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# Neurocognition in help-seeking individuals at risk for psychosis: Prediction of outcome after 24 months

Sibylle Metzler[a,*], Diane Dvorsky[b], Christine Wyss[b], Carlos Nordt[b], Susanne Walitza[c], Karsten Heekeren[a,b], Wulf Rössler[a,d,e], Anastasia Theodoridou[a,b]

[a] The Zurich Program for Sustainable Development of Mental Health Services (ZInEP), University Hospital of Psychiatry Zurich, Switzerland
[b] Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry Zurich, Switzerland
[c] Department of Child and Adolescent Psychiatry, University of Zurich, Switzerland
[d] Collegium Helveticum, a joint Research Institute between the University of Zurich and the Swiss Federal Institute of Technology Zurich, Switzerland
[e] Institute of Psychiatry, Laboratory of Neuroscience (LIM 27), University of Sao Paulo, Sao Paulo, Brazil

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ABSTRACT

An important aim in schizophrenia research is to optimize the prediction of psychosis and to improve strategies for early intervention. The objectives of this study were to explore neurocognitive performance in individuals at risk for psychosis and to optimize predictions through a combination of neurocognitive and psychopathological variables. Information on clinical outcomes after 24 months was available from 118 subjects who had completed an extensive assessment at baseline. Subjects who had converted to psychosis were compared with subjects who had not. Multivariate Cox regression analyses were used to determine which baseline measure best predicted a conversion to psychosis. The premorbid IQ and the neurocognitive domains of processing speed, learning/memory, working memory and verbal fluency significantly discriminated between converters and non-converters. When entered into multivariate regression analyses, the combination of PANSS positive/negative symptom severity and IQ best predicted the clinical outcomes. Our results confirm previous evidence suggesting moderate premorbid cognitive deficits in individuals developing full-blown psychosis. Overall, clinical symptoms appeared to be a more sensitive predictor than cognitive performance. Nevertheless, the two might serve as complementary predictors when assessing the risk for psychosis.

## 1. Introduction

In line with a neurodevelopmental model of schizophrenia, evidence exists that neurocognitive and intellectual deficits are apparent before the onset of overt psychotic symptoms (Bora et al., 2014; Cannon et al., 2006; Fusar-Poli et al., 2012a; Giuliano et al., 2012; MacCabe et al., 2013; Woodberry et al., 2008). Therefore, it seems likely that predicting a transition to psychosis may be improved by combining clinical symptoms with specific neurocognitive measures (Riecher-Rössler et al., 2009). Moreover, individuals at clinical high-risk (CHR) for psychosis suffer from sub-threshold psychotic symptoms and often show a functional decline. They are labelled as being in a putative prodromal phase that has a transition risk to schizophrenia of 23–36% at two years, or 10–18% at one year if one accounts for a reduction in transition rates in previous years (Fusar-Poli et al., 2012b; Yung and Nelson, 2013). Therefore, it is obvious that the CHR state is associated with a heightened risk for psychosis but it is still a large proportion of individuals initially at risk will not convert. Meanwhile, labelling a person as at risk for psychosis might give rise to unintended consequences such as stigma and discrimination (Yung et al., 2010), which can subtly reduce the well-being of young individuals (Rüsch et al., 2014). Because unnecessary and potentially harmful treatment strategies such as an increased use of antipsychotic medicaments in young, treatment-naive individuals, are a cause for concern (Corcoran et al., 2010; Fusar-Poli et al., 2013), it seems crucial that researchers try to improve the accuracy of such predictions and analyze the characteristics and course of individuals with sub-threshold symptoms who do not convert to psychosis.

Evidence is growing that individuals at risk for psychosis perform more poorly than healthy controls across a range of neurocognitive domains (Bora et al., 2014; De Paula et al., 2015; Fusar-Poli et al., 2012a; Giuliano et al., 2012). However, there is no consensus on which changes are specific to the development of full-blown psychosis. Several reports on baseline neurocognitive predictors of progression from the at-risk state to frank psychosis have highlighted memory impairments as being linked with the increased risk of transition (Bang et al., 2015;

* Correspondence to: Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry Zurich, Militärstrasse 8, 8021 Zurich, Switzerland.
*E-mail address:* sibylle.metzler@dgsp.uzh.ch (S. Metzler).

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Brewer et al., 2005; Pukrop et al., 2006; Seidman et al., 2010; Woodberry et al., 2010). While working memory may be associated with the transition to psychosis (Brewer et al., 2006; De Herdt et al., 2013), deficits in processing speed might also be involved (Frommann et al., 2011; Kelleher et al., 2013; Seidman et al., 2010).

Researchers have proposed that different neuroregressive processes, such as excessive pruning or an developmental neuroinflammation that begins in adolescence and early adulthood, are the neurobiological substrate for cognitive deficits in schizophrenia (Bora and Murray, 2014; Insel, 2010). Taken together, exaggerated developmental changes may handicap performance within different neurocognitive domains. Although their co-occurrence with psychotic symptoms might help to identify individuals who are truly at risk for psychosis, methodological problems interfere with comparability between studies. As such, there is no consensus about which single neurocognitive instruments, measures, and/or composite scores are best suited for detecting deficits. Moreover, neurocognitive impairments may fluctuate and can emerge or be aggravated as the disease develops (Reichenberg et al., 2010).

The present study's aim was to investigate the usefulness of neurocognitive impairments as predictive markers for transition to psychosis. In this context, a sample of individuals at risk for psychosis was followed prospectively up to 24 months. We hypothesized that individuals with a transition to psychosis would show more severe neurocognitive impairments than individuals without transition. Because little is known about the large proportion of subjects initially at risk who do not convert to psychosis, we also analyzed the association between neurocognition and functional outcomes for non-converting subjects.

## 2. Methods

### 2.1. Subjects

Individuals from the canton of Zurich, Switzerland, were recruited within the context of a study on early recognition of psychosis (ZInEP; in German: Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie; www.zinep.ch). Potential participants either had learned about this study from a project website, flyers, or newspaper advertisements, or were referred to our staff by general practitioners, school psychologists, counselling services, psychiatrists, or psychologists. All subjects spoke proper German and had normal or corrected-to-normal vision, normal hearing, and normal motor limb functions. Exclusion criteria for study participation were manifest schizophrenic, substance-induced, or organic psychosis; current substance or alcohol dependence; or an estimated verbal IQ $<80$. Those aged $\geq 18$ years provided informed consent, while minors ($<18$ years) gave assent in conjunction with parental informed consent. The study was approved by the canton's Ethics Committee and was performed in accordance with the Declaration of Helsinki (for the detailed study protocol, see Theodoridou et al., 2014).

At baseline, psychopathological and neuropsychological data were obtained from initially 207 participants who fulfilled the inclusion criteria (see psychopathological assessment below) for high-risk (HR), ultra-high-risk (UHR), or at-risk bipolar (HRBip) categories (see also Theodoridou et al., 2014). The present study is based on 178 individuals meeting schizophrenic HR or UHR risk criteria.

### 2.2. Psychopathological assessment

HR, i.e. high risk, status for psychosis, as assessed by the Schizophrenia Proneness Interview, SPI-A (Adult version) or SPI-CY (Children-Youth version) (Schultze-Lutter et al., 2007; Schultze-Lutter and Koch, 2009) was defined as: having at least one cognitive-perceptive basic symptom or at least two cognitive disturbances, and not meeting any of the UHR inclusion criteria. UHR, i.e. ultra-high-risk, status for psychosis was rated by the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003) as: having at least one attenuated psychotic symptom, or at least one brief limited intermittent psychotic symptom (BLIPS), or a state–trait criterion [reduction in global assessment of functioning (GAF; Endicott et al., 1976) of $>30\%$ in the past year, plus either a schizotypal personality disorder or a first-degree relative with psychosis]. A transition to psychosis was diagnosed if participants met criteria for schizophrenia in the International Classification of Psychiatric Symptoms, version 10 (ICD-10). Quantitative measures of psychopathology were further obtained as follows: psychotic symptoms (Positive and Negative Syndrome Scale, PANSS; Kay et al., 1987), current axis-I comorbidity via MINI (Sheehan et al., 1998), general functioning per GAF (Endicott et al., 1976), depressive symptoms with the Hamilton Depression Rating Scale (HAMD, Schutte and Malouff, 1995), anxiety with Beck Anxiety Inventory (BAI, Steer et al., 1997) and obstetric complications with Obstetric Complications Scale (OCS, Owen et al., 1988). All assessments were conducted by trained, experienced psychiatrists or psychologists.

### 2.3. Neurocognitive assessment

At baseline, a set of well-established neuropsychological tests was administered in a fixed order. Verbal IQ was estimated with a German word recognition test (MWT-B; Lehrl, 1989) for adults or a test of receptive vocabulary for minors (PPVT; Dunn and Dunn, 2003). In addition to intelligence tests, the baseline test battery included the following tests: Trail Making Test, Version A and B (TMT-A/B; Reitan and Wolfson, 1985); Digit Symbol Coding Test (DSCT; Subtest of Wechsler Adult Intelligence Scale, German Version; Aster et al., 2006); Continuous Performance Test (CPT-OX; Beck et al., 1956); Rey Auditory Verbal Learning Test (RAVLT; Helmstaedter et al., 2001); Rey Visual Design and Learning Test (RVDLT; Spreen and Strauss, 1991); Digit Span and Letter-Number Sequencing (DS and LNS; Subtests of Wechsler Adult Intelligence Scale, German Version, Aster et al., 2006); Verbal Fluency Test (in German: Regensburger Wortflüssigkeits-Test, RWT; Aschenbrenner et al., 2000).

With the aim of deriving homogenous and up-to-date test norms, a group of 50 healthy controls with comparable socio-demographic backgrounds completed the neurocognitive assessment (for test scores and sample descriptions, see Metzler et al., 2014). The test scores of at-risk subjects were standardized by computing z-scores based on the performance of the control group. Further, a factor analysis was performed for the purpose of data reduction and also to derive separate and independent cognitive domains, because using single and arbitrary test measures or a composite score with an unconfirmed factor structure might give rise to a number of methodological concerns (see also Frommann et al., 2011). The result of the factor analysis is reported in Metzler et al. (2014). The following measures loaded on each factor and were therefore grouped as a domain: processing speed (TMT-A/B, time to complete test; DCST, number correct); attention (CPT, reaction time, omissions); learning / memory (RAVLT, trial 1, sum trials 1–5, recall, recognition; RVDLT, trial 1, sum trials 1–5, recall, recognition); working memory (DS, number correct; LNS number correct), verbal fluency (RWT, S-words and animals).

### 2.4. Statistical analyses

Preliminary between group analyses were performed to examine any differences between individuals, with and without information on follow-up. Group comparisons were calculated on demographics, clinical symptoms and neurocognition between individuals with (converter group) and without (non-converter group) a transition to psychosis. Next, we used Cox regression analyses to find predictors for transition to psychosis. The dependent variable was time to transition (29 censored at 12 months, and 64 censored at 24 months).