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REVIEW ARTICLE

Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder

K. E. Lewandowski*, B. M. Cohen and D. Öngur

McLean Hospital and Harvard Medical School, Boston, MA, USA

Background. Neurocognitive dysfunction in schizophrenia (SZ), bipolar (BD) and related disorders represents a core feature of these illnesses, possibly a marker of underlying pathophysiology. Substantial overlap in domains of neuropsychological deficits has been reported among these disorders after illness onset. However, it is unclear whether deficits follow the same longitudinal pre- and post-morbid course across diagnoses. We examine evidence for neurocognitive dysfunction as a core feature of all idiopathic psychotic illnesses, and trace its evolution from pre-morbid and prodromal states through the emergence of overt psychosis and into chronic illness in patients with SZ, BD and related disorders.

Method. Articles reporting on neuropsychological functioning in patients with SZ, BD and related disorders before and after illness onset were reviewed. Given the vast literature on these topics and the present focus on cross-diagnostic comparisons, priority was given to primary data papers that assessed cross-diagnostic samples and recent meta-analyses.

Results. Patients with SZ exhibit dysfunction preceding the onset of illness, which becomes more pronounced in the prodrome and early years following diagnosis, then settles into a stable pattern. Patients with BD generally exhibit typical cognitive development pre-morbidly, but demonstrate deficits by first episode that are amplified with worsening symptoms and exacerbations.

Conclusions. Neuropsychological deficits represent a core feature of SZ and BD; however, their onset and progression differ between diagnostic groups. A lifetime perspective on the evolution of neurocognitive deficits in SZ and BD reveals distinct patterns, and may provide a useful guide to the examination of the pathophysiological processes underpinning these functions across disorders.

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Introduction

Substantial evidence exists of shared genetic liability between schizophrenia (SZ) and bipolar disorder (BD) (e.g. Tsuang *et al*. 1980; Kendler *et al*. 1998; Torrey, 1999; Valles *et al*. 2000; Craddock *et al*. 2006). Examination of the nature of the development, expression and longitudinal course of major features of illness may help to illuminate the extent to which specific pathological processes are shared or distinct in these disorders. Patients with SZ, BD and related disorders exhibit persistent neuropsychological deficits after, and often before, onset of overt illness. Such deficits may reflect pathophysiology and neurodevelopment. However, despite substantial overlap in biological and clinical features of psychotic disorders, the longitudinal trajectory of neuropsychological dysfunction across diagnoses remains unclear. Clarification of the onset and evolution of neurocognitive deficits in psychosis is crucial for identifying relevant cognitive phenotypes and clarifying the pathophysiological processes that are reflected by neuropsychological assessment.

Method

The literature examining neuropsychological deficits in SZ, BD and related disorders is extensive. The present work focused on meta-analyses and cross-diagnostic studies examining neuropsychological functioning in patients with SZ, BD, schizo-affective disorder (SZA) and related disorders such as major depressive disorder with psychosis (MDD) and psychosis not otherwise specified (NOS). PubMed searches were performed (most recently on 31 March 2010) using the search phrases 'schizophrenia AND

* Address for correspondence: Dr K. E. Lewandowski, AB347, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA.
(Email: klewandowski@mclean.harvard.edu)

bipolar AND cogniti*', 'schizophrenia AND bipolar AND neurocogniti*' and 'schizophrenia AND schizoaffective AND cognit*'. Additionally, a review was conducted examining pre-morbid and prodromal cognitive functioning in psychosis. We performed searches in PubMed using the terms 'pre-morbid', 'at-risk' or 'prodrom*' AND 'schizophrenia', 'schizo*' or 'bipolar' AND 'cognition', and 'neuropsycholog*' or 'neurocogniti*'. References within articles were reviewed for those germane to the topic. Selected papers had a major focus on the measurement and reporting of neuropsychological deficits in patients with SZ, BD and SZA. Articles whose primary focus was genetics or neuroimaging were excluded, as were treatment outcome studies unless neurocognitive functioning at baseline was a primary variable of interest and the results of the neurocognitive testing were clearly reported. Studies that focused on patients with comorbid substance or developmental disorders were also excluded because detailed examination of their effects on neurocognitive functioning is outside the scope of this paper. Studies that examined neuropsychological functioning using well-validated measures and in domains identified as relevant to SZ or BD were prioritized, as were recent meta-analyses. We did not have *a priori* hypotheses regarding the relationship of cognitive development to diagnosis in terms of cross-sectional studies or longitudinal course. Thus, papers were not prioritized for inclusion based on the nature of the reported findings.

Results

Neuropsychological deficits in SZ and BP

Neuropsychological dysfunction is thought to represent a core feature of psychotic illnesses including SZ and BD (Green, 1996; Heinrichs & Zakzanis, 1998; Murphy & Sahakian, 2001). Global cognitive processing is reported to be impaired in patients with SZ (e.g. Cornblatt & Erlenmeyer-Kimling, 1985; Dickinson *et al*. 2004); however, other findings suggest that specific neurocognitive domains, including working memory, executive functioning, sustained attention and processing speed, may be especially impaired (Park & Holzman, 1992; Gold & Harvey, 1993; Goldman-Rakic, 1994; Aloia *et al*. 1996; Cohen *et al*. 1996; Heinrichs & Zakzanis, 1998; Lenzenweger & Dworkin, 1998; Green *et al*. 2000; Kuperberg & Heckers, 2000; Riley *et al*. 2000; Weickert *et al*. 2000; Keefe *et al*. 2006*a*). A recent meta-analysis of 2204 patients in the first episode demonstrated neurocognitive impairments across multiple domains that approached or equaled the level of impairments measured in chronically ill patients (Mesholam-Gately *et al*. 2009). Studies that matched patients with SZ and control participants for Wechsler Adult Intelligence Scale (WAIS) IQ continued to detect impairments in executive functioning, memory and processing speed in SZ participants (Elliott *et al*. 1995; Weickert *et al*. 2000; Leeson *et al*. 2010), suggesting that patients experience pronounced deficits both in specific domains of neuropsychological functioning and in broad cognitive dysfunction. This is consistent with findings using structural equation modeling, showing that cognitive dysfunction in SZ is largely generalized across functional domains, with smaller, domain-specific direct effects (in this case, verbal memory and processing speed) (Dickinson *et al*. 2008). Patients with BD also exhibit cognitive deficits relative to healthy adults, with specific impairments in memory, executive function and processing speed (Rubinsztein *et al*. 2000; Robinson *et al*. 2006). A meta-analysis of patients with BD in euthymic ($n=1197$), manic or mixed ($n=314$) or depressed ($n=96$) episodes found that patients experience neuropsychological impairment at all phases of illness, although deficits in some domains are found to worsen with disease exacerbation (Kurtz & Gerraty, 2009).

Impairment in executive functioning, working memory, attention and processing speed has also been documented in people presumed to share a genetic liability to psychosis, including patients with SZ spectrum disorders, first-degree relatives of SZ or BD probands (Saykin *et al*. 1991; Voglmaier *et al*. 1997; Robinson & Ferrier, 2006; Seidman *et al*. 2006*b*), people psychometrically identified as at risk for the development of SZ (Lenzenweger & Dworkin, 1998; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling *et al*. 2000), and non-psychotic children with 22q11 deletion syndrome (22q11DS), a genetic microdeletion thought to confer liability to the development of psychosis (Henry *et al*. 2002; Bearden *et al*. 2004; van Amelsvoort *et al*. 2004; Lewandowski *et al*. 2007). These findings suggest that neuropsychological deficits are associated with liability to illness in the absence of acute psychosis.

Neuropsychological deficits across disorders and subtypes

The extent to which neuropsychological deficits are comparable across diagnoses is unclear. Studies examining neuropsychological functioning in cross-diagnostic samples are summarized in Table 1. In general, patients across diagnostic groups are impaired on all neurocognitive measures compared to controls. A majority of findings report that patients with SZ are quantitatively more impaired than patients with BD on neurocognitive measures, although a sizable

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minority report that patients are not statistically different across groups. Similarities in executive functioning between patients with BD and SZ are most commonly reported, although studies have also found comparable levels of impairment in working memory, attention, verbal and visuospatial learning and memory, verbal fluency and motor control across groups. In many cases, however, other potentially influential factors regarding patient characteristics are not reported or controlled, including lifetime history of psychosis in BD patients, duration of illness, medication, or severity of state symptomatology at the time of testing.

The presence of neuropsychological deficits in related disorders is less well studied. On average, patients with SZA perform better than patients with SZ, but exhibit deficits relative to healthy populations (Stip *et al*. 2005; Heinrichs *et al*. 2008). Group differences remained in patients matched for symptom severity and when assessed over time (Stip *et al*. 2005). A comparison of patients with SZ, SZA, BD and MDD found a similar pattern of neuropsychological performance across groups, including deficits in memory, executive functions, and attention and processing speed; however, SZ patients were the most impaired, suggesting that differences in neurocognitive performance between patient groups may be quantitative but not qualitative (Reichenberg *et al*. 2009).

Although group significance testing indicates that, on average, patients perform worse than controls on neuropsychological measures, scores may not be normally distributed in patient populations. One study reported a bimodal distribution of Wisconsin Card Sorting Test (WCST) scores in patients with BD, with some patients at near-control levels and others significantly impaired (Altshuler *et al*. 2004). In a cross-diagnostic study, the prevalence of normal-level neuropsychological functioning on tasks of executive, memory and attention ranged from 16% to 45% in SZ, 20% to 33% in SZA, 42% to 64% in BD and 42% to 77% in MDD (Reichenberg *et al*. 2009). It is unclear whether patients who are functioning at normative levels have maintained healthy levels of neurocognitive functioning, or whether their pre-morbid functioning was higher than normal.

In patients with SZ, cognitive functioning is most commonly associated with negative symptoms (Andreasen *et al*. 1990; Berman *et al*. 1997; Nieuwenstein *et al*. 2001; Leeson *et al*. 2009). Patients classified as positive symptom or paranoid subtype tend to perform better on neurocognitive tasks than negative or disorganized subtype patients (Zalewski *et al*. 1998; Hill *et al*. 2001; Brazo *et al*. 2002; Cvetic & Vukovic, 2006; Wang *et al*. 2008). However, not all studies report differences in neurocognitive functioning by SZ subtype (Tam & Liu, 2004). Neuropsychological dysfunction in BD may also be related to symptom type and severity, and has been associated with earlier age of onset (Osuji & Cullum, 2005). Cognitive deficits seem to be more pronounced in patients experiencing manic or mixed states, especially in verbal fluency (Dixon *et al*. 2004), working memory, spatial attention and problem solving (Sweeney *et al*. 2000). We did not find publications examining neurocognitive dysfunction in the same patients in both depressed and manic phases. Additionally, history of psychosis in BD has been associated with greater cognitive dysfunction (Glahn *et al*. 2006, 2007; Martinez-Aran *et al*. 2008; Simonsen *et al*. 2009); however, these findings are not always replicated (Selva *et al*. 2007; Sanchez-Morla *et al*. 2009).

Longitudinal course of neuropsychological deficits

Pre-morbid cognitive functioning

Although the onset and experience of psychosis may play a role in the manifestation of cognitive impairment, both retrospective and prospective studies of patients with SZ suggest that cognitive deficits are present prior to the onset of psychotic symptoms. Retrospective studies suggest that, on average, general intelligence is lower in individuals who later develop SZ, and may diverge from normal well before symptom onset (Jones *et al*. 1994; McIntosh *et al*. 2005; Reichenberg *et al*. 2005; Kremen *et al*. 2006; Osler *et al*. 2007; Woodberry *et al*. 2008). General cognitive deficits have been reported as early as age 7 (Seidman *et al*. 2006*a*), and a 'follow-back' study of patients with SZ found significant deficits in academic achievement by the first grade, with patients performing between 0.8 and 1.1 grade equivalents below their peers (Bilder *et al*. 2006). These deficits increased throughout the school years, such that pre-SZ children lagged 1.5 to 1.8 grade levels behind their peers by the 12th grade. Another report found that children who went on to develop SZ exhibited non-significant deficits between grades 4 and 8, and cognitive performance declined significantly between grades 8 and 11 (Fuller *et al*. 2002).

In addition to general intellectual deficits, children who later develop SZ exhibit neuropsychological deficits in several domains. In high-risk samples, non-psychotic children exhibit attention deficits that may predict later decompensation (Cornblatt *et al*. 1989, 1992). Children at risk for MDD also exhibited attention deficits; however, deficits were of a smaller magnitude than in children of parents with SZ, were not stable over time, and did not predict subsequent clinical manifestations (Cornblatt *et al*. 1989). A large cohort study found that children who later develop SZ

Table 1. *Summary of cross-diagnostic studies of neurocognitive functioning*

Study[a]	Sample characteristics[b]	Materials	Findings
Barrett *et al*. 2009	BD/mania ($n=32$, age = 37) SZ (SZ = 44, SZA = 2, age = 29) Controls ($n=67$, mean age = 32)	WASI; NART; Digit Span; WMS Paired Associates; Corsi Block Tapping; ROCFT; Hayling and Brixton Tests; COWAT; Perin's Spoonerisms; Finger Localization Test	By first episode, all patients impaired on tests of memory, executive functioning and language BD better on response inhibition, verbal fluency and callosal functioning Compared SZ with 'preserved' IQ *v.* BD: no group differences and similar 'pattern' of deficits
Simonsen *et al*. 2009	SZ ($n=102$, age = 32) SZA ($n=27$, age = 34) BD I or II ($n=136$, age = 36) [BD with psychosis = 75] Controls ($n=280$, age = 36)	WMS-III Logical Memory; CVLT-II; WAIS-III Coding, Digit Span; Verbal Fluency Test D-KEFS; WM-Mental Arithmetic; 2-Back; Color Word Interference Test	All patients with a history of psychosis performed poorly on all measures Groups with psychosis did not differ from each other, but performed worse than the BD no psychosis group BD without psychosis < Controls on processing speed only
Sanchez-Morla *et al*. 2009	BD ($n=73$, mean age = 44) (Type I = 55, Type II = 18) SZ ($n=88$, mean age = 39) Controls ($n=67$, mean age = 44)	WCST; Tower of Hanoi; COWAT; Animal Naming; Trails B; Stroop; Digits Backward; Degraded Stimulus CPT; CVLT; ROCFT; WAIS-R Voc	All patients < Controls on all tasks SZ = BD: WCST, Stroop, Tower of Hanoi, CPT, Letter Fluency, Animal Naming, most verbal learning and memory SZ < BD: Trails B, ROCFT, Digits Backward, some CVLT BD with psychosis = BD without Duration of illness correlated with executive, verbal memory and visual memory in BD
Reichenberg *et al*. 2009	SZ ($n=94$, age = 29) SZA ($n=15$, age = 25) MDD w/ psychosis ($n=48$, age = 29) BD I w/ psychosis ($n=78$, age = 29)	WAIS-R Voc, Info, Picture Completion, Coding; WMS Verbal Paired Associates, Visual Reproduction; Stroop; Trails A/B; Symbol-Digit Modalities Test; Finger Tapping Test; Facial Recognition Test; Letter Fluency; Sentence Repetition	Comparable 'patterns' in all groups: deficits in memory, executive functioning, attention, processing speed SZ most impaired in all cognitive domains Prevalence of normal-range scores by group: 16–45% SZ, 20–33% SZA, 42–64% BD, 42–77% MDD
Smith *et al*. 2009	SZ ($n=72$, age = 39) SZA/BD w/ psychosis (grouped as PMDs; $n=25$, age = 41) Controls ($n=72$, age = 40)	WAIS-III Voc, Matrix; WMS- III Digits, Sequencing, Spatial Span, Logical Memory, Recall of Family Pictures; CPT; Trails B; Verbal Fluency; WCST	SZ = PMD on working memory, episodic memory, and executive functioning domains SZ and PMD < Controls SZ < PMD, Controls on IQ
Heinrichs *et al*. 2008	SZ ($n=103$, age = 43) SZA ($n=48$, age = 39) Controls ($n=72$, age = 41)	WAIS-III Voc, Matrix, Sequencing, Symbol Search; CVLT-II; COWAT; WRAT Reading	SZ < SZA on all tasks No evidence for unique predictive validity of any neurocognitive task
Schretlen *et al*. 2007	SZ ($n=106$, age = 42) BD ($n=66$, age = 40) Controls ($n=316$, age = 55)	Grooved Pegboard; Trails A/B; Brief Test of Attention; CPT; WCST (modified); Verbal Fluency; Design Fluency; HVLT-R; BVMT-R	SZ < Controls on all measures BD < Controls on most measures Similar pattern of deficits, but SZ quantitatively more impaired than BD

Depp *et al*. 2007	BD ($n=67$, age = 58) SZ ($n=150$, age = 57) Controls ($n=85$, age = 64)	WAIS-R Voc, Digits, Coding, Blocks; BNT; Digit Vigilance(time); Story Memory Test; CVLT; Figure Memory Test; Trails A/B; Letter Fluency; Grooved Pegboard; WCST	Different 'pattern' of deficits in BD *v*. SZ: BD < Controls on all measures except Voc, Story Memory and BNT; SZ < BD on Voc, BNT, CVLT, Story Memory, Coding, Trails A/B By domain, BD < Controls in all domains; BD = SZ on reasoning/problem solving and visual memory Effect size greater for BD *v*. Controls than for SZ *v*. BD
Glahn *et al*. 2006	SZ ($n=15$, age = 37) SZA depressed ($n=15$, age = 36) BD w/ psychosis ($n=11$, age = 35) BD w/o psychosis ($n=15$, age = 37) Controls ($n=32$; age = 39)	WAIS-III Digits; Spatial Delayed Response Task (DRT)	All patients impaired on digits backward Only patients with history of psychosis impaired on spatial DRT Digits forward: BD with psychosis, SZA and SZ mildly impaired; BD w/o psychosis = Controls
Balanza-Martinez *et al*. 2005	BD I ($n=15$, age = 42) SZ ($n=15$, age = 30) Controls ($n=26$, age = 42)	WCST; Verbal Fluency; Assessed at baseline and 3 years; Stroop; Coding; Babcock Story Recall; Trails A/B	Patients < Controls on most tasks at baseline and follow-up; 'Profile' similar for BD and SZ SZ = BD on all tests (controlling for age and duration of illness)
Stip *et al*. 2005	SZ ($n=44$, age = 36) SZA ($n=13$, age = 33)	CANTAB Motor Screening; Reaction Time; Paired Associate Learning; Stockings of Cambridge	Patients assessed four times over 2 years SZ < SZA on motor screening and paired associates at baseline and over time
McIntosh *et al*. 2005	SZ, SZ family ($n=27$, age = 38) BD, BD family ($n=25$, age = 39) BD, 'mixed' family ($n=20$, age = 41) UA, SZ family ($n=25$; age = 39) UA, BD family ($n=24$, age = 34) UA, 'mixed' family ($n=27$, age = 34) Controls ($n=50$, age = 36)	NART; WASI; E-RBMT; Verbal Fluency; Stockings of Cambridge; Hayling Sentence Completion; Coding; Simple Reaction Time; Choice Reaction Time	SZ < BD, relatives, Controls: current verbal intelligence, pre-morbid IQ, reaction time SZ, BD, relatives < Controls: memory SZ, BD and SZ or Mixed relatives < Controls: executive functioning Intellectual abnormalities associated with SZ, whereas memory dysfunction associated with all patients
Altshuler *et al*. 2004	SZ ($n=20$, age = 50) BD ($n=40$, age = 50) Controls ($n=22$, age = 52)	NART; CVLT; WCST; Verbal Fluency; ROCFT; Trails A/B; WAIS-R Blocks; Stroop; Star Mirror Tracing Task; Pursuit Rotor Test	SZ, BD < Controls: WCST (PE), CVLT (except Recognition), and ROCFT SZ < BD, Controls: NART, WCST (categories), Trails A/B, Stroop Bimodal distribution in BD
Dickerson *et al*. 2004	SZ ($n=229$, age = 42) BD ($n=117$, age = 41) Controls ($n=100$, age = 36)	RBANS – includes 12 subtests used to calculate five index scores: Immediate Memory, Visuospatial/Constructional, Language, Attention, Delayed Memory	SZ < BD < Controls in all domains SZ < BD after controlling for demographic and symptom variables
Tam & Liu, 2004	SZ – positive ($n=30$, age = 25) SZ – negative ($n=22$, age = 26) BD ($n=27$, age = 26) Controls ($n=28$, age = 25)	CogLab: Mueller-Lyer, Illusion, Combined Reaction Time, Size Estimation, Card Sort, Backward Masking, CPT	SZ < BD < Controls on WCST SZ = BD on all other measures SZ subtypes did not differ
McClellan *et al*. 2004	SZ ($n=27$, age = 15) BD ($n=22$, age = 15) Psychosis NOS ($n=20$, age 15) Age of onset prior to 18 years	WISC-III or WAIS-III; WCST; CVLT-C; COWAT; WRAML Visual Learning; VMI	No differences across groups Compared to norms, SZ < on general cognition, verbal learning, recall, effort, social knowledge BD and Psychosis NOS < on verbal learning, recall, and sustained effort

[*continues overleaf*

Table 1 (*cont.*)

Study[a]	Sample characteristics[b]	Materials	Findings
Tabares-Seisdedos *et al*. 2003	SZ ($n=30$, Positive FH = 6) BD I ($n=24$, Positive FH = 12)	WCST; COWAT; Babcock; Story Recall; Trails A/B; Stroop; WAIS-R Coding, Voc; Finger Tapping	SZ < BD: Verbal memory Positive FH associated with poorer Coding and Stroop interference
Seidman *et al*. 2003	SZ, chronic ($n=79$) BD I, chronic ($n=14$)	ROCFT	SZ < BD < Controls
Seidman *et al*. 2002	SZ ($n=87$) BD with psychosis ($n=15$) Controls ($n=94$)	Verbal ability: WAIS-R Voc, WRAT Reading and Spelling; Visual-Spatial Ability: WAIS-R Blocks; HVLT; Line Orientation; Abstraction/Executive: WCST, Visual-Verbal Test; Verbal Declarative Memory: WMS Logical Memory; Executive-Motor Functions: Graphic Sequences; Luria Perceptual-Motor Skills: Trails A and B; WAIS-R Coding; Mental Control: WAIS-R Digit Span; WRAT-R Arithmetic; Sustained Attention/Vigilance: Auditory CPT; Dichotic Listening	Patients had similar profile patterns Severity differed among groups Performance: SZ < BD < Controls
McGrath *et al*. 2001	SZ ($n=19$, age = 32) Mania ($n=12$, age = 40) Controls ($n=19$, age = 34)	Working Memory Task (Visuospatial memory task)	Tested at baseline and 4 weeks WM deficits in both patient groups with similar improvement over time
Rossi *et al*. 2000	SZ ($n=66$, age = 33) BD ($n=40$, age = 36) Controls ($n=64$, age 26)	WCST	SZ < BD < Controls (controlling for age and education)
Mojtabai *et al*. 2000	SZ ($n=102$, age = 30) Psychotic affective disorders) (BD w/ psychosis, $n=72$, age = 31) (MDD w/ psychosis, $n=49$, age = 31	Trails A/B; Stroop; Symbol Digit Modalities; Test of Facial Recognition; Sentence Repetition; Silly Sentences; COWAT; Finger Tapping Test; WAIS-R Coding, Picture Completion, Voc, Info; WMS-R Visual Reproduction, Verbal Paired Associates	SZ < BD, MDD on tests of attention, mental tracking/working memory, visual memory and verbal fluency after adjusting for covariates (age, gender, race, education, and Voc and Info scores) in patients within 2 years of first admission

Block, WAIS Block Design subtest; BD, bipolar disorder; BNT, Boston Naming Test; Coding, WAIS Digit Symbol Coding subtest; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; CVLT-C, California Verbal Learning Test-Children's Version; D-KEFS, Delis–Kaplan Executive Function System; E-RBMT, Extended Rivermead Behavioural Memory Test; FH, family history; Line Orientation, Judgment of Line Orientation Test; MDD, major depressive disorder; NART, National Adult Reading Test; NOS, not otherwise specified; PC, WAIS Picture Completion subtest; PMD, psychotic mood disorder; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; ROCFT, Rey–Osterrieth Complex Figure Test; Sequencing, WAIS Letter Number Sequencing; Stroop, Stroop Color and Word Test; SZ, schizophrenia; SZA, schizo-affective disorder; UA, unaffected; VMI, Test of Visual Motor Integration; Voc, WAIS Vocabulary subtest; WAIS-R/-III, Wechsler Adult Intelligence Scale (Revised/Third Edition); WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WISC-III, Wechsler Intelligence Scale for Children, Third Edition; WM, working memory; WMS, Wechsler Memory Test; WRAML, Wide Range of Memory and Learning Test; WRAT, Wide Range Achievement Test.

[a] See Altshuler *et al*. (2004) for review of earlier studies.

[b] 'Age' refers to mean group age, rounded to the nearest year.

exhibited deficits in verbal reasoning early in childhood, with increasing working memory, attention and processing speed burden through adolescence (Reichenberg *et al*. 2010). Similarly, the Edinburgh High-Risk Study reported that verbal learning deficits are present years before illness onset and predict later decompensation (Johnstone *et al*. 2005). IQ did not predict later decompensation; however, the mean IQ of the high-risk participants was nearly 10 points below that of control subjects, consistent with the above literature.

Several lines of evidence suggest that pre-morbid cognitive functioning in BD is very different from that in SZ. Retrospective investigations and record reviews suggest that children who later develop BD exhibit good academic functioning prior to illness onset (Quackenbush *et al*. 1996; Kutcher *et al*. 1998). A study of patients with BD ($n=53$) and SZ ($n=39$) failed to find deteriorating pre-morbid functioning in patients with BD, as was found in patients with SZ (Uzelac *et al*. 2006). A large study comparing the Israeli Draft Board Registry to the National Psychiatric Hospitalization Case Registry found that subjects at age 16–17 who went on to develop BD did not differ from people who remained healthy on any measure of neurocognitive functioning, in contrast to patients who later developed SZ or SZA (Reichenberg *et al*. 2002). Finally, a study of multiply affected families with BD and SZ reported that patients differed in terms of pre-morbid IQ by diagnosis (SZ < BD), although not in general intelligence after illness onset (Toulopoulou *et al*. 2006). Thus, it seems that children who later develop BD do not share the same pre-morbid cognitive impairments as children who go on to develop SZ (Murray *et al*. 2004).

Despite the absence of gross deficits in cognitive and academic functioning in children who later develop BD, subtle neurocognitive abnormalities may be present prior to illness onset. A prospective investigation of executive functioning in adolescents at risk for mood disorders found that significantly more participants who later developed BD exhibited WCST deficits compared with participants who later developed unipolar depression or no mood disorder (Meyer *et al*. 2004). A large Finnish cohort study examining verbal, arithmetic and visuospatial reasoning in healthy male conscripts (mean age 19.9 years) found that pre-morbid visuospatial deficits were associated with later development of both BD and SZ (mean time to follow-up, 7.1 years) (Tiihonen *et al*. 2005). Pre-BD children do not exhibit the same degree of deficits in general cognitive ability or school performance as pre-SZ children, although subtle neurocognitive abnormalities may exist. This gap seems to narrow considerably by the time of first episode.

Neuropsychological functioning from prodrome to first episode

Although children who later develop SZ exhibit cognitive deficits as early as elementary school, the onset of frank psychosis may be immediately preceded by a more precipitous decline in cognitive functioning. In a group of adolescents who later developed SZ, repeated testing with a standard aptitude assessment in 11th and 12th grades showed a significant drop in scores (Bilder *et al*. 2006). Additionally, in a large cohort of Israeli conscripts, risk for the development of SZ spectrum disorders was associated with declining IQ scores over 2 years (Reichenberg *et al*. 2006). Patients at risk for psychosis exhibit neurocognitive deficits in verbal learning and memory, verbal fluency (Becker *et al*. 2010) and overall neurocognitive functioning compared to healthy controls (Jahshan *et al*. 2010). High-risk subjects who converted to psychosis showed deterioration in working memory and processing speed over a 6-month follow-up, as did participants in the first episode (Jahshan *et al*. 2010). Thus, neuropsychological functioning may decline throughout the prodrome and into the first episode, with patients in the early prodrome exhibiting less impairment than patients in a later prodromal stage (Schultze-Lutter *et al*. 2007; Simon *et al*. 2007), and patients in the first episode exhibiting poorer functioning than prodromal participants (Hawkins *et al*. 2004; Keefe *et al*. 2006*b*). This is consistent with a cross-sectional investigation of neurocognitive functioning in patients classified as being in various stages of prodrome and post-onset psychosis, which reported that neurocognitive deficits increased at each 'stage' of illness (Pukrop *et al*. 2006). However, a recent review hypothesized that cognitive decline must occur prior to the prodrome, with the same degree of cognitive impairment seen by the first episode present throughout the prodromal period (Harvey, 2009). Not all studies have detected neurocognitive decline during the prodrome or an association between neurocognitive change and conversion to frank psychosis (Hawkins *et al*. 2008; Becker *et al*. 2010). Some of these inconsistencies may be associated with differences in defining the period of the SZ prodrome (Harvey, 2009).

Despite controversy regarding the timing of neurocognitive decline in the prodrome, by the onset of frank psychosis patients show pronounced deficits in multiple cognitive domains. A meta-analysis of first-episode patients with SZ found that all neurocognitive domains were impaired by first episode nearing or at the level typically seen in patients with chronic illness. IQ impairments were also significantly greater than in pre-morbid phases, suggesting that cognitive

functioning deteriorates between pre-morbid and first-episode phases of illness (Mesholam-Gately *et al*. 2009). A sample of never-medicated first-episode adolescents exhibited deficits in all cognitive domains compared to controls, with the largest effect sizes in the areas of executive functioning, attention and memory (Brickman *et al*. 2004). In a group of 44 first-episode SZ patients tested as part of the Israeli Draft Board procedures and again after a first episode of psychosis, patients exhibited deficits in abstract reasoning, processing speed and concentration relative to non-psychotic comparison participants after illness onset (Caspi *et al*. 2003).

Little is known about neurocognitive functioning in a BD prodrome. In fact, there is considerable controversy regarding the nature of a prodrome in BD more generally. However, immediately following illness onset adolescents with BD exhibit significant deterioration in cognitive and social domains (Quackenbush *et al*. 1996). This is consistent with other findings of deficits in general intellectual functioning and neurocognitive deficits in executive functioning, sustained attention, perceptuomotor skills and processing speed in first-episode BD patients (Nehra *et al*. 2006; Gruber *et al*. 2008).

Neuropsychological functioning following diagnosis

Cognitive functioning in adults with SZ seems to be relatively stable at the group level after diagnosis. A 10-year longitudinal study found that patients had significant neurocognitive impairment at first episode, and that these deficits were stable over the follow-up period (Hoff *et al*. 2005). This is consistent with other reports of relative neurocognitive stability in SZ patients over time and across domains, including verbal functioning, memory, cognitive flexibility, psychomotor speed, attention and learning (e.g. Goldberg *et al*. 1993; Heaton *et al*. 2001). Neurocognition does not seem to decline in early-stage SZ, and may even improve in some domains in well-treated patients (Gold *et al*. 1999). Additionally, change in clinical symptoms is not reliably associated with change in neurocognitive functioning in SZ patients (Heaton *et al*. 2001; Hoff *et al*. 2005). A report of patients assessed first as in-patients and again as out-patients found that deficits were relatively independent of acute phase of illness (Rosmark *et al*. 1999), and patients assessed at baseline and 1 year showed significant reduction in symptoms but no change in performance on a task of processing speed (Leeson *et al*. 2010). Similarly, attention deficits are reported to remain comparable in acute and remitted phases in patients with SZ, and are not strongly associated with clinical variables such as chronicity or severity of illness (Orzack & Kornetsky, 1966, 1971; Wohlberg & Kornetsky, 1973; Asarnow & MacCrimmon, 1978). However, a cross-sectional investigation found that patients with SZ experiencing multiple episodes exhibited more pronounced deficits than prodromal or first-episode patients (Pukrop *et al*. 2006). Of note, group data may reflect a mixture of patients who improve, decline or remain stable, making it difficult to identify trends in individuals. Overall, whereas some cross-sectional evidence suggests that neurocognitive functioning worsens with illness progression in SZ, longitudinal findings indicate that neurocognitive deficits are relatively stable at the group level and not tightly linked to symptom severity after illness onset and possibly prior to a first break.

Substantial evidence suggests that neurocognitive impairments are associated with duration of illness and disease course in BD (Zubieta *et al*. 2001; Robinson & Ferrier, 2006). A study of 49 relatively stable patients with BD found that patients with more severe and frequent affective episodes performed more poorly on cognitive testing (Denicoff *et al*. 1999). However, a recent study assessing neuropsychological functioning in 15 euthymic BD patients and 15 controls over a 2-year interval found that executive, attention and processing speed deficits were stable over the follow-up period (Mur *et al*. 2008). In addition, a report comparing first-episode and multi-episode patients found that first-episode patients performed significantly worse on tests of executive functioning, sustained attention and perceptuomotor functioning (Nehra *et al*. 2006). These findings diverge from the literature, highlighting the need for additional large, well-controlled longitudinal investigations.

Cognitive decline in psychosis represents a departure from typical development

The trajectories of cognitive functioning in SZ and BD are distinct not only from one another but also from healthy development. General intelligence is relatively stable beginning in early to mid-childhood, and changes very little through early and middle adulthood (e.g. Schaie, 1980, 1994; Cunningham, 1987; Larsen *et al*. 2008). Furthermore, although variability exists in terms of longitudinal course of cognitive constructs (e.g. perceptual speed, inductive reasoning), most cognitive domains remain relatively stable through middle age (Schaie, 1994). Thus, neurocognitive performance in patients with psychosis represents a deviation from typical cognitive functioning, probably indicating specific abnormalities in development, neuroplasticity and pathophysiology.

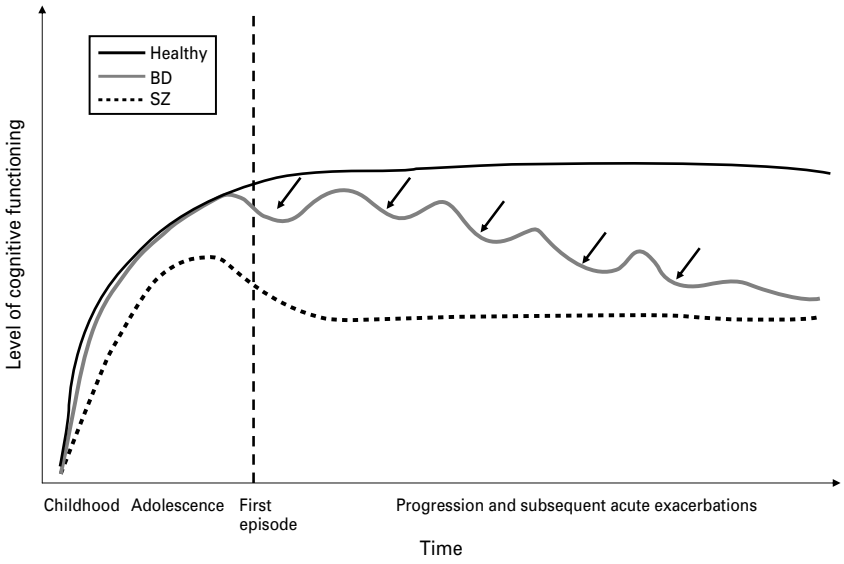

Fig. 1. Cognitive development in subjects with schizophrenia (SZ), bipolar disorder (BD) and healthy comparisons.

Discussion and future directions

Neuropsychological dysfunction represents a measurable component and characteristic feature of psychotic disorders. However, the evolution of neurocognitive dysfunction seems to follow distinct courses in SZ and BD (see Fig. 1). Consistent with a neurodevelopmental model (e.g. Weinberger, 1987; Andreasen, 1999; Marenco & Weinberger, 2000), children who go on to develop SZ exhibit cognitive deficits relative to their peers pre-morbidly. Beginning in the early prodromal phase, patients are found to experience deterioration in cognitive functioning relative to both their peers and their own prior levels of functioning (Fuller *et al*. 2002; Bilder *et al*. 2006). Thus, neurocognitive functioning in pre-morbid SZ may reflect an abnormal neurodevelopmental process that is present as early as objective testing is available, and that lays the foundation for neurodegeneration or continued maldevelopment around the time of the SZ prodrome, as reflected by a decline in both relative and absolute neurocognitive performance. By contrast, patients with BD exhibit relatively intact cognitive functioning throughout childhood and adolescence. It is not until the time of overt symptom onset that neuropsychological functioning is found to deteriorate, with neuropsychological deficits detectable by the time of initial diagnosis. After diagnosis, neuropsychological functioning worsens, with acute exacerbations and in conjunction with the presence of psychotic symptoms. This longitudinal course suggests that neurodevelopmental factors play, at most, a minor role in the emergence of neuropsychological dysfunction in BD, whereas psychopathological factors during the course of the disorder itself are associated with neuropsychological deterioration. Additionally, as discussed later, the neurotoxic or neuroprotective role of medication may affect cognitive functioning after diagnosis in both SZ and BD.

Although post-onset assessments of neuropsychological functioning reveal patterns of deficits that seem to be similar qualitatively and perhaps quantitatively across groups, the pathways by which patient groups arrive at these points differ. These differences in evolution of neuropsychological dysfunction may reflect contrasting pathogenic pathways in the etiology of neuropsychological deficits and other symptoms. Such findings may provide a theoretical framework for studying the development of neuropsychological symptoms, and these disorders more generally. By juxtaposing the longitudinal course of neuropsychological deficit evolution across disorders, we are better positioned to examine their etiological and pathogenic processes by capitalizing on what is known to differ and what is known to overlap, and the timing of each.

We now turn to some methodological and conceptual debates relevant to this literature.

Identifying the emergence of symptoms pre-morbidly

Perhaps the greatest barrier to clarifying patterns of development in psychosis over time is a lack of systematic study beginning pre-morbidly and continuing into illness phases. Most reports of pre-morbid cognitive functioning in children who later develop psychosis rely on retrospective reports of pre-morbid IQ or review of academic records. Although these measures are useful in estimating pre-morbid cognitive functioning, they may be confounded by selection bias or by a host of variables that interfere with

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academic functioning and cannot be adequately accounted for (e.g. early emergence of subclinical symptoms or social skills deficits; Malmberg *et al*. 1998; Davidson *et al*. 1999; Cannon *et al*. 2001).

In addition, broad assessments of cognition, even prospectively, may fail to detect the emergence of more specific deficits and may obscure patterns of neuropsychological dysfunction. Pre-morbid global dysfunction is widely reported in patients who later develop SZ, but it is unclear when specific deficits in executive functioning, attention and memory emerge. Conversely, in children who later develop BD, global cognitive functioning seems to be preserved, but specific neuropsychological deficits may be emerging during this time. Reports examining specific neuropsychological deficits pre-morbidly in SZ and BD suggest that deficits in working memory, executive functioning, verbal learning and attention may be detectable above and beyond global deficits in children at risk for SZ (e.g. Cornblatt & Erlenmeyer-Kimling, 1985; Caspi *et al*. 2003; Bearden *et al*. 2004; Johnstone *et al*. 2005; Lewandowski *et al*. 2007) and in children who later develop BD despite reports of preserved global cognitive and academic functioning (Meyer *et al*. 2004; Tiihonen *et al*. 2005).

Studies of at-risk populations should aim to measure cognitive functioning in the domains predicted to represent core neuropsychological deficits in psychosis, including executive functioning, working memory, verbal and visuospatial memory, and attention, in addition to global cognitive functioning to ascertain the degree to which impairment lies in specific neuropsychological domains. Repeated assessments can also illuminate the timing of the emergence of such deficits. These findings speak more directly to pathogenesis than does the detection of deficits after illness onset, as neurodevelopment of brain structures thought to underlie these processes is well described (Jernigan *et al*. 1991; Chugani & Chugani, 1997; Giedd *et al*. 1999; Casey *et al*. 2000; Rubia *et al*. 2000; Sowell *et al*. 2001). Finally, studies of neurocognitive development in psychosis should take a lifetime development perspective to address issues of aging, including the relationship of neurocognitive dysfunction to the emergence of dementia in patients with SZ and BD.

Issues of measurement and comparison

The diversity of measures and terms used to describe neurocognitive dysfunction in psychosis can make findings difficult to integrate. For example, a PubMed search with the phrase 'schizophrenia AND executive function' returned 593 papers. A non-exhaustive review revealed the following terms (among others) used as synonyms for or components of executive functioning: initiation speed and response suppression; strategic retrieval process and monitoring; planning; set-shifting; inhibition; initiation; social regulation; abstract problem solving; abstract reasoning. Some tools for the measurement of these domains included: Intradimensional/Extradimensional shift task; WCST; Tower of London; Hayling sentence completion; Dysexecutive Questionnaire; Category Fluency; Letter Fluency; Zoo map test; Stroop; Trails. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative has attempted to overcome some of these difficulties by the development of a consensus battery for the assessment of cognition in SZ (Green *et al*. 2004). As yet, no such consensus battery exists for the study of BD, making a cross-diagnostic synthesis of the literature difficult.

Although the MATRICS has attempted to address issues of problematic heterogeneity of methodology and terminology, caution must be exercised in avoiding reification by conflating assessments and constructs. A thorough review of other approaches for measuring cognitive functioning in clinical samples is beyond the scope of this work; however, it should be noted that several methods besides traditional neuropsychological assessment techniques are used regularly. For instance, several cognitive paradigms map relevant cognitive processes onto specific symptoms, such as reality or source-monitoring deficits and auditory hallucinations (e.g. Ditman & Kuperberg, 2005), or abnormalities in emotional perception of stimuli and delusions (e.g. Holt *et al*. 2006). Such approaches offer face validity and tighter links between cognition and clinical symptomatology.

Furthermore, cognitive neuroscience paradigms attempt to isolate specific cognitive processes in a more reductionistic fashion, as some cognitive constructs (e.g. working memory, attention, executive function) probably tap many basic processes simultaneously (Carter & Barch, 2007). Several neurocognitive domains thought to be central to psychosis, including processing speed, attention and executive functioning, have been found to be composed of more than one component of functioning, not all of which may suffer from the same degree of impairment in patients (Dickinson & Gold, 2008; Kerns *et al*. 2008; Luck & Gold, 2008). The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project has attempted to identify candidate mechanisms that are associated with SZ (Carter & Barch, 2007). This approach has several advantages, including offering explanatory power to neuropsychological factor overlap. Better understanding of the mechanisms by which cognitive functioning in various domains is achieved may enhance our

understanding of how separate domains are related and may speak more specifically to the neurobiology of various processes.

Medication effects

The effect of psychotropic medications on neurocognitive functioning in psychosis is unclear. Several reports have found that medications, in particular second-generation antipsychotics, are associated with statistically significant but small improvements in neurocognitive functioning in SZ (Harvey *et al*. 1990; Keefe *et al*. 1999, 2007; Harvey & Keefe, 2001; Woodward *et al*. 2005). However, 'real-world' medication usage, including polypharmacy and high dosing of antipsychotics (e.g. 5–6 mg risperidone equivalents per day), may be associated with poorer cognitive performance in patients with SZ or SZA (Elie *et al*. 2009). In patients with BD, antipsychotic medication is associated with poorer performance on IQ, memory and working memory assessments (Donaldson *et al*. 2003). Findings of cognitive side-effects with lithium and anticonvulsants are mixed, with some studies reporting poorer neuropsychological functioning in patients receiving medication (Stip *et al*. 2000; Pachet & Wisniewski, 2003) and others finding no changes over time while on medication (Engelsmann *et al*. 1988), or only modest deficits (Drane & Meador, 1996; Goldberg & Burdick, 2001). Medications may also affect cognitive domains differentially (Holmes *et al*. 2008) and dosage and polypharmacy have been reported to be adversely associated with cognitive functioning in patients with BD (Drane & Meador, 1996; Goldberg & Burdick, 2001).

The direction of cognitive change due to medication effects seems to differ by medication, cognitive domain of interest and perhaps even diagnosis. Cognitive side-effects may occur as a direct consequence of the drug's mechanism of action or indirectly through side-effects such as sedation (e.g. Harvey *et al*. 2007). Post-onset neuropsychological functioning is likely to be confounded by several factors including medication, making it difficult to comment on the relevance of neuropsychological deficits to etiology or development. A better understanding of developmental processes pre-morbidly may clarify some of these issues, and, cross-diagnostically, elucidate some of the ways in which disorders that share features post-onset look alike or different developmentally.

Cross-diagnostic issues

After more than a century of debate, the classification of psychotic disorders remains a challenging problem. There is considerable overlap between SZ, SZA, BD and related conditions and it is not clear how well these diagnoses correspond to putative natural disease entities (Heckers, 2008). We suggest that useful patterns emerge from this literature through a lifelong perspective on the evolution of neurocognitive deficits in psychotic disorders. Despite the substantial overlap in neuropsychological deficits among patients (Dickinson *et al*. 2006; Gonzalez-Blanch *et al*. 2006; Genderson *et al*. 2007), the evolution of deficits does distinguish patients in these diagnostic categories. The distinction between SZ and BD may be biologically informative from a perspective in which SZ is associated with neurodevelopmental neurocognitive deficits and a stable chronic course, as opposed to BD in which pre-morbid development is relatively normal and disease exacerbations are associated with a growing neuropsychological burden. Future work should examine these relationships longitudinally, beginning in pre-morbid or prodromal phases when possible. The association of neurocognitive development with variables such as psychosis in BD, anxiety symptoms or mood symptoms in SZ and SZ spectrum disorders should also be examined, as such features may moderate the relationship between neurocognitive development and diagnosis. Such major symptom clusters may ultimately be found to be more highly associated with neurocognitive trajectories across the lifespan than are diagnostic groupings; however, those relationships remain to be addressed.

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Declaration of Interest

None.

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