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Cardio-respiratory fitness is associated with a verbal factor across cognitive domains in schizophrenia

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ABSTRACT

Objective: We investigated whether the relationship between cardio-respiratory fitness (CRF) and cognition in schizophrenia is general, or due to selective relationships between CRF and specific aspects of cognitive function.
Method: Eighty outpatients with schizophrenia spectrum disorders participated. Neurocognition was assessed with the Wechsler Adult Intelligence Scale version 4 General Ability Index (WAIS GAI), the MATRICS Consensus Cognitive Battery (MCCB) and the Emotion in Biological Motion (EBM) test. CRF was assessed with peak oxygen uptake measured directly during maximum exercise using a modified Balke protocol. Partial correlations, controlling for sex and age, were obtained for the perceptual and the verbal indices of WAIS GAI, six cognitive domains of MCCB, and the EBM total score. A factor analysis was conducted on all 15 subtests of the WAIS GAI and the MCCB, and the factors were subjected to separate regression analyses with CRF as predictor.
Results: Significant, moderately sized correlations were found between CRF and all cognitive domains except processing speed. The correlation appeared strongest for CRF and the Verbal Comprehension Index of WAIS GAI ($r = 0.29$, $p = .005$). The factor analysis identified three factors: one speed/attention/executive function factor, one verbal factor, and one perceptual factor. Regression analyses showed that VO_{2peak} explained a significant amount of variance in the verbal factor only ($R^2 = 0.06$, $\beta = 0.329$, $p = .03$).
Conclusion: The results indicate that the relationship between CRF and cognition in schizophrenia is selectively tied to a modality-specific association with verbal cognitive abilities. These findings have implications for understanding the relation between cognitive factors and physical health in schizophrenia.
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1. Introduction

At group level, individuals with schizophrenia display low cardio-respiratory fitness (CRF) (Andersen et al., 2018; Heggelund et al., 2011; Scheewe et al., 2012; Strassnig et al., 2011), and impaired cognition is a central clinical feature in schizophrenia (Aleman et al., 1999; Dickinson et al., 2007; Mesholam-Gately et al., 2009). Hence, the relationship between CRF and cognition is of particular interest with regard to this patient group. Intervention studies have reported associations between CRF and specific cognitive functions, both in the general population and in various patient groups (Hotting and Roder, 2013; Kramer et al., 1999; Malchow et al., 2015; Oertel-Knochel et al., 2014; Pajonk et al., 2010; Smiley-Oyen et al., 2008; Su et al., 2016; Voelcker-Rehage and Niemann, 2013). This has formed the basis for models connecting CRF with cognition (Kramer et al., 1999; Voss, 2016). A meta-analysis on ten intervention studies with individuals with schizophrenia reported significant effects of increased CRF on overall cognitive performance, and for working memory, attention/vigilance and social cognition specifically (Firth et al., 2016).

However, we believe that the question of differential associations between CRF and specific cognitive functions has not yet been thoroughly investigated in this population. Depending on the particular study and the specific cognitive tests included, improvements in a range of cognitive functions have been reported. Still, limited sample sizes and the varying selections of cognitive functions tested in the single studies constitute a suboptimal foundation for evaluating differentiated associations between CRF and specific cognitive functions. Moreover, while intervention studies are necessary to evaluate the

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modifiability of the variables in question, this approach may not be sufficient to illuminate the long-term, life-span developmental processes behind the same variables. The investigation of naturally occurring associations between CRF and cognitive functions may provide important information about the natural processes on which the intervention studies are designed to intervene. Addressing this issue in a cross-sectional study, Kimhy and colleagues 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. The authors reported positive partial correlations between CRF and the specific domains of executive functioning, working memory and processing speed, and also social cognition, as well as a trend level association to visual learning (Kimhy et al., 2014). The authors conveyed these findings as preliminary and called for replication in a larger sample. In the current study, we wanted to examine the subject further in a larger sample of individuals with schizophrenia.

In a previous study, we found that CRF explained 8.2% and 9.0% of the variance in general intellectual ability (IQ) and state-sensitive cognitive functions (processing speed, attention, working memory, learning and executive functions) respectively (Holmen et al., 2018). The effect of CRF on cognition was significant beyond the impact of negative psychotic symptom load. Furthermore, years of education, duration of illness, body mass index (BMI) or cigarette smoking did not influence the relationship between CRF and cognition. The relationship between CRF and general intellectual ability was approximately as strong as the relationship between CRF and the more state-sensitive cognitive functions. However, CRF may be differentially connected to more specific aspects of cognition. Comparing correlations between CRF and the specific cognitive domains may provide an overview of such variations. Investigating differential effects may require a search beyond the levels of specific cognitive domains and the subtests of which they are comprised, as no subtest is completely function-pure (Moscovitch, 1994). For example, a test measuring executive functions can include a visual-spatial component, and a test measuring perceptual abilities may include a processing speed component. An elucidating alternative may be to enter all subtests into a factor analysis and thereby search for underlying dimensions which cut across the divisions between them. Identified factors may then be subjected to regression analyses, to assess and compare their respective relationships with CRF.

Firstly, we will examine differential associations between CRF and each of the cognitive domains and thereby replicate the study of Kimhy and colleagues (Kimhy et al., 2014) in a larger sample and extend it by also including general intellectual ability. Secondly, we will search for potential differential associations between CRF and underlying cognitive factors extending across the cognitive domains. We will subject all specific subtests to an exploratory factor analysis. Subsequently we will conduct regression analyses on all identified factors, with CRF as predictor.

2. Method

2.1. Design

The study was conducted using 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 5; American Psychiatric Association, 2013) criteria for schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, and schizophreniform disorder). Demographic and clinical characteristics are presented in Table 1. Diagnoses were established using the Structured Clinical Interview for DSM axis I disorders (SCID I) (First et al., 2002). Interviews were conducted by a clinical psychologist or a specialist in psychiatry. Members of the assessment staff attended the SCID training program from UCLA (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; or other medical conditions incompatible with participation.

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). The DDD is the assumed average maintenance dose per day for a drug used for its main indication on adults and provide a fixed unit of measurement independent of dosage form, providing a rough estimate of pharmaceutical drugs consumption. Additional regular anxiolytic and/or antidepressant or mood stabilizing medication was received by 9, 15 and 11 participants, respectively. Eighteen participants received clozapine (12) or other types of medication (6) with potential anticholinergic effects.

Psychoactive substance use among the participants was assessed with the Alcohol Use Scale (Drake et al., 1990) and the Drug Use Scale (Mueser et al., 1995). On these, subjects are rated by assessing clinician on a 5-point scale, based on the one worst month period of substance use/abuse over the past six months: 1 = abstinent, 2 = use without impairment, 3 = abuse, 4 = dependence and 5 = dependence with institutionalization. Scores of 3 or higher correspond to DSM criteria for substance abuse or dependence. The scales have been validated for individuals with severe mental illness (Drake et al., 1993; Moller and Linaker, 2010). Two individuals scored 3 on the AUS. Three individuals scored 3, one individual scored 4 and one individual scored 5 on the DUS. None of these was excluded from the study. However, participation would have been postponed for any participant appearing visibly influenced by alcohol or drugs during testing situations.

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

Attribute	Mean (SD)
Male n = 50 (63%)	
Age (years)	36.7 (14.2)
Education (years)	12.0 (2.4)
Duration of illness (years)[g]	15.4 (12.7)
GAF-S[a,g]	43.4 (7.6)
GAF-F[b,g]	44.0 (7.7)
PANSS[c] total	65.6 (16.4)
WAIS-IV GAI[d]	87.5 (15.8)
MCCB NCS[e]	34.1 (8.6)
VO_{2peak} (ml/kg/min)	30.0 (11.2)
Antipsychotics DDD[f]	1.6 (0.9)

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

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 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.

2.3. Procedure

The current study was based on neurocognitive and clinical assessments, and a CRF test, all conducted within a two-week period. Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and psychosocial functioning was assessed with the Global Assessment of Functioning scale (GAF) (Endicott et al., 1976). Neurocognition was assessed with the six subtests of the Wechsler Adult Intelligence Scale version 4 (2008, NCS Pearson Inc. San Antonio, TX, USA) included in the Verbal Comprehension and the Perceptual Reasoning sub-indices. Together, these comprise a General Ability Index that may be regarded as a core IQ measure not contaminated by state-dependent reductions in processing speed and memory. Furthermore, nine subtests of the MATRICS Consensus Cognitive Battery were applied as measures of the state-sensitive cognitive functions, covering six domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning and problem solving (Green et al., 2014). The Norwegian version of MCCB has retained the original psychometric properties (Holmen et al., 2010), with the possible exception of the test intended to measure social cognition, which was not included in the current study. Instead, an emotion-interpretation aspect of social cognition was measured utilizing the Emotion in Biological Motion (EBM) test. The test consists of 22 video clips of point-light display walkers, requiring scorers to interpret emotional tone by choosing from the five alternatives of 'angry', 'happy', 'sad', 'fearful' or 'neutral/no emotion' (Couture et al., 2010; Heberlein et al., 2004). Vaskinn and colleagues standardized the test on a Norwegian sample of 101 healthy controls, which was used as basis for calculating a total score for each participant (Vaskinn et al., 2015). A proportional scoring method was utilized; each of the participant's single item scores was rated on basis of the proportion of healthy controls that scored accordingly, and an individual total score was then calculated for each participant.

CRF, as measured by peak oxygen uptake (VO_{2peak}; ml/kg/min), was measured during a maximum exercise test on a treadmill using a modified Balke protocol (Balke and Ware, 1959), where speed was held constant at 5 km/h and the inclination angle was increased by one degree every minute until exhaustion. Gas exchange was sampled continuously into a mixing chamber every 30 s by having the participants breathe into a Hans Rudolph 2-way breathing valve (2700 series, Hans Rudolph Inc., Kansas City, MO, USA) connected to a Jaeger Oxycon Pro gas analyzer (Erich Jaeger GmbH, Hoechberg, Germany), which measures the oxygen and carbon dioxide content. Before conducting the CRF test, somatic health was thoroughly assessed through general medical examination, including medical history, medication record, and physical examination with blood pressure assessment and electrocardiography. For various reasons some individuals may fail to reach a true VO_{2max}, and for the sake of conservative reporting we therefore use the term VO_{2peak}.

For one participant, the data from the MCCB visual learning subtest BVMT-R was missing. To retain the individual's data in all analyses the entry was substituted with a calculated mean of t-scores of the remaining eight MCCB subtests.

2.4. Statistical analyses

Analyses were made using The Statistical Package for the Social Sciences (IBM SPSS Version 22.0, IBM Corp, Armonk, NY, USA). Visual inspection of histograms and values of skewness and kurtosis indicated that all data were normally distributed, and no outliers needed to be addressed. Partial correlations, controlling for sex and age, were obtained for the Verbal Comprehension (VCI) and the Perceptual Reasoning (PRI) indices of the WAIS IV, the six domain scores of the Neurocognitive Composite Score of MCCB (MCCB NCS), and the EBM total score, respectively. These variables are correlated and partly overlapping, and the modest sample size provides limited statistical power. Due to the related increase in risk of type II-errors, no corrections for multiple testing were applied in these analyses. Results when utilizing a more conservative approach to significance, in line with a Bonferroni correction, are also displayed in Table 2. Significance tests were set as *one-tailed*, as predicted direction of the associations was given from the results of a previous study (Holmen et al., 2018). In this previous study we also controlled for a range of possible confounders, including negative psychotic symptom load, years of education, duration of illness, body mass index (BMI) and cigarette smoking, which were shown not to exert significant influence on the general relationship between CRF and cognition. We therefore did not control for these variables in the current context.

Next, the six subtests of the WAIS VCI and PRI and the nine MCCB NCS subtests were deemed suitable for factoring according to the Kaiser-Meyer-Olkin measure (KMO = 0.91) and subjected to a principal axis factoring analysis using Varimax rotation. The main purpose of the factor analysis was to search for underlying cognitive factors extending across the single domains and tests. Inherently, this procedure also addresses the issue of multiple testing by reducing the number of variables to a statistically manageable number for further analyses. Factors with Eigenvalues > 1 were retained and subsequently subjected to regression analyses, with each factor as dependent variable and VO_{2peak} as predictor.

3. Results

Partial correlations are displayed in Table 2, showing significant correlations between VO_{2peak} and both the VCI and PRI indexes of the WAIS and five of the six MCCB NCS domains. All significant correlations are positive, ranging from $r = 0.23$ to $r = 0.29$. The correlation appears strongest for CRF and the Verbal Comprehension Index of WAIS GAI ($r = 0.29$, $p = .005$). The domain of processing speed is close to reaching significance ($r = 0.17$, $p = .06$). The social cognition measure of the EBM total score also emerges with a significant positive correlation to VO_{2peak} ($r = 0.21$, $p = .04$).

The factor analysis of all 15 subtests reveals three factors: one whereon processing speed, attention, working memory and executive function loaded highly (Eigenvalue = 7.0, 46.7% of variance explained); one appearing as a verbal factor (Eigenvalue = 1.3, 8.6% of variance

Table 2
Partial correlations between VO_{2peak} and cognitive domains controlling for sex and age (N = 80).

Index/test	Partial correlation with VO_{2peak}
Verbal Comprehension[a]	**0.29****
Perceptual Reasoning[a]	**0.24***
Processing speed[b]	0.18
Attention[b]	**0.26***
Working Memory[b]	**0.28***
Verbal Learning[b]	**0.23***
Visual Learning[b]	**0.22***
Reasoning[b]	**0.25***
EBM[c]	**0.21***

Note: Significant correlations are in boldface.
[a] Wechsler Adult Intelligence Scale version IV.
[b] MATRICS Consensus Cognitive Battery.
[c] Emotion in Biological Motion test total score.
* $p < .05$.
** $p < .005$.

explained); and one appearing as a perceptual factor (Eigenvalue = 1.2, 7.9% of variance explained). Factor loadings are displayed in Table 3. Controlling for sex and age, regression analyses showed that VO_{2peak} significantly predicted 6% of the variance of the verbal factor (R^2 = 0.060, β = 0.329, *F-change* (3.76) = 5.110, p = .03). The other two factors were not significantly related to VO_{2peak} in this material (speed/attention/executive function factor: R^2 = 0.028, β = 0.221, *F-change* (3, 76) = 2.132, p = .15; perceptual factor: R^2 = 0.013, β = 0.154, *F-change* (3.76) = 1.173, p = .28).

4. Discussion

CRF, as measured by VO_{2peak}, was significantly associated with the whole span of cognitive domains, with the exception of the domain of processing speed, where a trend-level association appeared in the expected direction. Also the EBM test of emotion interpretation, which constitutes one aspect of social cognition, showed a significant but small relationship to CRF. Thus, the main trend in the preliminary results from the study of Kimhy and colleagues (Kimhy et al., 2014) was replicated in our larger sample, and shown to extend also to general intellectual ability/IQ. Sex and age were controlled for in the current study, while depression and antipsychotic medication were controlled for in the study by Kimhy and colleagues (Kimhy et al., 2014). This difference in selection of control variables may have contributed to discrepancies in the specific results.

By splitting up the cognitive indices and domains into separate subtests, subjecting these to a factor analysis, and conducting regression analyses on the factor scores, we were able to investigate the associations in further detail. We thereby discovered a modality-specific association, where the overall association between CRF and cognition appeared selectively attributed to a modality-specific relationship between CRF and a verbal cognitive factor. This underlying factor extends across the division between general intellectual ability and state-sensitive cognitive functions, and also across singular cognitive domains and functions. This result corresponds with the finding that the Verbal Comprehension Index of WAIS IV had the largest single partial correlation to CRF.

We do not know why the association between CRF and cognition appears selectively tied to a verbal factor. It is contrary to a proximal modality effect of CRF on cognitive functions, as is suggested by some theories in the field. The selective improvements hypothesis (Kramer et al., 1999) and the motor fitness hypothesis (Voss, 2016) hold that various exercise activities may induce selective improvements in executive functions and/or perceptual cognitive abilities, and thus CRF should appear with a stronger link to these functions and/or abilities. Conversely, from the current results, the association appears selectively linked to a verbal modality. However, the hypotheses on proximal modality effects of CRF on cognitive functions are partly based on intervention studies (Kramer et al., 1999; Voss, 2016). The effects CRF-enhancing interventions have on specific cognitive functions may involve different processes than those implicated in the naturally occurring, life-long development of associations between these variables.

Interestingly, Pajonk and colleagues found significant increases in hippocampal volume both in people with schizophrenia and healthy participants following an exercise intervention, as compared to no changes in control subjects with schizophrenia playing table soccer (Pajonk et al., 2010). The exercise condition was followed by significantly improved performance on a verbal short-term memory test for the individuals with schizophrenia only (possibly due to a ceiling effect of the particular test for the healthy controls). Moreover, the improvement in verbal short-term memory was significantly associated with the increase in hippocampal volume in the individuals with schizophrenia. More generally, in a recent meta-analysis on the effect of exercise on hippocampal volume in the general population, Firth and colleagues found a significant positive effect on left hippocampal volume exclusively (Firth et al., 2018). Primary language centers are located in the dominant left hemisphere in most of the human population, and there are indications that the left side of hippocampus is particularly important to verbal learning and verbal memory (Ezzati et al., 2016; Rausch and Babb, 1993; Saling et al., 1993; Sass et al., 1992). Thus, previous lines of research have provided clues to a link between CRF and verbal cognitive abilities both in individuals with schizophrenia and in the general population. Furthermore, at group level, verbal memory is among the cognitive functions most severely affected in schizophrenia (Dickinson et al., 2013; Kravariti et al., 2009). This may fortify any specific relation between verbal cognitive abilities and CRF existing in the general population; individuals with schizophrenia may have more to gain in language-related cognitive functioning by improving their CRF.

In a previous study, we found that CRF explained as much variance in general intellectual ability as in the state-sensitive cognitive functions (Holmen et al., 2018). We interpreted this finding as an indication that the association between CRF and cognition in schizophrenia is established at the time when general intellectual ability is consolidated in the young person. This implies that genes in interaction with earlier environmental circumstances may be more influential on this relationship, than recent or current life-style. Moreover, heritability estimates of the perceptual and verbal components of general intellectual ability are relatively similar in size (Plomin et al., 2000), while the results of the present study indicate that only the latter is significantly related to CRF. Åberg and colleagues controlled for genetic heritability in their large-scale cohort study, and concluded that the correlations between CRF and cognition in the general population are predominantly determined by the non-shared environment (Aberg et al., 2009). Taken together, this arguably points to a possible primacy of environmental and life-style factors, particularly during childhood, adolescence and early adulthood, in establishing the relationship between CRF and cognition in schizophrenia.

The study has several limitations. In the absence of a control group, we do not know whether the selective association between CRF and verbal cognitive abilities is specific for individuals with schizophrenia or also applies to the general population. The cross-sectional design of the study leaves any propositions about causal pathways inferential. Several possible third-variable influences on the relationship between CRF and cognition in schizophrenia have been controlled for in a previous study (Holmen et al., 2018), but the possibility of other third variables contributing to the association, such as genetic factors, cannot be ruled out. Furthermore, in the present study we controlled for age and sex in all analyses, to account for general sex- and age-differences in

Table 3
Factor loadings for exploratory factor analysis with Varimax rotation of specific cognitive functions (N = 80).

Test	Speed/working memory/attention/executive factor	Verbal factor	Perceptual factor
TMT[a]	**0.59**	0.18	0.22
BACS[a]	**0.79**	0.32	0.30
HVLT[a]	0.32	**0.57**	0.27
WMS[a]	0.32	0.23	**0.58**
LNS[a]	**0.57**	0.37	0.28
NAB mazes[a]	**0.52**	0.27	0.39
BVMT-R[a]	**0.43**	0.19	**0.49**
Fluency[a]	0.22	**0.57**	0.07
CPT[a]	**0.63**	0.17	0.15
Similarities[b]	0.10	**0.74**	0.38
Vocabulary[b]	0.20	**0.67**	0.25
Information[b]	**0.40**	**0.65**	0.27
Block design[b]	0.36	0.24	**0.53**
Matrix reasoning[b]	0.20	0.23	**0.61**
Visual puzzles[b]	0.18	0.23	**0.83**

Note: Factor loadings > 0.40 are in boldface.
[a] MATRICS Consensus Cognitive Battery *t*-scores.
[b] Wechsler Adult Intelligence Scale version IV General Ability Index scaled scores.

CRF as measured by VO_{2peak}. All cognitive measures used in the analyses are normed, and thus age corrected. If there is a direct relationship between VO_{2peak} and aspects of cognition decaying with age, this effect may have been overcorrected in the analyses. Changes in processing speed, which was the only cognitive function not associated with VO_{2peak} in the current study, is often considered the underlying mechanism mediating all cognitive changes in aging (Salthouse and Madden, 2008). It is possible that some of this effect is directly and causally related to an age-contingent reduction in oxygen uptake, as measured by VO_{2peak}. Such an effect would have been controlled away when controlling for age. Hence, using a normed speed measure corrected for the large changes between young and old age, and correcting for age when considering the association to VO_{2peak}, may have deflated genuine associations that would be present in a more age homogeneous sample.

Conclusively, the broad association between CRF and several cognitive domains in schizophrenia seems to be driven by a verbal cognitive factor which was specifically identified in the factor analysis. Possible underlying mechanisms should be investigated in future experimental studies.

Contributors

All authors contributed to the manuscript in accordance with the Vancouver Protocol.

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Conflict of interest

The authors declare that they have no competing interests.

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