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Physical activity and childhood trauma experiences in patients with schizophrenia or bipolar disorders

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ABSTRACT

Background: Physical activity promotes resilience and reduces stress. Here we aimed to clarify the impact of physical activity and childhood trauma experiences on current mood and cognitive function in patients with schizophrenia (SZ) or bipolar disorders (BD).

Methods: Three-hundred-and-six patients with DSM-IV schizophrenia (SZ) or bipolar disorder (BD) were included in the study. Diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Physical activity was measured as hours spent on any regular physical activity per week. All patients underwent a neuropsychological test battery. History of Childhood trauma was assessed using the Childhood Trauma Questionnaire and mood symptoms were assessed with the Inventory of Depressive Symptoms.

Results: Patients with childhood trauma who were physically inactive (<90 min per week) had the most severe clinical profile, characterised by the highest depressive symptoms (p < 0.001) and lowest performance on working memory tasks (p < 0.001). Among patients with childhood trauma, those who were physically active (\geq 90 min per week) had better working memory performance than physically inactive patients (p = 0.02).

Discussion: A history of childhood trauma was associated with poorer working memory and more depressive symptoms only in patients who were physically inactive, suggesting a possible protective factor of physical activity in severe mental disorder.

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KEYWORDS

Childhood trauma; physical activity; schizophrenia (SZ); bipolar disorder (BD); clinical features

Introduction

Childhood trauma increases the risk of developing severe mental disorders in adulthood (Varese et al. 2012), accounting for nearly 32% of severe mental disorders (Green et al. 2010). Patients with schizophrenia (SZ) who report childhood trauma experiences are more prone to adverse clinical features such as depressive symptoms, suicide attempts, and poorer functioning (Yung et al. 2015). The literature in bipolar disorder (BD) also demonstrates that patients with childhood trauma are more likely to have an earlier age of onset, more mood episodes, and suicide attempts (Daruy-Filho et al. 2011; Agnew-Blais and Danese 2016), however, studies are often small (<100 participants), lacking structured clinical interview for diagnosis and without using standardised trauma assessments (Daruy-Filho et al. 2011).

Although childhood trauma experiences are linked to the development of more severe clinical profile in schizophrenia (SZ) and in bipolar disorder (BD), treatment studies specifically focussing on childhood trauma experiences such as, for example, Eye Movement Desensitisation Reprogramming (EMDR) or trauma focussed Cognitive Behavioural Therapy (CBT) are still sparse (Alameda et al. 2020). Physical activity promotes resilience and reduces stress levels (Deuster and Silverman 2013), including reducing negative

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emotions following a stress task (Childs and de Wit 2014) and protects against adverse behavioural and metabolic consequences of stressful events (Silverman and Deuster 2014). A recent study report differences in hair cortisol as a measure of stress over time in adult patients with childhood trauma experiences (Aas, Pizzagalli, et al. 2019). Although this study was small (only 16 had moderate to severe trauma experiences), SZ and BD patients who reported childhood abuse had higher cortisol levels measured in hair than patients who did not report childhood trauma experiences, indicating long-term changes of the biological stress system, the Hypothalamus Pituitary Adrenal (HPA) Axis. It is possible that physical exercise may relieve some of the clinical burdens following childhood maltreatment experiences in SZ and BD, however, this has yet to be addressed in the literature. Studies show that interventions of at least \geq 90 min of moderate to vigorous physical activity, such as aerobic exercise, fast walking, cycling, or football playing per week have a positive effect on cognitive function (mostly studied is memory) as well as mood and physical health (Firth et al. 2015; Aas, Djurovic, et al. 2019). At a biological level, findings suggest that physical activity increases Brain-Derived Neurotropic Factor (BDNF) mRNA levels (Zoladz and Pilc 2010; Aas, Djurovic, et al. 2019). However, whether patients who report childhood trauma events with subsequent stress abnormalities (Heim et al. 2008; Pruessner et al. 2017; Aas, Pizzagalli, et al. 2019) have less severe clinical characteristics if physically active remains to be investigated. In Aas, Djurovic, et al. (2019), we found that patients who were physically active for at least 90 min per week had better working memory performance, as well as fewer depressive symptoms, compared to the inactive patients, however, the role of childhood trauma on this association was not clarified. In the current study, we investigated the role of physical activity in patients with SZ or BD diagnoses stratified into those with and without childhood trauma experiences. We hypothesised that patients with childhood trauma experiences that were physically active would do better on working memory tasks and have fewer depressive symptoms than patients reporting childhood trauma who were physically inactive, using physical activity at 90 min per week as cut-off (Firth et al. 2015; Aas, Djurovic, et al. 2019). Secondly, we hypothesised that patients who were physically active and who did not have childhood trauma experiences had the best working memory performance and the fewest depressive symptoms, whilst patients who were physically inactive with a history of traumatic

events had the poorest working memory performance and the most severe depressive symptoms. We focussed on working memory as working memory is a pivotal cognitive domain in both SZ and BD and linked to poorer illness trajectories (Flashman and Green 2004; Reichenberg et al. 2009; Bourne et al. 2013; Aas et al. 2014).

Methods

Participants and assessments

Three hundred and six patients with broad DSM-IV SZ or BD diagnoses were included in the study. Working memory was assessed by the Letter-Number Sequencing, Digit Span forwards, and Digit Span backwards (Wechsler 2003). The computation of the working memory data has been described elsewhere (Aas et al. 2012). To examine performance, raw scores within the working memory domain were averaged together. As described in Aas et al. (2012), confirmatory correlational analyses were conducted to ensure that test scores within each domain shared similar variance and could therefore be considered part of the same cognitive construct. Pearson correlation coefficient of 0.50 or higher was applied for considering the tests to belong to the same construct (Brickman et al. 2004).

Depressive symptomatology and premorbid functioning were measured by the Inventory of Depressive Symptoms (IDS) and the National Adult Reading Test (NART) (Rush et al. 1996; Vaskinn and Sundet 2001), respectively. Remission status was assessed by the Structured Clinical Interview for DSM-IV (Spitzer et al. 1992), and current anxiety was measured by the Positive and Negative Syndrome Scale (PANSS) item G2 (Kay et al. 1987). The PANSS subitem for anxiety was the only measure available for current anxiety symptoms across both disease groups. Positive, negative and general psychopathology was also assessed by the PANSS subscales (Kay et al. 1987). Symptom severity and function were rated separately by the split version of the Global Assessment of Functioning Scale (GAF; Pedersen et al. 2007). The current elevated mood was captured using the Young Mania Rating Scale, YMRS (Young et al. 2000). Substance use was assessed by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al. 1993) and the Drug Use Disorders Identification Test (DUDIT) (Berman et al. 2005). A detailed description of the recruitment process of the study, as well as clinical, and cognitive assessments, are described in Aas, Djurovic, et al. (2019) and Aas et al. (2012). Moreover, a history of childhood maltreatment was collected using the Childhood Trauma Questionnaire (CTQ; see Aas et al. 2012). Trauma was defined as having at least one subtype of childhood maltreatment reaching a level of moderate to severe childhood trauma from CTQ (Bernstein et al. 1994). Physical activity was assessed by self-report of time spent on any physical activity per week (see Aas, Djurovic, et al. 2019). Self-reported physical activity has been found to have high validity (Kurtze et al. 2008). The calculated Defined Daily Dose (DDD) of medication was calculated in accordance with the guidelines from the World Health Organisation Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atcdd). DDD and chlorpromazine equivalent (CPZeq) methods are compatible in calculating total antipsychotic dose (Sweileh et al. 2014). The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. All participants gave written informed consent. The participants were divided into 4 groups; *active*: Physical activity (>90 min of physical activity per week compared to *inactive*: < 90 min of physical activity per week) stratified into those with a history of childhood trauma, Trauma, and those without a history of childhood trauma, non-Trauma.

Statistics

Data were analysed using the Statistical Package for Social Sciences, Version 25.0 (IBM company). A Chisquare test was performed to assess reports of physical activity (\geq 90 min compared to <90 min) stratified into those with and without a history of childhood trauma. As both the physical activity and childhood trauma data were skewed also after log transformpredefined cut-off scores were applied ation, (Bernstein et al. 1994; Firth et al. 2015). Working memory and IDS were log-transformed before added into the parametric analyses. Ninety minutes of physical activity per week was both the median of time reported in our sample, as well as the time recommended to have an effect on cognition, mood and physical health in the meta-analysis by Firth et al. (2015). Analyses of Variance (ANOVA) and Analyses of Covariance (ANCOVA) were performed stratifying the sample into four groups based on reports of physical activity and childhood trauma (active/no trauma, inactive/no trauma, active/trauma, and inactive/ trauma; see Figures 1 and 2). Post hoc comparisons between the four groups were Bonferroni corrected. As age, sex and diagnosis (SZ or BD) can influence the cognitive and clinical features investigated in this study, these variables were added as confounders in the model. Further, to rule out that neuroleptics influenced cognitive performance or differences in clinical characteristics between groups, use of medication (yes, no) was entered into the model a confounder. To control for the possibility of cognition being affected by disease status (secondary to the disease), which could bias the relationship between physical activity and working memory during disease onset, we also adjusted for premorbid IQ. We computed Cohen's d as an estimate of effect size (Cohen 1977). Lastly, sensitivity analyses were conducted to rule out that substance

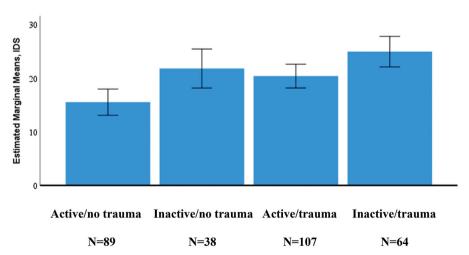
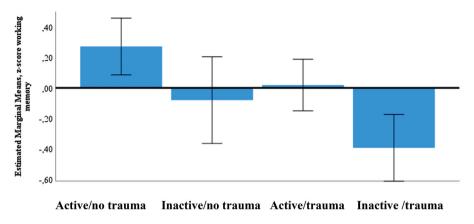


Figure 1. Childhood trauma, physical activity and Inventory of Depressive Symptoms (IDS). ANCOVA, F = 4.59, p = 0.004. Adjusted for age, sex, medication and diagnosis. Higher score equals more depressive symptomatology. Bonferroni corrected group comparison: active/no trauma vs. inactive /trauma: p < 0.001, Cohen's d = 0.73. No other statistical significant group differences were observed. Inactive ≤ 90 min of physical activity per week. Active ≥ 90 min of physical activity per week. Figure presents the mean and standard deviation, SD.



N=89 N=38 N=107 N=64

Figure 2. Childhood trauma, physical activity and working memory. ANCOVA, F = 6.21, p < 0.001. Adjusted for age, sex, medication, and diagnosis. Lower score equals lower functioning. Compare groups: active/no trauma vs. inactive /trauma: p < 0.001, Cohen's d = 0.73. Compare groups: active/trauma vs. inactive/trauma: p = 0.02, Cohen's d = 0.50. No other statistical significant group differences were observed. Inactive ≤ 90 min of physical activity per week. Active ≥ 90 min of physical activity per week. Figure presents the mean and standard deviation, SD.

use assessed by AUDIT and DUDIT, anxiety symptoms (measured by PANSS item G2) or being in a mood or psychotic episode influenced the results. The threshold for statistical significance was set at p < 0.05.

Results

Physical activity and childhood trauma

There was no significant difference in reports of childhood trauma in the physically active versus inactive group ($\chi^2 = 1.82$, df = 1, p = 0.18). The mean age of the total sample was 29 and 50% were males. 58% (n = 177) had an SZ diagnosis and 42% (n = 129) had a BD diagnosis. 86% of the patients were taking regular psychotropic medication. Of the patients who were treated with antipsychotic medication (n = 215), 95% received second-generation antipsychotic medication. No difference in antipsychotic medication Daily Defined Dose (DDD) was observed between the groups, see Table 1. The majority of patients with bipolar disorder had at least one lifetime psychotic episode (n = 73, 59%). No difference in age, sex, BMI, medication, or being in a mood episode was observed between the physically active and the inactive group. The inactive group had significantly poorer working memory and more depressive symptoms than the active group (See Table 1). Patients in the active/no trauma group were less likely to be in a current psychotic episode or have a diagnosis of SZ compared to the other groups. Patients in the physically active group with no trauma did better across the clinical and cognitive assessments adjusted for age, medication, sex, and diagnosis (SZ/BD), see Table 1.

Investigating the clinical and cognitive characteristics more in detail showed differences at trend or significance level within the trauma subgroup for depressive symptoms and working memory. ANCOVA analyses revealed a significant difference in depressive symptoms and working memory scores across groups (see Table 1, Figures 1 and 2, ANCOVA, F = 4.59, p = 0.004, and F = 6.21, p < 0.001, respectively). The most severe depressive symptoms and lowest working memory functioning was observed in the inactive/ trauma group. Analyses were adjusted for age, medication, sex, and diagnosis (SZ/BD). Post hoc Bonferroni corrected tests showed that the active/trauma group had a trend level (p = 0.08) of less severe depressive symptom severity compared to the inactive/trauma group. The active/trauma group did better on working memory tasks compared to the inactive/trauma group (p = 0.02, Cohen's d = 0.50). Follow-up analyses showed that the findings remained after adjusting for premorbid IQ from the NART. The largest differences for both depressive symptoms and working memory performance were observed between the active/no trauma vs. the inactive/trauma group (p < 0.001, Cohen's d = 0.73 for both depressive symptoms and working memory, see Figures 1 and 2). Sensitivity analysis revealed that group differences in working memory in the active/no trauma vs. the inactive/trauma group remained after adjusting for current depressive symptoms (F = 8.37, p < 0.001, Cohen's d = 0.50), being in a mood or psychotic episode (F = 7.06, p < 0.001, Cohen's d = 0.70; F = 6.71, p < 0.001, Cohen's d = 0.70, respectively), substance use from AUDIT and DUDIT (F = 7.63, p = 0.007, Cohen's d = 0.50), or current

Posthoc

1 < 2,3,4

1 < 2,3,4

1 < 4

1 > 4

< 4, 3 < 4

	1	2	3	4		
	Active/no trauma	Inactive/no	Active/	Inactive/trauma		
	(<i>n</i> = 89)	trauma (<i>n</i> = 38)	trauma (<i>n</i> = 107)	(<i>n</i> = 64)	Statistics	F
Age, mean ± SD	30.9 ± 12.8	28.5 ± 9.5	29.5 ± 9.9	29.6±9.6	F = 0.57, p = 0.64	
Sex, males, n (%)	48 (53.9)	20 (52.6)	52 (48.6)	31 (48.4)	$\chi^2 = 0.75, p = 0.86$	
Antipsychotic medication, DDD mean \pm SD	1.0 ± 0.7	0.8 ± 0.4	1.0 ± 0.7	0.9 ± 0.6	F = 0.78, p = 0.50	
Antipsychotics, n (%)	64 (71.9)	32 (84.1)	75 (70.0)	44 (68.8)	$\chi^2 = 3.35, p = 0.34$	
Mood regulators, n (%)	34 (38.2)	12 (31.6)	31 (29.0)	20 (31.3)	$\chi^2 = 1.99, p = 0.58$	
Antidepressants, n (%)	23 (25.8)	17 (44.7)	35 (32.7)	25 (39.0)	$\chi^2 = 5.41, p = 0.14$	
BMI, mean \pm SD	26.2 ± 4.8	25.9 ± 6.6	26.4 ± 5.7	26.8 ± 5.0	F = 0.28, p = 0.84	
AUDIT, mean \pm SD	6.8 ± 6.0	9.7 ± 7.2	7.6 ± 7.2	7.3 ± 8.4	F = 1.30, p = 0.27	
DUDIT, mean \pm SD	1.8 ± 4.4	4.2 ± 6.6	3.5 ± 7.9	3.2 ± 6.9	F = 1.50, p = 0.22	
Diagnosis, SZ n (%)/BD n (%)	39 (43.8)/50 (56.2)	23 (60.5)/15 (39.5)	67 (62.6)/40 (37.4)	42(65.6)/22 (34.4)	$\chi^2 = 9.82, p = 0.02$	
Current in a psychotic episode, yes %	28 (32.6)	20 (57.1)	56 (52.8)	32 (51.6)	$\chi^2 = 10.61, p = 0.01$	
Current in a mood episode, yes %	15 (17.0)	10 (28.6)	23 (21.7)	17 (28.3)	$\chi^2 = 3.33, p = 0.33$	
IDS, mean \pm SD ^{\$}	15.3 ± 9.2	22.0 ± 11.2	20.4 ± 11.7	25.1 ± 13.3	F = 4.59, p = 0.004	
Working memory, mean \pm SD ^{#\$}	0.3 ± 1.0	-0.06 ± 0.8	0.02 ± 0.9	-0.4 ± 0.8	F = 6.21, p < 0.001	1 <
PANSS, positive symptoms, mean \pm SD ^S	12.3 ± 5.2	13.1±4.8	14.8 ± 5.4	14.76 ± 5.21	F = 3.16, p = 0.025	
PANSS negative symptoms, mean \pm SD ^{\$}	12.2 ± 6.1	16.0±7.9	13.9 ± 5.9	13.8 ± 5.2	F = 1.84, p = 0.14	
PANSS general symptoms, mean \pm SD ^{\$}	28.1 ± 8.5	32.5 ± 8.6	33.0 ± 9.4	32.6 ± 8.6	F=3.48, p=0.017	
GAF-F, mean \pm SD ^{\$}	49.8 ± 13.8	42.8 ± 10.6	42.9 ± 10.4	42.9 ± 10.4	F = 4.39, p = 0.005	
GAF-S, mean \pm SD ^{\$}	50.6 ± 14.0	43.1 ± 12.3	44.2 ± 13.1	43.2 ± 11.3	F = 3.24, p = 0.02	

Bonferroni adjusted posthoc tests.

SZ: schizophrenia; BD: bipolar disorders; IDS: Inventory of Depressive Symptomatology; BMI: body mass index; DDD: daily defined dose.

*At least one subtype of childhood trauma reaching level of moderate to severe childhood trauma from the Childhood Trauma Questionnaire (Bernstein et al. 1994). 2 patients in the inactive group and 6 participants in the active group had missing data on childhood trauma, giving a total sample of 298. For a full demographic description, see Aas et al. Aas et al. (2019a). #z-Scores based on healthy controls mean and standard deviation (see Aas et al. 2014 for detailed information). ^SAdjusted for sex, age, antipsychotic medication (yes/no), mood stabilisers (yes/no), antidepressants (yes/no), and diagnosis (schizophrenia, bipolar disorders).

anxiety from PANSS (F = 5.54, p = 0.001, Cohen's d = 0.60). Within the BD patients currently in an active mood episode, 79% were in a depressive state, while whilst 13% were in a current mixed episode and 8% in an elevated mood episode. Separating into SZ and BD showed that SZ patients with trauma who were physically active did better on working memory tasks than the group with trauma that was physically inactive (p = 0.019), however, this was no longer statistically significant in BD, see Supplementary Material Tables S1 and S2.

Discussion

Our study demonstrated that patients with SZ or BD who reported a history of childhood trauma had poorer working memory performance and more severe depressive symptoms if they were physically inactive. Patients with childhood trauma who were physically active did not have significantly more severe working memory impairments or more depressive symptoms than patients without a history of childhood trauma. Our findings were adjusted for current medication use. These cross-sectional findings are in line with the hypothesis that physical activity is important and suggest physical activity as a potential low-cost treatment option in adult patients with childhood trauma experiences. In fact, moderate to large effect size differences were observed for depressive symptoms and working memory comparing the active/no trauma vs. the inactive/trauma group (Cohen's d = 0.73), indicating the clinical relevance of both physical activity and childhood trauma within this population. To disentangle the role of trauma and physical activity we then compared the active/trauma to the inactive/trauma group demonstrated moderate effect size differences (Cohen's d = 0.50) for better working memory in the group with trauma who were physically active. These moderate effect sizes clearly indicate the clinical relevance of physical activity, especially in individuals with early traumatic experiences. From the neuronal diathesis-stress perspective, chronic exposure to stress is harmful to the brain, and psychopathology is a potential consequence of this exposure in vulnerable individuals (Walker and Diforio 1997; Pruessner et al. 2017), supported by long-term changes of the HPA axis in adults with childhood trauma experiences (Heim et al. 2008; Aas, Pizzagalli, et al. 2019). A recent meta-analysis suggests that physical activity promotes a reduction in cortisol levels in individuals with a mental illness (Beserra et al. 2018), possibly due to an upregulation of glucocorticoid receptors (Stranahan et al. 2008). Moreover, physical activity promotes a positive self-concept and improves stress management (Alfermann and Stoll 2000). We postulate that physical activity, in conjunction with regular treatment may reduce the physiological or subjective stress response, and potentially lessen some of the adverse longterm effects of childhood trauma in SZ and BD.

Given the importance of childhood trauma in the prognosis and illness course of patients with SZ and BD (Nemeroff 2016; Teicher et al. 2016; Pruessner et al. 2017), evidence-based interventions addressing long-term effects of trauma experiences are needed (Alameda et al. 2020). Although there was no difference in body mass index between groups in the current study, a history of childhood trauma has been associated with higher body mass index and C-reactive protein (CRP) (Aas et al. 2017; Moraes et al. 2017) and poorer physical health behaviour in general (Grigsby et al. 2020) demonstrating the need to improve physical health in individuals with trauma experiences.

The current study has several limitations. We asked participants how many hours of physical activity they normally performed each week without information about the type of activity. However, a review by Firth et al. (2015) concluded that any moderate to vigorous exercise including jogging, cycling, sports or resistance training, independent of the type and with a duration of at least 90 min per week has a positive effect on mood symptoms and cognitive functioning, supporting our broad non-specific approach to physical activity. However, it should be mentioned that 90 min maybe a rather arbitrary cut-off. Furthermore, our study only included a self-reported estimate of physical activity, thus more objective measures of activity would be helpful, in particular in case-control comparisons (Firth et al. 2018). Albeit, within-patient population self-report has been found to correlate with objective measures (Firth et al. 2018), and we only investigated physical activity within the patient group. We have ruled out that those with better premorbid cognitive functioning exercised more and thus had better working memory after illness onset. Our crosssectional study cannot answer a question about causality. However, despite the limitations, our paper highlights that not all patients with childhood trauma experiences have poorer cognition and more severe current symptoms. In fact, this is not found in physically active patients. This is important new information that should be used to set up furthermore controlled studies to test the hypothesis of physical activity as a buffer against the negative consequences of severe stressors on the body and mind.

It is also a common belief that trauma needs to be of a certain character of severity to influence clinical features of mental illness in adulthood (Bernstein et al. 1994) which is why moderate to severe trauma scores were chosen for this study. Also, the physical activity scores were skewed, thus we chose to use the same predefined cut-off scores for physical activity as previous studies (Firth et al. 2015; Aas, Djurovic, et al. 2019). Information on childhood trauma was collected using the CTQ, which is a retrospective assessment with the inherited weakness of its retrospective design. A recent meta-analysis suggests a low overlap between retrospective and prospective collection of childhood trauma (Baldwin et al. 2019). However, the study by Baldwin and colleagues reported a large degree of heterogeneity between samples. It could be due to the different inclusion of trauma cases in prospective versus retrospective data. Reassuringly, both prospective and retrospective data collection have shown to be associated with a similar outcome, demonstrating convergent validity (Tajima et al. 2004). However, as Widom (2019) emphasises (Widom 2019), cross-sectional studies based on retrospective reports cannot conclude that childhood adversities cause particular outcomes. Future studies should aim to clarify and adjust for potential recall biases in retrospective assessments. 86% of the patients were treated with psychopharmacological agents at the time of the assessment (antipsychotics, mood stabilisers or antidepressants) which could have influenced the variables tested. However, there was no difference in the number of participants on antipsychotics, mood stabilisers or antidepressants in the physical active compared to the inactive group, and analyses in the Result section were adjusted for medication, thus it is unlikely that the use of medication has significantly influenced our results.

It should also be mentioned that the IDS was originally designed to measure depressive symptoms in MDD and BD, however, the scale is reported to be valid also in patients with psychotic features (Rush et al. 2006). A shorter version of the IDS (the Quick Inventory of Depressive Symptomatology-Self-Report) has also been validated in SZ (Ma et al. 2015). To rule out that current symptoms or substance use influenced the relationship between physical activity and working memory, sensitivity analyses were performed adjusting for current depressive or anxiety symptoms, being in a current mood or psychotic episode, or substance use. It should be mentioned that only a subitem from the PANSS was used to measure anxiety covering anxiety symptoms during the last seven days. Lastly, the four groups separated by activity level and trauma had different N per group, ranging from n = 38 to n = 107, however the two groups that may be most interesting (both reporting childhood trauma with and without 90 minutes of physical activity per week), were relatively large, and both groups had n above 50 (n = 107, and n = 64, respectively), strengthening the statistical power in the analysis.

To sum up: Our findings support physical activity as a potentially important factor in severe mental disorders. There is a need to clarify if physical activity can relieve some of the long-term pathophysiological characteristics following childhood trauma experiences in adults with severe mental disorders.

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Disclosure statement

None to declare.

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