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Changes in inflammation are related to depression and amount of aerobic exercise in first episode schizophrenia

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Abstract

Introduction—Elevated levels of pro-inflammatory cytokines have been reported in meta-analyses of multi-episode schizophrenia patients when compared to controls. However, little is known about whether these same relationships are present in the early course of schizophrenia.

Objective—To assess first episode schizophrenia patients for depression and to assay blood samples collected at baseline and at 6 months for interleukin-6 (IL-6).

Materials and Methods—Trained raters used the Brief Psychiatric Rating Scale to assess depressive symptoms and a standard lab assay kit to assess for IL-6 levels in plasma.

Conclusions—Decreases in pro-inflammatory IL-6 levels were significantly related to decreases in depressive symptoms. Within a subset of patients in a 6-month aerobic exercise protocol, the number of exercise sessions completed was significantly correlated with the amount of decrease in IL-6. The reductions observed in IL-6 with aerobic exercise suggest exercise is a promising intervention to reduce brain inflammation effects in schizophrenia patients.

Keywords

aerobic exercise; BPRS; depressive symptoms; first episode schizophrenia; IL-6; inflammation

1 | INTRODUCTION

1.1 | Broad overview

Research continues to show that persistent inflammation may be one mechanism through which genetic, biological or environmental risk factors might impact the psychopathology of schizophrenia. Elevated circulating levels of pro-inflammatory cytokines have been reported in meta-analyses of patients with established schizophrenia when compared to normal

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DATA AVAILABILITY STATEMENT

Permission to share data was not obtained from participants.

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controls (Müller, Weidinger, Leitner, & Schwarz, 2015). Similar findings were described in a meta-analysis in first episode schizophrenia patients for cytokines such as interleukin-1 beta (IL1β), soluble interleukin-2 receptor (sIL2r), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) (Upthegrove, Manzanares-Teson, & Barnes, 2014). Certain cytokines might be key participants in the regulation of neuro-inflammation in schizophrenia. Specifically, IL-6, a pro-inflammatory cytokine, might act as a primary regulator. In fact, in patients with schizophrenia, IL-6 has been associated with the severity of various types of symptoms in cross-sectional analyses (Dahan et al., 2018; Goldsmith et al., 2018). In particular, researchers have found that a depressive symptom profile of first episode psychosis (FEP) patients was significantly associated with pro-inflammatory cytokines IL-6, TNF-alpha and IL-17 (Noto et al., 2015). Still, little is known about the role these cytokines play in first episode schizophrenia patients, how they behave over time, and how best to reduce their adverse impact.

1.2 | The link between brain inflammation and depression

The pro-inflammatory cytokine IL-6 has been linked to the severity of depressive symptoms in patients with schizophrenia, major depression disorders and bipolar disorder (Brietzke et al., 2009; Frommberger et al., 1997; Sasayama et al., 2013). Using structured assessments of psychiatric symptoms, most of the studies have found that elevated levels of IL-6 in patients with schizophrenia, major depressive disorder and bipolar illness were associated with the severity of depressive symptoms (Brietzke et al., 2009; Frommberger et al., 1997; Sasayama et al., 2013). Interestingly, after remission, IL-6 concentrations in depressed and schizophrenia patients were reported to decrease to levels that did not differ significantly from controls. In a more recent study, FEP patients with moderate or severe depressive symptoms had higher levels of the pro-inflammatory cytokines IL-4 and TNF-α compared to those patients without depression (Noto et al., 2015). The authors hypothesized that these increased levels of depressive symptoms were linked with their observation that FEP had increased levels of IL-6 (compared to controls). This suggested to the authors that a related cytokine IL-6 acts as a mediator in the physiology and pathology of schizophrenia. These studies suggest the presence of IL-6 might be an important biomarker that is associated with several aspects of psychopathology and so is an important treatment target. However, there are no longitudinal studies on this topic in FEP.

1.3 | Exercise as a treatment that reduces inflammation

The beneficial impact of exercise has been widely associated with capitalizing on the inherent plasticity of the immune and neuroendocrine systems. In the general population of adults, exercise has been shown to prevent age-related cognitive decline and to reduce the risk of long-term inflammatory illnesses and age-associated inflammation (Simpson & Bosch, 2014). In addition, studies have found positive outcomes associated with physical exercise in several psychiatric populations including patients with schizophrenia (Dauwan, Begemann, Heringa, & Sommer, 2015; Gómez-Rubio & Trapero, 2019; Knöchel et al., 2012). In the only study on this topic, the effects of one exercise session (<30 minutes) on heart rate variability and IL-6 suggested that exercise might lower the overall levels of inflammation in schizophrenia patients (Ostermann et al., 2012). However, the relationship between a regular physical exercise intervention and inflammatory cytokines has not been

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examined in schizophrenia. Although the mechanism by which exercise impacts symptoms in patients with schizophrenia still remains unclear, the role of the immune system and the anti-inflammatory response seems to be a promising direction. Although preliminary, this promising work suggests exercise as a specific intervention for the reduction of pro-inflammatory cytokines associated with depression or other co-morbidity in schizophrenia. However, there are no studies in first episode patients examining the potential beneficial effects of exercise on IL-6.

2 | METHODS

2.1 | Subjects

The sample consisted of 25 first-episode schizophrenia patients who were on average 22.6 (3.7) years old (range: 18–35) and had 13.1 (1.5) years of education (range: 11–16). All patients were required to have had an initial onset of psychosis within 2 years of study entry and had an average psychosis onset at age 21.4 (3.7) years. In fact, most patients had a very recent psychotic episode onset averaging less than 9 months prior to the study entry, M = 8.1 (SD = 6.0) months (range: 1–22 months). All patients met DSM-IV criteria for schizophrenia, paranoid subtype (n = 3, 12%), schizophrenia catatonic subtype (n = 1, 4%), schizophrenia, undifferentiated subtype (n = 14, 56%), schizophreniform disorder (n = 5, 20%) or schizoaffective disorder depressed type (n = 2, 8%) based on the Structured Clinical Interview for DSM-IV (SCID-IV) which was administered by trained raters (Ventura et al., 1998). Exclusion criteria were (a) evidence of a neurological disorder, (b) evidence of significant and habitual drug abuse or alcoholism in the 6 months prior to hospitalization or of substance use that triggered the psychotic episode, and (c) estimated IQ <70.

2.2 | Procedures

All patients were enrolled in the UCLA Aftercare Research Program, an outpatient clinic that provides treatment in the form of antipsychotic medication, individual case management, psychoeducation, family education and group and individual therapy focused on recovery and practical life skills. Patients were participants in a randomized controlled trial of Cognitive Training alone vs Cognitive Training & Exercise (CT&E; for theoretical rationale and design, see (Nuechterlein et al., 2016). The in-clinic training consisted of a combination of moderate intensity aerobic exercises (1-minute intervals) and moderate to high intensity strength and callisthenic conditioning (1-minute intervals) for 45 minutes twice a week. Participants were instructed on correct technique and form for five different exercises and completed three rounds of the five sets of the aerobic and strength training. The at-home exercise program was similar to the in-clinic program and consisted of two 30-minutes sessions per week in which the patient was encouraged to achieve the same exercise goals. Total exercise time = 150 minutes per week. All patients were initially assessed at baseline after being on a stable outpatient dose of oral risperidone for at least 3 weeks. Using the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993), symptoms were assessed at baseline and monitored every 2 weeks up to the 6-month study end point. Patient’s blood levels were assayed for the cytokine IL-6 collected at two points, baseline and 6 months using previously reported methods (Kruse et al., 2018). All participants gave written informed consent prior to data collection.

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3 | RESULTS

Using Pearson correlation coefficients, we examined the relationship between baseline to 6 month changes in the pro-inflammatory cytokine IL-6 and the changes in depression from baseline to the 6-month follow-up point. We found that decreases in levels of IL-6 were significantly related to decreases in BPRS depressive symptoms (n = 25, $r = .40$, $P = .04$) over the 6 months of study. Within the CT&E group, we found that the relationship between decreases in IL-6 and decreases in depression was also present and significant (n = 13, $r = .55$, $P = .05$). Furthermore, within the CT&E group the number of aerobic exercise sessions completed by the participant was significantly correlated with the amount of reduction in inflammation as measured by IL-6 (n = 13, $r = -.63$, $P = .02$) (Figure 1).

4 | DISCUSSION

This is the first study to examine the longitudinal relationship between change in cytokine levels and change in depressive symptoms in first episode schizophrenia patients. The study findings indicate that a decrease in a pro-inflammatory cytokine was associated with a decrease in depressive symptoms during the first 6 months of outpatient treatment. These findings are conceptually consistent with a previous study of drug native first episode schizophrenia patients showing a relationship between higher levels of pro-inflammatory cytokines IL-4 and TNF-alpha and depressive symptoms (Noto et al., 2015). However, those studies reported on cross-sectional analyses rather than longitudinal assessments. We hypothesized that decreases over time in depressive symptoms in schizophrenia would be associated with decreases in IL-6. Associations found in this study between cytokine level and depression support previous research suggesting that inflammation might have deleterious effects on the early course of symptoms in schizophrenia. These prior and current findings provide additional evidence for IL-6 as a possible target for intervention in schizophrenia.

Because we found a relationship between brain inflammation, as indicated by IL-6 levels, and depression, we examined the effects of aerobic exercise on inflammation as a treatment target. Exercise can play important role in promoting brain plasticity, leading to improvements in brain function and mitigating age-related increases in inflammation (van Praag, 2009). Specifically, aerobic exercise has been shown to afford many positive effects in schizophrenia patients, including reductions in psychiatric symptoms (Firth, Cotter, Elliott, French, & Yung, 2015). As far we know, this is the first study in schizophrenia patients in the early phase of illness to examine the effects of exercise on inflammation as measured by IL-6. We found that the amount of participation in exercise sessions was associated with reduction in IL-6. These reductions suggest that exercise may be a promising non-psychopharmacological intervention to reduce the deleterious effects of brain inflammation in schizophrenia. One of the important determinants of premature mortality among people treated for psychosis is cardiovascular disease which is strongly linked to elevated inflammation (Willerson & Ridker, 2004). This study adds to the encouraging literature from the normal aging population on the implementation of a regular exercise program to modulate IL-6 levels to promote good physical health in individuals with FEP. Study limitations include the small sample size and the correlational design. The study was

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correlational so directionality can only be inferred from the examination of changes over time. Whether IL-6 contributes to depression or vice versa is unclear. However, the possibility that IL-6 levels influenced the amount of exercise participation does not seem plausible. Another limitation is the inability to control for other relevant variables such as medication effects or other biological parameters.

Evidence is continuing to mount that indeed IL-6 is an important index for brain-inflammation-related psychopathology in schizophrenia and for the beneficial effects that exercise has on depression. The role that IL-6 plays in the development and symptomatology of schizophrenia in only starting to be better understood.

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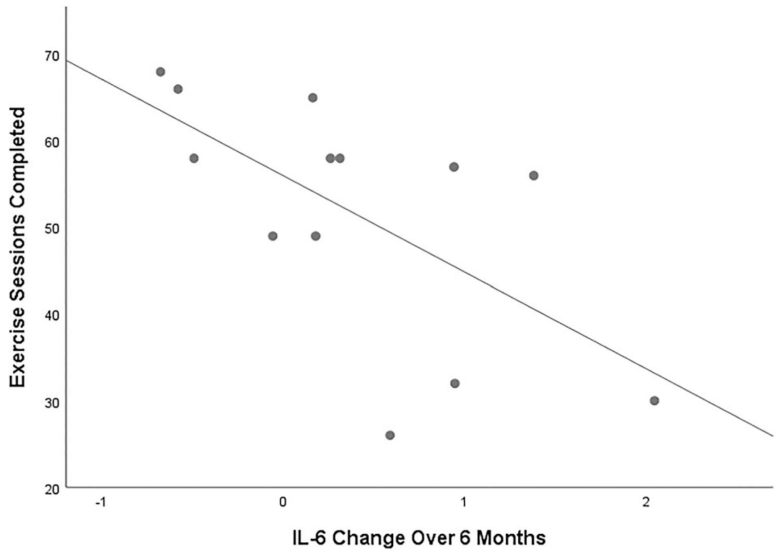

FIGURE 1.

Scatter plot of the relationship between exercise sessions completed in the CT&E group and IL-6 change over 6 months. CT&E, Cognitive Training & Exercise; IL-6, interleukin-6