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EDITORIAL

The role of cognitive functioning in the outcome of those at clinical high risk for developing psychosis

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Although it is well established that cognitive impairment is a common feature of schizophrenia, only recently has cognitive functioning been prospectively studied in individuals at clinical high risk (CHR) for developing psychosis. To date, both cross-sectional and longitudinal studies have been conducted in the CHR population and in the context of later conversion to psychosis. A comprehensive review of the literature suggests that CHR individuals have general and specific baseline cognitive deficits compared to healthy controls. As a group, their cognitive course, tends to remain stable over time and in this way does not differ from healthy controls. For those who go on to develop a full-blown psychotic illness compared to those who do not convert, there appeared to be minimal differences at baseline with respect to cognition, although over time the converters may show deterioration in certain cognitive abilities compared to the non-converters. However, for many cognitive domains results are mixed, and may result from methodological limitations.

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Key words: Cognition, high risk, prodrome, psychosis, schizophrenia.

Introduction

Cognitive deficits are considered to be a core symptom of schizophrenia in that they precede the presentation of clinical symptoms (Reichenberg, 2010), and can impact functioning (Green *et al.* 2004). Cognition tends to remain relatively stable over the course of the illness, at most improving modestly, with those at the first episode exhibiting impairment of a similar severity to those with a more chronic course of illness (Mesholam-Gately *et al.* 2009).

It is possible that some of the cognitive impairment that occurs in schizophrenia is already present before the first episode (Jones *et al.* 1994). The increase in prospective research (Addington & Heinssen, 2012) which examines individuals who are at clinical high risk (CHR) for developing psychosis, offers an excellent opportunity to determine whether there is evidence of cognitive impairment prior to the onset of fully blown psychosis. In an earlier comprehensive review of 17 studies, Brewer and colleagues (Brewer *et al.* 2006) reported that the association between cognition and emerging psychosis was not well understood. These authors highlighted a lack of consistency in the literature, with contrasting results about the putatively impaired cognitive domains. However, they did conclude that general cognitive ability appeared to remain intact and was a poor predictor of developing psychosis. We have updated Brewer's review of 2006 to determine the impact of the increased attention to cognition for those at CHR of psychosis to determine whether we have an increased understanding of the role of cognition on outcome for these young CHR individuals.

Methods

Cognitive studies in CHR populations were identified through computerized searches of Pubmed, Medline and PsychINFO bibliographic databases. The terms searched included combinations of: *prodromal*, *prodrome*, *ultra high risk*, *clinical high risk*, *neurocognition*, *cognition*, *neurocognitive*, *cognitive*, *neuropsychological* and *neuropsychology*. Since the Brewer review was published in 2006 (Brewer *et al.* 2006), we have only included studies published between June 2006 and December 2011. Studies were included if participants were identified as being at *CHR, UHR* or *prodromal*, if they had evidence of basic symptoms, or if specific criteria or measures were used and described to make this diagnosis. Acceptable criteria and measures included: the Criteria oF Prodromal Syndromes (COPS) criteria based on the Structured Interview for Prodromal Syndromes (McGlashan *et al.* 2010), the Personal Assessment and

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Crisis Evaluation (PACE) criteria based on the Comprehensive Assessment of an At Risk Mental State (CAARMS) (Yung *et al.* 1998), the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rossler *et al.* 2007)/Brief Psychiatric Rating Scale (BPRS) (Ventura *et al.* 1993), specific DSM-III-R prodromal symptoms (Jackson *et al.* 1995), the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (Vollmer-Larsen *et al.* 2007), the Schizophrenia Prediction Instrument-Adult Version (SPI-A) (Klosterkotter *et al.* 2001), the Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos) (Hafner *et al.* 2004) and the Cognitive Assessment and Risk Evaluation (CARE) program criteria (Eastvold *et al.* 2007). Studies were excluded if they included frankly psychotic or genetic high-risk participants (without clinical symptoms or functional decline) mixed into their CHR, UHR or prodromal sample (Cosway *et al.* 2000; Myles-Worsley *et al.* 2007).

Results

The literature search yielded 23 publications that were deemed appropriate for review. These are presented in Table 1. Some studies are cross-sectional, whereas others are longitudinal. Some studies compared the performance of the CHR group with that of healthy controls, whereas others compared the performance of CHR individuals who later converted to psychosis to that of CHR individuals who did not convert.

In a few of these publications, the CHR group was divided into two groups, usually on the basis of the severity of symptoms. The less severe group typically met what are known as basic symptoms while the more severe group met criteria for either an Attenuated Positive Symptom Syndrome or a Brief Intermittent Psychotic Syndrome. In such cases only data from the more severe group, i.e., those meeting the more typical criteria were considered in the review. The summary of the results presented below are based on the 23 studies reviewed and listed in Table 1.

Comparison of CHR individuals with healthy controls

There is increasing evidence from the studies reviewed that compared to healthy controls CHR individuals are significantly impaired in cognition when a composite cognitive score is considered. Otherwise, there is some evidence suggesting impairment in specific domains of cognition but for most domains of cognition results are mixed. For example about half of the studies we reviewed that assessed intelligence reported significant impairment in verbal intelligence in the CHR group, while the remainder found no difference. However, there was less evidence of non-verbal IQ impairment in this population.

Impaired verbal memory was reported in eight studies using a range of tasks such as list learning and the Wechsler Memory Scale Logical Memory subtest, but five studies did not support this finding. Interestingly, the majority of studies do not support a difference in visual memory (Niendam *et al.* 2006, 2007; Pukrop *et al.* 2006; Becker *et al.* 2010*b*; Lindgren *et al.* 2010). Both verbal and visuo-spatial working-memory deficits have frequently been reported in the CHR population (Brewer *et al.* 2006); however, recent results are inconsistent with four to five studies demonstrating working-memory deficits and the same number reporting no differences. Similar results are observed for processing speed, sustained attention, executive functioning and fine motor function with several studies reporting impairment in the CHR group and several failing to highlight a difference between CHR and healthy control groups. The one exception was verbal fluency for which impairment has been consistently observed.

Thus, the results from a comprehensive selection of studies comparing CHR individuals with healthy controls on the majority of cognitive tasks are consistently contradictory. It is possible that the inconsistency can be accounted for by the use of different tasks across different studies; for example, tests such as digit symbol coding are known to be sensitive for the detection of subtle impairment, while others may have limited sensitivity. Nonetheless, this is not always the case as contrasting results often come from studies that used the same measure.

Conversion to psychosis

One of the important aims of CHR research is to discover predictors of developing psychosis. Several studies compared baseline scores of those CHR participants who went on to develop psychosis to those who did not. Unfortunately, once again consistent results are rare. There are reports that those who converted were significantly impaired on a composite score of cognition or had lower verbal IQ but in each case there are contradictory studies. There is support for poorer performance on tests of verbal memory, verbal fluency and processing speed for those who converted, but this was not consistently supported. However, results supporting a lack of significant difference in visual memory, verbal or spatial working memory, executive functioning, attention or finger tapping between the converters and non-converters are consistently reported. Studies are limited but there is

Table 1. *Studies of cognition in individuals at CHR for psychosis*

Study	Participants	Mean age	Tasks	Follow-up (months)	Rate of conversion	Anti-psychotic use	Clinical tool
Eastvold *et al.* (2007)	40 CHR 36 Controls	21 22	Vocabulary, block design, Stroop colour naming, Stroop colour-word, numeric attention, letter number sequencing, spatial span, HVLT, WCST	12	17%	NA	SIPS/SOPS
Frommann *et al.* (2010)	89 CHR 87 Controls	25 25	MWT-B, RAVLT, self-ordered pointing task, trails A and B, digit symbol coding, letter fluency, CPT, letter number sequencing	–	–	Yes (10%)	ERIraos
Pflueger *et al.* (2007)	54 CHR 51 Controls	27 23	MWT-A and LPS scale 3, tower of Hanoi, WCST, TAP (go/no go, working memory), CPT-OX		–	Yes (7%)	BSIP/BPRS
Pukrop *et al.* (2006)	90 CHR 179 Controls	25 29	MWT-B, visual backwards masking, CPT-IP, spatial working memory task (dot location), RAVLT, Rey–Osterrieth complex figure test, category and letter fluency, WCST	–	–	No	SIPS/SOPS
Simon *et al.* (2007)	69 CHR Normative data	20 NA	MWT-B, letter number sequencing, trails A and B, category and letter fluency, WCST, RAVLT, TAP (sustained attention, alertness)	–	–	No	SIPS/SOPS
Jahshan *et al.* (2010)*	48 CHR 29 Controls	19 19	Vocabulary, block design, WCST, Stroop colour-word, numeric attention, Stroop colour naming, HVLT, letter number sequencing, spatial span	6	12.5%	Yes (21%)	SIPS/SOPS
Keefe *et al.* (2006)*	37 CHR 47 Controls	21 24	Premorbid IQ (NART), category and letter fluency, CPT-IP, CVLT, digit symbol coding, spatial working memory task (dot location), letter number sequencing, finger tapping	12	39%	No	SIPS/SOPS
Seidman *et al.* (2010)	304 CHR 193 Controls	18 19	Vocabulary, block design, digit symbol coding, trails B, letter fluency, WCST, stories/logical memory, list learning, CPT-IP	30	29%	NA	SIPS/SOPS
Woodberry *et al.* (2010)	73 CHR 34 Controls	16 16	Premorbid IQ (WRAT), vocabulary, block design, similarities, matrix reasoning), CPT-IP, CVLT, stories/ logical memory, category fluency, trails 4, WCST, letter number sequencing, finger tapping, B-SIT	24	50%	Yes	SIPS/SOPS
Lindgren *et al.* (2010)	62 CHR 72 Controls 112 HSC	16 16	Vocabulary, block design, reaction time, category and letter fluency, trails A, B, and C, digit symbol coding, CVLT, prose learning, visual reproductions, digit span, visual span, similarities, matrix reasoning, dot cancellation, counting backwards, dual task numbers, dual task dots, Purdue pegboard, spatial tapping	–	–	NA	SIPS/SOPS

Continued

Table 1. *Continued*

Study	Participants	Mean age	Tasks	Follow-up (months)	Rate of conversion	Anti-psychotic use	Clinical tool
Ozgurdal *et al.* (2009)	54 CHR Normative data	25 NA	MWT-B, LPS section UT3, category and letter fluency, trails B, Stroop colour-word, CPT-IP, AVLT (German version), WCST	–	–	Yes (31%)	SIPS/SOPS and BSABS
Hurlemann *et al.* (2008)	16 CHR 30 Controls	27 28	MWT-B, RAVLT	18	31%	No	ERIraos
Niendam *et al.* (2006)	45 CHR Normative data	18 NA	Full scale WISC/WAIS current IQ, trails A and B, digit symbol coding, category and letter fluency, matrix reasoning, visual reproductions, digit span, CVLT, stories/logical memory, finger tapping	–	–	Yes (42%)	SIPS/SOPS
Niendam *et al.* (2007)*	35 CHR Normative data	17 NA	WASI IQ, trails A and B, digit symbol coding, letter fluency, matrix reasoning, visual reproductions, digit span, CVLT, stories/logical memory, finger tapping	8	25%	Yes (50%)	SIPS/SOPS
Becker *et al.* (2010*b*)*	40 CHR 17 Controls	20 19	Premorbid IQ (NART), CVLT, category and letter fluency, CPT, finger tapping, spatial working memory test (dot location), complex figure of Rey	18	41%	NA	SIPS/SOPS and BSABS
Pukrop *et al.* (2007)	83 CHR 44 Controls	24 25	MWT-B, visual backwards masking, CPT-IP, dual tasking test, letter number sequencing, subject ordered pointing task, spatial working memory task (dot location), RAVLT, Rey-Osterrieth complex figure task, digit symbol coding, trails A and B, WCST, category and letter fluency	At least 12	53%	No	SIPS/SOPS
Fusar-Poli *et al.* (2010)*	15 CHR 15 Controls	25 24	Premorbid IQ (NART), paired associate learning	12	13%	No	CAARMS
Becker *et al.* (2010*a*)	47 CHR 42 Controls	21 20	Category and letter fluency	24	38%	Yes (25%)	SIPS/SOPS and BSABS
Magaud *et al.* (2010)	77 CHR 61 HSC	21 20	Category and letter fluency	–	–	Yes (13%)	CAARMS
Hawkins *et al.* (2008)*	60 CHR No controls	18 –	Vocabulary, block design, information, finger tapping, CPT-IP, VIDA, letter number sequencing, Ruff figural fluency, Benton line orientation, CVLT, visual reproductions, digit symbol coding, Stroop colour and word, trails A and B, category and letter fluency, WCST	12	35%	Yes (50%)	SIPS/SOPS

Wood *et al.* (2007)*	16 CHR 17 Controls	19 20	Premorbid IQ (NART), block design, information, digit span, arithmetic, similarities, picture completion, digit symbol coding, logical memory, visual reproductions, digits forwards and backwards, paired associates, RAVLT, trails A and B, letter fluency	12	44%	Not at baseline, but one after	CAARMS
Riecher-Rossler *et al.* (2007)	53 CHR No controls	26 –	MWT-A, LPS scale 3, Tower of Hanoi, TAP (go/no go, working memory), CPT-OX	53	40%	Yes (7%)	BSIP/BPRS
Linszen *et al.* in Abubaker *et al.* (2008)†	CHR HSC	NA NA	CPT-IP, RAVLT, Verbal fluency test, finger tapping, spatial working memory test	18	NA	NA	SIPS and BSABS-P

Note: *, Longitudinal studies; IQ, intelligence quotient; RPMIP, Royal Park multidiagnostic instrument for psychosis; BSABS, Bonn scale for the assessment of basic symptoms; ERIraos, early recognition inventory/interview for the retrospective assessment of the onset of schizophrenia; CAARMS, comprehensive assessment of at risk mental state; SIPS, structured interview for prodromal syndromes; SOPS, scale of prodromal symptoms; ICD, international classification of diseases; BSIP, Basel screening instrument for psychosis; BPRS, brief psychiatric rating scale; HSC, help seeking controls; NART, national adult reading test; WRAT, wide range achievement test; CPT-IP, continuous performance test-identical pairs; CVLT, California verbal learning test; RAVLT, Rey auditory verbal learning test; HVLT, Hopkins verbal learning test; VIDA, variable interval delayed alternation; LPS, performance test system; MWT, multiple choice vocabulary intelligence test; WCST, Wisconsin card sorting test; TAP, test of attentional performance; WISC/WAIS, Wechsler intelligence scale for children/Wechsler adult intelligence scale; B-SIT, brief smell identification test; UPSIT, university of Pennsylvania smell identification test; †, unpublished data.

indication that converters are more impaired in olfaction (Woodberry *et al.* 2010). Thus, it may be that, in general, those who convert do have more cognitive impairment but this is not always reported and not for specific tasks.

One possibility is that although, in several studies there is little to differentiate converters from non-converters, at baseline those who do convert may evidence some cognitive decline over time. At this stage longitudinal research is limited, but most studies found that cognitive functioning in both converters and non-converters remains stable over time and that the cognitive course of these two groups does not differ from one another.

Discussion

In this article, we drew our conclusions from the review of 23 recent studies published in the last 6 years that assessed cognition in individuals at CHR for developing psychosis. Some general conclusions can be drawn from the studies reviewed and presented in Table 1. First, individuals at CHR for psychosis, as a group, demonstrate impairment in cognition relative to healthy controls when a composite score created by factor analysis is used as well as on a few individual cognitive tasks, specifically verbal fluency and olfaction. Second, from the longitudinal studies that exist cognitive functioning appears to remain stable over time for some aspects but to date there is not a great deal of evidence to suggest a decline. Third, with respect to conversion, there do not seem to be any tasks that consistently differentiate the converters from the non-converters, although often those who convert tend to have lower verbal IQ, verbal memory, verbal fluency and speed of processing. Results comparing the longitudinal course of cognitive functioning between those who convert and those who do not are inconsistent. However, longitudinal studies are rare and the available data do not allow solving the controversial issue of whether there is a decline in cognition during the prodromal period or whether the decline occurs post the development of psychosis. It is not unreasonable to assume that as individuals developed psychosis there would be a decline in cognition since it has been demonstrated that CHR individuals exhibit cognitive impairment intermediate between first episode patients and healthy controls (Brewer *et al.* 2006). However, current data are unable to demonstrate when that decline may occur. Perhaps further work needs to follow converters cognitively longitudinally once psychosis has been established.

Overall, our results are consistent with those previously published by Brewer *et al.* (2006). Interestingly,

since our review, there has been published in 2012 two meta-analyses (Giuliano *et al.* 2012; Fusar-Poli *et al.* 2012*a*). The first meta-analysis (Giuliano *et al.* 2012) suggests small-to-medium impairments across nine of ten cognitive domains. Furthermore, for those who developed psychosis their baseline performance was generally more impaired than those who did not convert. The more specific results of the paper by Giuliano *et al.* may be due to a narrower selection of studies, i.e. only 14 studies that appear to be with samples that met the criteria based on the SIPS or CAARMS and to the fact that cognitive tasks were grouped into cognitive domains. The second meta-analysis by Fusar-Poli *et al.* (2012*a*) using 18 studies (although three of the studies only contained measures of social cognition) suggests that CHR participants were impaired on tests of general intelligence, executive functioning, verbal and visual memory, attention and working memory. Later, transition to psychosis was associated with poorer verbal fluency and memory. Unlike the earlier meta-analysis, papers with participants meeting the basic symptom criteria were included. This paper focused mainly on cross-sectional studies but did investigate moderators. They found no effect for year of publication, exposure to antipsychotics, age and sex.

Taken together these results offer some preliminary insights into the neurodevelopmental trajectory of psychosis. The finding that CHR individuals present in many studies with cognitive impairment suggests that these young individuals may already exhibit neural abnormalities, possibly in the prefrontal cortex given its association with most of the discussed cognitive abilities (Fuster, 2001). Moreover, functional imaging studies have consistently found prefrontal cortical dysfunction during cognitive tasks in CHR individuals (Benetti *et al.* 2009; Broome *et al.* 2009; Crossley *et al.* 2009). Although not consistently demonstrated, there is evidence of greater impairment for those who go on to develop psychosis compared with those who do not.

Some of the inconsistency may result from several limitations. Firstly, sample sizes tended to be relatively small, especially for longitudinal studies, although the meta-analysis with larger samples was more supportive of the results of our review. Secondly, some of the longitudinal studies had somewhat short follow-up periods, typically ranging from 6 to 18 months, which certainly at the lower end may not be long enough to determine conversions. This is particularly relevant since the risk of transition to psychosis seems to increase with the duration of the follow-up period (Fusar-Poli *et al.* 2012*b*). Thirdly, the rate of participant drop out is relatively high, and it may be that those who drop out may experience a different clinical or cognitive course. Fourthly, a variable rate of participants medicated with antipsychotics was reported in some studies. However, this did not seem to account for the inconsistent results as in most of these studies additional analyses were conducted to exclude any correlation between cognitive performance and the use of antipsychotics, with only one study reporting an influence of olanzapine on visual memory (Hawkins *et al.* 2008).

Fifthly, there is a wide variation in tasks used across the different studies, with some being potentially more sensitive for detection of subtle impairment. It is also possible that low performance in cognitive tests may reflect an impairment in general intellectual ability more than deficits in specific domains (Abubaker *et al.* 2008). Moreover, as Brewer *et al.* (2006) pointed out, some cognitive domains are neuropsychologically complex, each including discrete sub-processes which may be compromised in a different way, and therefore further examination of the sub-processes involved in each task is still needed.

Finally, the lack of homogeneity within the CHR group may partially explain this pattern of results. In fact, outcomes from recent studies with longer follow-up periods (at least 2 years) suggest that help-seeking individuals who meet CHR criteria cluster into several groups, some of them developing a psychotic illness, others remitting from their symptoms, others improving modestly, (Addington *et al.* 2011), and that at least one-third of individuals identified as CHR are likely to represent false positives (Schlosser *et al.* 2011).

In summary, given the limited nature of the current available results, further research is required before the role of cognition in the prediction of psychosis can be well understood. Future studies need to attend to the increasing use of antipsychotics in CHR populations, greater matching of controls on premorbid IQ, more understanding of the potential of moderator variables, longer follow-up periods and specifically selected cognitive tasks. More recent studies such as the ongoing North American Longitudinal Prodromal Study are using batteries such as the MATRICS that have been well-established in samples with schizophrenia. The definition of conversion may also be important. In these high-risk studies, definitions of conversion range from schizophrenia to a diagnosis of schizophrenia or other psychotic disorders or in some studies the attenuated symptoms reached a psychotic intensity over a given period of time. As Brewer *et al.* (2003) demonstrated in an examination of olfaction, lower cognition at initial assessment in those who convert may be limited to those whose end diagnosis is schizophrenia.

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