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The association between cardio-respiratory fitness and cognition in schizophrenia☆

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ABSTRACT

Objective: Schizophrenia is associated with reduced cardio-respiratory fitness (CRF), and impaired cognition is a core feature of the disorder. Despite their particular significance to schizophrenia disparately, the relationship between these two variables has not yet been thoroughly assessed. In this study we aimed to investigate naturally occurring associations between CRF and all cognitive domains within this patient population.
Method: Eighty outpatients with schizophrenia spectrum disorders participated in the study. Neurocognition was assessed with the Wechsler Adult Intelligence Scale version 4 General Ability Index (WAIS GAI) and the MATRICS Consensus Cognitive Battery (MCCB). Oxygen uptake was measured directly by analyzing O_2 and CO_2 content in expired air during a maximum exercise session on a treadmill using a modified Balke protocol. Clinical symptom load was assessed with the Positive and Negative Syndrome Scale (PANSS). Hierarchical multiple regression analyses were conducted, controlling for sex and age, and negative psychotic symptom levels.
Results: CRF explained a significant 8.2% and 9.1% of the variance in general intellectual ability and state-sensitive cognitive functioning respectively, beyond the impact of negative psychotic symptom load.
Conclusion: The study indicates a direct relation between CRF and cognition in schizophrenia. Impaired cognition is a difficult-to-treat expression of the disorder, and identifying modifiable factors possibly mediating cognition, such as CRF, is of great clinical value.

1. Introduction

At group level, schizophrenia patients display profoundly low cardio-respiratory fitness (CRF; Scheewe et al., 2012, Heggelund et al., 2011, Strassnig et al., 2011). Low CRF increases the risk of cardiovascular disease (CVD; Laursen et al., 2014, Wildgust and Beary, 2010), which is the largest single cause of death in schizophrenia (Hennekens et al., 2005). Moreover, impaired cognition is a central clinical feature in schizophrenia (Dickinson et al., 2008). The naturally occurring associations between CRF and cognitive functions have not been thoroughly investigated in this particular patient group.

Several lines of research have indicated an association between CRF and cognition in the general population (Voss et al., 2011; Etnier et al., 2006). In a large-scale cohort study on young men aged 15 to 18 years by Åberg et al. (2009), small to moderate correlations were found between CRF and all measured cognitive functions, including full-scale IQ. In a review including all age groups and both cross-sectional, cohort, and intervention studies, Hötting and Röder (2013) concluded that physical exercise is positively associated with cognitive functioning, and that the effects are specific to both type of exercise and age group. Evidence is scarcer on the relationship between CRF and cognition in schizophrenia patients. Kimhy et al. (2014) investigated naturally occurring associations between CRF and the subset of cognitive functions included in the MATRICS Consensus Cognitive Battery (MCCB) in a sample of 32 schizophrenia patients. Positive correlations were reported for the specific domains of executive functioning, working memory, processing speed and social cognition, and CRF was found to explain a substantial 22% of the variance in the overall MCCB composite score. The authors conveyed the findings as preliminary and called for replication in a larger sample. Several exercise intervention studies have also shown positive effects from enhanced CRF on particular cognitive domains in schizophrenia. A recent meta-analysis by Firth et al. (2016) included 10 studies, whereof six reported positive changes in one or more cognitive domains. The meta-analysis was conducted on a total of 186 participants in CRF-enhancing exercise activities and 199 control subjects, and revealed that exercise interventions significantly improved overall cognitive performance. The authors concluded that the effect was robust, with an effect size of $g = 0.33$ and low statistical

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heterogeneity between studies. Regarding specific domains, significant effects were found for working memory, attention/vigilance, and social cognition.

Cognitive impairment is deemed a core feature of schizophrenia, albeit its connections to the most prominent clinical features continue to be under investigation and debate (Bagney et al., 2015; Ventura et al., 2010; Reichenberg and Harvey, 2007). The impairment has been conveyed as global, although with differences in magnitude on the functions affected, and large individual variations in degree and profile of impairment (Dickinson et al., 2008; Reichenberg and Harvey, 2007; Weickert et al., 2000). It may be that these and other disorder-related circumstances elicit a different relationship between CRF and cognition in schizophrenia, compared to the general population. This may occur in at least two different ways, paved in opposite directions. Firstly, negative psychotic symptoms may compromise the participants' engagement and lead to subability performance in both the physical and neurocognitive testing situations. This may inflate the association between CRF and cognition, and thus create an artificial relationship between the two variables in a given sample. This risk may be countered through controlling for negative psychotic symptom load. Secondly, the direct expression of the disorder in impaired cognition may overshadow any associations to other factors such as CRF, and thus obscure a true relationship between the two variables. Furthermore, the association with CRF may differ between types of cognitive functions. The cognitive impairments in schizophrenia appear to be most pronounced in memory, attention, executive functions, and processing speed (Dickinson et al., 2008; Reichenberg and Harvey, 2007; Nuechterlein et al., 2004). Several other lines of evidence suggest that these functions are more responsive to changes in psychological and physiological state, as compared to the functions that comprise general intellectual ability (IQ). Heritability estimates are lower for the former (Knopik et al., 2013); the functions of verbal learning, memory and psychomotor speed appear more prone to be temporarily negatively influenced by other mental illnesses such as depression (Douglas and Porter, 2009); and in the described intervention studies the effect of improved CRF appeared limited to, or more pronounced in, the domains of working memory, attention/vigilance, processing speed, and visual and verbal learning (Firth et al., 2016). Thus, these functions may be more prone to the influence of factors such as CRF. For this reason, and for the sake of simplicity, we henceforth refer to memory, attention, executive functions, and processing speed as *state-sensitive* cognitive functions, as compared to the core *IQ* functions of verbal comprehension and perceptual reasoning.

Based on these theoretical implications, we expected that the naturally occurring positive association between CRF and IQ present in the general population would be occluded by the disorder-related impact on cognition in schizophrenia. However, we expected that the positive association between CRF and the state-sensitive cognitive functions would be retained. Specifically, we predicted that CRF as measured by VO_{2peak} would explain a significant amount of the variance in the state-sensitive cognitive functions only, and that this influence would be present beyond the impact of negative psychotic symptom load.

2. Method

2.1. Design

The study was conducted on baseline data from the randomized, controlled, observer-blinded clinical trial 'Effects of Physical Activity in Psychosis' (EPHAPS) (ClinicalTrials.gov, registration number NCT02205684; Engh et al., 2015).

2.2. Participants

Eighty participants aged 20–67 years were recruited from August 2014 through February 2017 from catchment area-based and publicly funded outpatient psychiatric clinics in Vestfold County, Norway. A subgroup of patients was referred from primary health care to the outpatient clinics for participation in the project specifically. Eligible for the study were patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-V; American Psychiatric Association, 2013) criteria for schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, and schizophreniform disorder). Demographic and clinical characteristics are presented in Table 1. Diagnosis was established using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders axis I (SCID I; First et al., 2002). Interviews were conducted by a clinical psychologist or a specialist in psychiatry. Members of the assessment staff attended a course based on the SCID training program at the University of California Los Angeles (Ventura et al., 1998), and all participated in diagnostic consensus meetings.

Additional inclusion criteria were: Age between 18 and 67; understanding and speaking a Scandinavian language. Exclusion criteria were: pregnancy; chest pain during CRF test; unstable angina pectoris; recent myocardial infarction; uncontrollable cardiac arrhythmia; severe hypertension (>180/110 mm Hg); comorbid diagnosis of mild mental retardation; and/or other medical conditions incompatible with participation. The study was approved by the Regional Committee for Medical and Health Research Ethics of Southern and Eastern Norway (file number 2014/372/REK SØR-ØST).

Initial information about the EPHAPS study was given to eligible patients by clinical staff in the outpatient clinic or in primary health services. Contingent on understanding the nature of the research and willingness to participate, written consent was obtained by a project coworker. Seventy-seven participants received antipsychotic medical treatment. Defined daily doses (DDD) were calculated in accordance with guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd). Additional regular anxiolytic and/or antidepressant or mood stabilizing medication was received by 9, 15 and 11 participants, respectively. Eighteen participants received clozapine medication (Green, 1996) or other types of medication (Douglas and Porter, 2009) with potential anticholinergic effects.

2.3. Procedure

The current study was based on neurocognitive and clinical assessments and a CRF test, all conducted within a two-week period. Neurocognition was assessed with the six subtests of the Wechsler Adult Intelligence Scale version 4 (2008, NCS Pearson Inc. San Antonio,

Table 1
Demographic and clinical characteristics of participants ($N = 80$).

Attribute	Mean	SD
Male $n = 50$ (63%), female $n = 30$		
Age (years)	36.7	14.2
Years of education	12.0	2.4
Duration of illness ($n = 79$[a])	15.4	12.7
GAF-S[1] ($n = 79$[a])	43.4	7.6
GAF-F[2] ($n = 79$[a])	44.0	7.7
PANSS[3] total	65.6	16.4
PANSS negative factor	15.3	6.6
WAIS-IV GAI[4]	87.5	15.8
MCCB NCS[5]	34.1	8.6
VO_{2peak}	30.0	11.2
Antipsychotics DDD[6]	1.6	0.9

Note:
[1] Global Assessment of Functioning-Symptom scale.
[2] Global Assessment of Functioning-Function scale.
[3] Positive and Negative Syndrome Scale.
[4] Wechsler Adult Intelligence Scale version IV General Ability Index.
[5] MATRICS Consensus Cognitive Battery Neurocognitive Composite Score.
[6] Defined daily doses.
[a] Data on GAF-scores and duration of illness were missing for one individual.

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