Understanding cognitive heterogeneity in psychosis and high risk individuals
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THE DUTCH TRANSLATION OF THE MATRICS: FIRST ASSESSMENT IN ULTRA HIGH RISK SUBJECTS AND SCHIZOPHRENIA PATIENTS COMPARED TO CONTROLS

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Submitted for publication
ABSTRACT

Background: The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was designed to assess cognitive treatment effects in clinical trials of patients with schizophrenia. This study addressed whether a first Dutch translation of the MCCB may differentiate between patients with first-episode schizophrenia (FES) and healthy controls. As an exploratory study, the MCCB was assessed in ultra high risk (UHR) individuals.

Methods: The MCCB was assessed in fifty-four FES patients, 23 UHR individuals and 23 healthy controls. To test whether cognitive profiles were significantly different in UHR and FES participants compared to controls, one-way multiple analysis of (co)variance (MAN(c)OVA) was performed with diagnostic group as fixed factor and cognitive scores as dependent variables.

Results: MANOVA revealed an overall effect of diagnostic group (UHR/FES/Control) on cognitive performance (F(16)=2.34; P<0.004). Post-hoc comparisons between FES versus control subjects were significant for all domains except visual learning. After co-varying for years of education, group differences for speed of processing, verbal learning and working memory remained significant. UHR individuals performed intermediate to FES and control subjects but differences were insignificant.

Conclusion: Preliminary findings add to the growing body of research on the presence of moderate cognitive alterations in the putative psychosis prodrome. Although results need replication in larger sample sizes, they suggest that the MCCB is sensitive to cognitive alterations in UHR individuals that are similar, albeit attenuated, compared to FES patients.
INTRODUCTION

Adolescents and young adults with an ultra high risk (UHR) for developing psychosis demonstrate cognitive alterations that are intermediate when compared to first-episode schizophrenia (FES) patients and healthy controls (Keefe et al., 2006; Eastvold, Heaton, & Cadenhead, 2007). UHR individuals with more cognitive alterations at baseline, as well as those experiencing further decline during the putative prodromal phase, may be more likely to develop psychosis at follow-up (Eastvold et al., 2007; Keefe et al., 2006; Becker et al., 2010; Lencz et al., 2006). There is however a lack of consensus on the time course and predictive value of specific cognitive alterations in the development of psychosis (Keefe et al., 2006).

Reliable assessment of the course of cognitive alterations during the UHR phase is important in understanding the pathogenesis of early psychosis and to enable the search for cognitive risk markers. The identification of such cognitive vulnerability markers may contribute to the development of a risk algorithm with greater predictive accuracy for psychosis than the clinical high risk criteria alone with an average 1-year transition rate of 36.7% (Ruhrmann et al., 2003). High rates of false-positives have raised both practical and ethical concerns about the development and implementation of interventions during the UHR phase (de Koning et al., 2009; McGorry et al., 2009).

The first intervention trials in UHR individuals mainly used pharmacological and psychological intervention strategies to reduce symptoms and to delay or prevent threshold psychotic symptoms (de Koning et al., 2009; McGorry et al., 2009). Although cognitive alterations in UHR individuals have been associated with lower levels of functioning independent of symptom severity (Niendam et al., 2006), there has been little focus on cognition as an outcome measure so far. It has been hypothesized that preventing or delaying the onset of frank psychosis may limit cognitive decline because alterations in the UHR phase are still mild (Simon et al., 2007). In addition, if cognitive skills, crucial for building adolescent relationships and academic performance, could be improved during the UHR phase, this might limit functional decline after psychosis onset (Hafner et al., 1995).

The current gold-standard for cognitive assessment in clinical trials for schizophrenia is the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008). Although similar domains are affected in schizophrenia and the UHR phase (Keefe et al., 2006; Eastvold et al., 2007), the MCCB has to the best of our knowledge not yet been administered in an UHR sample. Implementation of a standard cognitive battery as outcome measure in UHR individuals may provide the comparability that is required in this difficult to recruit and heterogeneous population. It would also be in line with the current view that UHR research needs to progress to studies with substantially larger samples, which is most effectively achieved through multicenter studies (McGorry et al., 2009).

The purpose of this cross-sectional study was to compare cognitive functioning on the MCCB in a sample of UHR individuals, first-episode schizophrenia (FES) patients, and age- and gender-matched healthy controls. Based on previous findings, we hypothesized that UHR individuals show cognitive alterations when compared with controls and that these alterations are mild compared with FES patients (Eastvold et al., 2007; Keefe et al., 2006).
METHODS

Sample and measures

Through the early psychosis department of the Academic Medical Centre (AMC) in Amsterdam, the Netherlands, 23 UHR individuals and 54 patients with first-episode schizophrenia (FES) were recruited. Twenty-three age- and gender-matched non-psychiatric controls (Co) were recruited through advertisements in a local newspaper. Participants received cognitive assessment with the MCCB (Nuechterlein et al., 2008; Kern 2008). The MCCB contains 10 tests to measure cognitive performance in 7 domains: attention/vigilance, speed of processing, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving and social cognition. The MCCB was translated by our research group according to guidelines for academic translations (Harvey et al., 2010) and assessed in all participants. A shortened version of the WAIS-III was assessed as an IQ-estimate (Blyler et al., 2000), consisting of the subtests information, digit symbol-coding, arithmetic and block design. UHR individuals were assessed with the Comprehensive Assessment for At-Risk Mental States (CAARMS; Yung et al., 2005). They were included if they fulfilled at least one of the following criteria: intermittent positive symptoms, attenuated positive symptoms, or a genetic risk/deterioriation syndrome (Yung et al., 2005). FES patients were included if they fulfilled DSM-IV schizophrenia diagnosis after stabilization of the first psychotic episode, assessed with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Substance use was assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization, 1990), section L. The study was approved by the ethics committee of the AMC.

Statistical Procedures

Statistical analyses were performed with SPSS 17.0 for Windows. Socio-demographic data were compared between diagnostic groups (FES/UHR/Co) by means of one-way analysis of variance (ANOVA) for continuous variables and χ² tests for categorical variables. Raw scores from each of the 10 tests were entered into the MCCB scoring program to produce age and gender corrected T-scores for the 7 cognitive domains (normative mean = 50; SD = 10). If the mean composite T-score of the controls fell within a 5% range of the American mean (T scores 47.5 to 52.5), our control group was assumed to represent the much larger MCCB norm population (Kern et al., 2011). If not, analyses were performed with study-specific z-scores that were calculated using means and SDs of our control sample (Holmen et al., 2010).

To test whether cognitive profiles were significantly different in UHR and FES participants compared to controls, a one-way multiple analysis of (co)variance (MAN(C)OVA) was performed with diagnostic group as fixed factor and T scores (or z-scores) as dependent variables, followed by Bonferroni post-hoc comparisons. Because lower educational achievement is likely to be an inherent part of the disorder, adjusting for education in psychotic samples may cause matching fallacy (Meehl, 1970). Therefore, the analyses were performed with and without years of education as a covariate. To correct for multiple testing, the alpha-level was set to p<.01.
RESULTS

Diagnostic groups did not differ significantly in mean age (UHR 21.6; FES 22.7; Co 22.3; F(2,97)=0.84; p=NS) or gender (UHR 78.4%; FES 85.2%; Co 74.0% males; $\chi^2(2)=1.48; p=NS$). None of the participants had used hard drugs over the past month and the groups did not differ in cannabis use over the past month (UHR 23.5%; FES 26.9%; Co 28.6%; $\chi^2(2)=9.15; p=NS$). There were significant differences between the groups in years of education (UHR 14.8 years; FES 14.5 years; Co 16.4 years; F(2,97)= 8.53; p<.01), as well as estimated IQ (UHR 101.8; FES 92.6; Co 108.9; F(2,97)=10.06; p<.01).

The MCCB cognitive profile of UHR and FES patients compared to controls is displayed in Figure 1. With the mean composite $T$ score of 51.2 in controls (SD 10.5), analyses were performed using $T$ scores. The MANOVA revealed an overall effect of diagnostic group (UHR/FES/Co) on cognitive performance ($F(16) = 2.34; p<.004$) (Table 1). Post-hoc comparisons between FES vs Co were significant for all domains except for visual learning. The comparisons between UHR vs Co did not yield significant results. After co-varying for years of education in a MANCOVA, group differences for speed of processing, verbal learning and working memory remained significant after correction for multiple comparisons ($p<.01$).

Figure 1. $T$ scores for MCCB domains in patients, UHR subjects and controls. SOP: speed of processing; A/V: attention/vigilance; WM: working memory; VerbL: verbal learning; VisL: visual learning; Reas: reasoning and problem solving; Soc: social cognition
DISCUSSION

Our results show that the MCCB is able to differentiate between FES patients and healthy controls. UHR individuals demonstrate intermediate performance on all domains which is in line with previous studies (Simon et al., 2007; Eastvold et al., 2007; Keefe et al., 2006; Niendam et al., 2006; Hawkins et al., 2008), although differences with the control group are not statistically significant. Moreover, FES patients show medium to large alterations that are significant in 6 out of 7 cognitive domains, with the exception of visual learning. After correction for years of education, the group differences between FES patients and controls remained significant for speed of processing, working memory and verbal learning.

Preliminary results indicate that the MCCB may be sensitive to detect cognitive alterations in the UHR phase, but findings need to be replicated in a larger population. The power to detect two-tailed group differences with an alpha value of .01 was only 64% for UHR individuals compared to 99% for FES patients (nQuery Advisor 7.0 power calculator). The mean composite T score in UHR individuals (Figure 1) is however similar to the mean difference of -0.81 SD that was reported in 67 UHR individuals that had completed a cognitive assessment covering 5 out of 7 MCCB domains (Simon et al., 2007). In that study, UHR individuals performed significantly worse than controls on almost every domain; however analyses were not corrected for multiple comparisons.

Table 1. Results from MAN(C)OVA with post-hoc comparisons

<table>
<thead>
<tr>
<th>Cognitive Domains</th>
<th>MANOVA (MANCOVA*)</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F (2)</td>
<td>p value</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>12.02</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td></td>
<td>(&lt;.001*)</td>
<td></td>
</tr>
<tr>
<td>Attention/vigilance</td>
<td>5.95</td>
<td>&lt;.004*</td>
</tr>
<tr>
<td></td>
<td>(&lt;.024)</td>
<td>NS</td>
</tr>
<tr>
<td>Working memory</td>
<td>8.39</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td></td>
<td>(&lt;.007*)</td>
<td>NS</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>10.95</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td></td>
<td>(&lt;.001*)</td>
<td>NS</td>
</tr>
<tr>
<td>Visual learning</td>
<td>1.97</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Reasoning and problem solving</td>
<td>4.77</td>
<td>&lt;.010*</td>
</tr>
<tr>
<td></td>
<td>(NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Social cognition</td>
<td>7.80</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td></td>
<td>(&lt;.026)</td>
<td>NS</td>
</tr>
<tr>
<td>Composite MATRICS</td>
<td>14.59</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td></td>
<td>(&lt;.001*)</td>
<td>&lt;.030</td>
</tr>
</tbody>
</table>

* years of education as covariate
* significant MAN(C)OVA after correction for multiple comparisons
The FES group displayed medium to large cognitive alterations compared to the control group on almost all domains, which is consistent with the view of a generalized cognitive deficit in schizophrenia (Chapman and Chapman 1973; Keefe et al., 2006). Absent group differences on visual learning illustrates that FES patients may experience relatively little problems with the recall of visual compared to verbal information (Kalkstein et al., 2010). This is further supported by our finding that out of 10 MCCB subtests, FES patients obtained highest scores on the Wechsler Memory Spatial Span that assesses visual working memory (T = 46.15, SD =11.12) (data not shown).

In chronic, clinically stable schizophrenia outpatients, the MCCB composite T score was 37.0, comparable to the mean composite score in our patients (Kern et al., 2010). Moreover, a Norwegian study that assessed the MCCB in patients with early onset schizophrenia spectrum disorders reported that impairment in patients ranged from -0.8 to -1.8 SD on all of the MCCB domains except for social cognition (Holmen et al., 2010). Authors reasoned that the subtest of use may not be appropriate to assess social cognition in adolescents, since the vignettes describing social situations were developed for an adult population. In our adolescent sample this task was however sensitive for group differences, which may be due to the fact that our FES patients were almost 7 years older than the Norwegian sample.

Alterations in verbal learning, working memory and speed of processing were present in FES patients after correction for years of education. It may be argued that these are the domains least affected by educational achievement in schizophrenia. This is not in line with the literature however, reporting that verbal memory is the MCCB domain correlating strongest with educational achievement in schizophrenia (Liu et al., 2006). A more plausible explanation might be that performance on all cognitive domains correlates with years of education in schizophrenia and that the statistical significance of only the top three MCCB domains is robust enough to withstand correction for it (Table 1). The group difference for social cognition however was equally statistically significant, but this domain did not survive correction for years of education. This is in line with the presumption that Theory of Mind, which is the subtype of social cognition assessed in the MCCB, might be more reflecting general intelligence rather than a “genuine compromised mental state” (Brune, 2003).

There are some limitations to the study. First, the power was too low to ‘prove’ cognitive alterations with small to moderate effect sizes in UHR individuals to be significant. Second, our study reports cross-sectional data and hence we do not know which of our UHR individuals will progress to develop a diagnosable psychotic disorder. Therefore we cannot draw conclusions about the course of cognitive alterations during the UHR phase and whether the MCCB may be useful to assess cognitive risk markers as has been suggested previously (Keefe et al., 2006).

In conclusion, these preliminary findings add to the growing body of research on the presence of moderate cognitive alterations in the putative psychosis prodrome. Although results need replication in larger sample sizes, they suggest that the MCCB is sensitive to cognitive alterations in UHR individuals that are similar, albeit attenuated, compared to FES patients. We therefore recommend further research on the use of the MCCB as a standardized cognitive outcome measure in both observational and intervention studies during the UHR phase.


