural activity are expected at high task demand when compensatory attempts fail and capacity limits are exceeded (Barulli and Stern, 2013; Heinzel et al., 2014; Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010). Thus, our findings point towards a reduced neural capacity in the WM network in MDD that becomes visible especially at high WM load. Although we had a very large sample of MDD patients compared to other WM MDD studies (Wang et al., 2015), we cannot conclude that alterations in the load-dependent modulation of neural activity are specific to MDD. To answer this question, large transdiagnostic samples need to be

tested in future research.

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

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

differences in age, however, results were corrected for age differences and both behavioral and fMRI results remained significant when controlling for age. Furthermore, we did not assess the duration of the disorder systematically. In future studies, this information should be obtained and included in the statistical analyses because disease duration may have an influence on working memory performance, physical fitness and associated brain functioning.

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

5. Conclusion

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

CRediT authorship contribution statement

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

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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

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