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ORIGINAL ARTICLE

Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis

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Background. Schizophrenia (SZ) is characterized by a broad global cognitive impairment that precedes the onset of the disease. By contrast, some studies suggest that premorbid deficits are absent, or even reversed, in bipolar disorder (BD). However, studies have shown impairments in cognitive functioning after the illness onset in both disorders. The aim of this study was to systematically review and meta-analyze those studies that compared premorbid and/or post-onset global cognitive function between SZ and BD.

Method. We searched Medline (PubMed), EMBASE and PsycINFO for studies where information on cognitive functioning was collected in both SZ and BD within the same study or using the same methods.

Results. Compared to healthy comparison groups, SZ patients showed a significant premorbid cognitive impairment [standardized mean difference (SMD) −0.597, 95% confidence interval (CI) −0.707 to −0.487, $p<0.0001$] and a large post-onset impairment (SMD −1.369, 95% CI −1.578 to −1.160, $p<0.0001$). We found small significant deficits in premorbid intellectual function in the BD group when this was assessed retrospectively (−0.147, 95% CI −0.238 to −0.056, $p=0.001$) but not prospectively (−0.029, 95% CI −0.199 to +0.142, $p=0.744$), and moderate cognitive impairment after onset (SMD −0.623, 95% CI −0.717 to −0.529, $p<0.0001$).

Conclusions. SZ is characterized by significant deficits in premorbid intellectual function but the evidence regarding premorbid function in BD is equivocal. After illness onset, patients with both disorders seem to suffer a further decline in cognitive function but the magnitude of the impairment remains greater in SZ than in BD.

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Key words: Bipolar disorder, cognitive function, first episode, intelligence, meta-analysis, pre- and post-onset, schizophrenia, systematic review.

Introduction

Despite the 'Kraepelinian' distinction between schizophrenia (SZ) and bipolar disorder (BD) and the categorical classification of current diagnostic systems such as DSM-5 (APA, 2013) and ICD-10 (WHO, 1992), there is considerable overlap between these disorders. Epidemiological, genetic and neuroimaging studies comparing SZ and BD show a complex range of epidemiological, pathophysiological and phenomenological similarities and differences (Demjaha *et al.* 2012). SZ and BD have overlapping genetic liabilities (Lichtenstein *et al.* 2009), with several genes such as *ANK3, CACNA1C, ZNF804A, G72/G30, DISC1, Neuregulin* and *Dysbindin* implicated in both disorders (Schumacher *et al.* 2004; Shifman *et al.* 2004; Craddock & Owen, 2005; Crow, 2008; Lett *et al.* 2011). Large copy number variants (CNVs), however, seem to be associated with SZ but not with BD (Bergen *et al.* 2012; Rees *et al.* 2014). We have previously suggested a model whereby both disorders share a common genetic liability but SZ is associated with additional risk factors that impair neurodevelopment (Murray *et al.* 2004; Demjaha *et al.* 2012).

Birth cohort and conscript studies report strong associations between poor performance on cognitive batteries and increased risk of later SZ (MacCabe, 2008; MacCabe *et al.* 2008). Moreover, a systematic review and meta-analysis confirmed the presence of a premorbid IQ deficit of around 0.5 standard deviations among young people who will later develop SZ (Woodberry *et al.* 2008). By contrast, premorbid deficits seem to be absent, or even reversed, in BD. Indeed, two longitudinal studies showed that individuals with better cognitive functioning in childhood or adolescence have an increased risk for later BD (Koenen *et al.* 2009; MacCabe *et al.* 2010).

Most studies on patients with established illness find deficits in both SZ and BD; thus, a meta-analysis

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revealed widespread general cognitive deficits in patients with SZ and with BD, with quantitative rather than qualitative differences between the diagnostic groups (Stefanopoulou *et al.* 2009). Cognitive deficits have been detected in samples of both bipolar type I (BD-I) and type II disorder (BD-II) patients, even during periods of euthymia (Martino *et al.* 2008; Harvey *et al.* 2010).

It is difficult to make direct comparisons between SZ and BD on the basis of studies that include one disorder but not the other. In general, studies of cognitive functioning in SZ are much more numerous than those in BD, tend to be older and thus have somewhat less rigorous methodology than the studies of BD. This difference probably reflects the growing interest in studies of BD in the past two decades. Restricting a meta-analysis to studies that have examined both disorders simultaneously removes any such bias and allows direct comparisons to be made. We therefore undertook this meta-analysis comparing premorbid and post-onset intellectual functioning between SZ and BD, restricting the analysis to studies that assessed both SZ and BD, using identical methods. We hypothesized that (*a*) SZ would show more severe deficits in premorbid intellectual function compared to BD but (*b*) both disorders would show a similar cognitive decline from pre- to post-illness onset.

Method

Literature search and selection criteria

In this study we followed the guidelines of the meta-analysis of observational studies in epidemiology (Stroup *et al.* 2000). Studies were identified through searches of Medline (PubMed), EMBASE and PsycINFO databases using the key words: 'schizophrenia AND bipolar disorder' combined with 'IQ', 'intelligence', 'intelligence quotient', 'cognitive', 'neuropsychological', 'neuropsychology', 'neurocognitive', 'neurocognition', 'intellectual' and 'premorbid'. Additional studies were identified by hand searching the bibliographies of each article found, and contacting individual authors where additional information was required.

We included studies that: (1) were published in peer review journals in English between January 1990 and December 2013; (2) included both BD and SZ patients and a healthy comparison group; (3) included standardized diagnostic criteria to ascertain diagnosis, namely Research Diagnostic Criteria (RDC), DSM-III or later, ICD-8 or later; (4) assessed general cognitive or academic ability before and/or following illness onset; (5) provided separate results for the group of subjects diagnosed with SZ or BD and the healthy comparison group, drawn from the same population, using the identical sampling methods for both disorders; and (6) provided means and standard deviations of the cognitive performance measures.

Exclusion criteria were: (1) assessment of specific cognitive functions without providing an overall estimation of intellectual function (or equivalent); (2) insufficient data to estimate effect size (means, standard deviations, number of subjects for each group); and (3) data that reported the same or an overlapping sample as a more complete or relevant study.

Where the same study was reported in more than one publication (for example where results for SZ and BD were reported separately), the data set was only included once. If means and standard deviations were not provided, authors were contacted directly by email. For sensitivity analysis, the largest study was excluded in each analysis.

Statistical analysis

Meta-analyses were performed with Stata version 10.1 (Stata Corporation, USA), using the Metan and Meta packages. Effect sizes for each original study are expressed as the standardized mean difference (SMD, Cohen's *d*) between SZ, BD and control group performance (Cohen, 1969). Standardized effect sizes were meta-analyzed using random effects models. Heterogeneity between studies was assessed with the *Q* test (DerSimonian & Laird, 1986). The I^2 statistic was calculated to express the proportion of variation between studies that was due to heterogeneity (Higgins *et al.* 2003). We used a random effects model because of heterogeneity in the study design and in the neuropsychological tests used.

Egger's test of publication bias was used to assess whether there was a tendency for selective publication of studies based on the nature and direction of results (Egger *et al.* 1997). Random effect meta-regression analyses were conducted for testing effects of the following potential effect modifiers: medications (percentage of patients receiving pharmacologic treatment for SZ or BD at the time of intellectual functioning assessment), duration of illness (years), age at time of cognitive assessment, clinical status ('remitted' or 'symptomatic') at the time of assessment, source population (continent where the study had been conducted), year of publication and cognitive measure [the National Adult Reading Test (NART; Nelson, 1982), the Wide Range Achievement Test (WRAT; Jastak & Wilkinson, 1984) or prospectively ascertained neuropsychological batteries to assess premorbid cognitive functioning; Wechsler scales or other quantitative measure for the assessment of post-onset cognitive functioning], using Stata version 10.1. A significance

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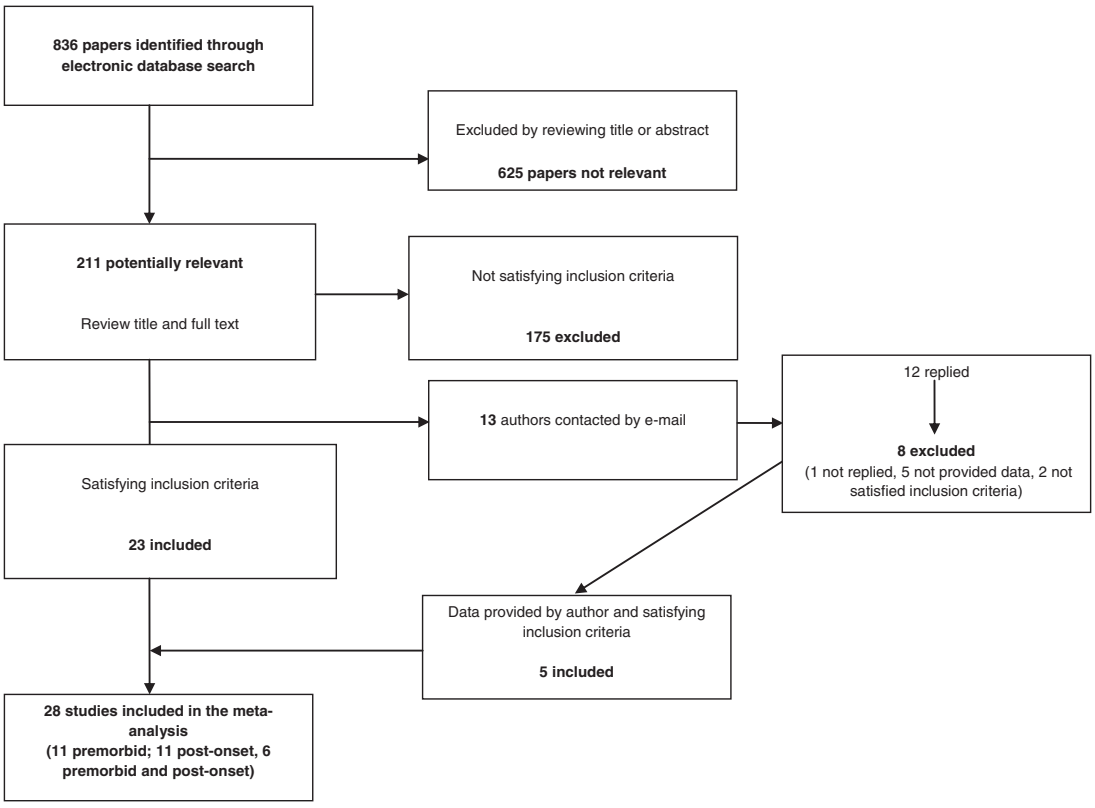

Fig. 1. Flow chart of published papers selected and excluded from the initial online database search to the publication included in the meta-analysis.

level of $p<0.05$ was used for the random effects model, homogeneity, publication bias, sensitivity and meta-regression analyses.

Results

The search identified a total of 836 studies (Fig. 1). On the basis of title and abstract, 625 studies were excluded. A total of 211 studies were considered potentially relevant and full text was assessed manually. Of these, 175 did not satisfy one or more of the inclusion criteria and were excluded while a total of 23 were selected. We contacted the authors for a further 13 possible studies, and the relevant data were obtained from five studies. In total, 28 studies were included in the review (11 providing a measure for premorbid intellectual function, 11 assessing post-onset intellectual function, and six providing both premorbid and post-onset measures of intellectual function) (Table 1).

Premorbid intellectual function

A measure of premorbid intellectual function was available from 17 studies. Of these, four were prospective cohort studies that used assessments of premorbid cognitive or intellectual functioning that were measured prior to illness onset, and 13 were retrospective case-control studies that estimated premorbid intellectual functioning based on reading tests conducted after the patient had developed the illness. There were 1993 SZ patients, 1270 BD patients and 772 138 healthy controls from the general population (Table 2).

SZ

SMD in premorbid cognitive function between SZ patients and controls was −0.597 [95% confidence interval (CI) −0.707 to −0.487, $p<0.0001$] (Fig. 2). There was significant heterogeneity in effect size between studies (68.50, S.D.=19, $p<0.0001$, $I^2=72.3\%$). SMD for prospective cohort studies was −0.406 (95% CI −0.500 to −0.312, $p<0.0001$) with a non-significant heterogeneity in effect size between studies (4.90, S.D.=3, $p=0.180$, $I^2=38.7\%$); SMD for studies that used retrospective measures of cognitive function was −0.675 (95% CI −0.810 to −0.539, $p<0.0001$) with a significant heterogeneity between studies (40.54, S.D.=15, $p<0.0001$, $I^2=63.0\%$).

BD

SMD in premorbid intellectual function between BD patients and controls was −0.113 (95% CI −0.202

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Table 1. *Studies included in the meta-analysis*

	Study	Design and setting	Diagnostic criteria	Codes		SZ (*n*)	BD (*n*)	Comparison group (*n*)	Cognitive measures	
				SZ	BD				Premorbid	Post-onset
Premorbid										
1	MacCabe *et al.* 2008, 2010[a]	Population-based historical cohort study The Swedish National Schools Register (born between 1973 and 1983)	ICD-9, ICD-10	ICD-9: 295.A–G, W, X ICD-10: F20.0–F20.9	ICD-9 (Swedish version): 296, 296. A, C–E, W, X ICD-10: F300–319	493	280	713 876	Scolastic achievement at age 15/16	
2	Osler *et al.* 2007[a]	Population cohort study Danish Psychiatric Register	ICD-8, ICD-10	ICD-8: 295.09–295.99 ICD-10: F20	ICD-8: 296.19, 296.29, 298.19 ICD-10: F30, F31, F34, F38	87	16	6774	Age 12: Härnquist test Age 18: Børge Priens (Mortensen *et al.* 1989)	
3	Zammit *et al.* 2004[a]	Historical cohort study Survey of Swedish conscripts (1969–1970) Swedish National Register of Psychiatric Care up to 1983	Nordic version ICD-8 (ICD-9 from 1987)	ICD-8 and ICD-9: 295.00–295.99	ICD-8: 296.1, 296.3, 298.1 ICD-9: 296.0, 296.2–296.5, 298.1	350	108	49 215	Verbal IQ, visuospatial ability, general knowledge and intelligence, mechanical knowledge subtests (see David *et al.* 1997)	
4	Cannon *et al.* 2002[a]	1-year birth cohort (1972–1973) Dunedin Multidisciplinary Health and Development Study	DSM-IV Schizophreniform disorder, mania diagnosis			26	16	531	Age 3: PPVT (Dunn, 1995) Age 5: the Stanford-Binet Intelligence Scales (Terman & Merrill, 1960) Ages 7, 9, 11, 13: WISC-R (Wechsler, 1974)	
5	Hill *et al.* 2009	Case-control study University of Illinois Medical Center	DSM-IV SZ and BD diagnosis			30	22 (psychotic bipolars)	41	Reading subtest of the WRAT-III (Jastak & Wilkinson, 1984)	
6	Simonsen *et al.* 2011	Case-control study Oslo, Norway	DSM-IV SZ and BD-I and BD-II diagnosis			102	61 (no history of psychosis 75 (history of psychosis)	280	NART (Nelson, 1982)	

7	Schretlen *et al.* 2007	Retrospective case-control study Johns Hopkins University and Hospital	DSM-IV SZ and BD diagnosis	106	66	316	NART	
8	Cannon *et al.* 1997	Case-control study Camberwell Collaborative Psychosis Study	DSM-III-R SZ and BD diagnosis	28	70	100	NART	
9	Altshuler *et al.* 2004[a]	Case-control study GLAVAMC	DSM-III-R SZ and BD diagnosis	20	22 euthymic out-patients	22	American NART (Grober & Sliwinski, 1991)	
10	Hartberg *et al.* 2011	Case-control study TOP Research Study, Oslo, Norway	DSM-IV SZ and BD-I and BD-II diagnosis	117	121	192	NART – Norwegian version (Sundet & Vaskinn, 2008)	
11	Hill *et al.* 2013	Case-control study B-SNIP consortium	DSM-IV SZ and BD with history of psychosis	293	227	295	WRAT-4 (Wilkinson & Robertson, 2006)	
Post-onset								
12	Chan *et al.* 2012	Case-control study Early psychosis intervention program, Hong Kong	ICD-10	38	40 (22 with unipolar mania)	37		Arithmetic, similarity and digit span subscales of the Chinese version of the WAIS-R (Gong, 1992)
13	Laes & Sponheim, 2006	Case-control study Minneapolis Veterans Administration Medical Center	DSM-III-R SZ and BD diagnosis	39	27	38		WAIS-R Vocabulary and Block Design age-scaled score (Booker & Cyr, 1986; Wechsler, 1997)
14	Dickerson *et al.* 2004	Case-control study Sheppard Pratt Health System, Baltimore	DSM-IV SZ or schizo-affective disorder, BD-I and BD-II	229	117	100		RBANS (Randolph, 1998)
15	Zalla *et al.* 2004	Case-control study Pitie-Salpetriere and Albert Chenevier Hospitals (AP-HP, Paris)	DSM-IV SZ and BD-I diagnosis	25	37	20		Four-subtest version of the WAIS-R (Wechsler, 1981; Cyr & Brooker, 1984)

Table 1 (*cont.*)

	Study	Design and setting	Diagnostic criteria	Codes		SZ (*n*)	BD (*n*)	Comparison group (*n*)	Cognitive measures	
				SZ	BD				Premorbid	Post-onset
16	Varga *et al.* 2007	Case-control study Ulleval University Hospital, Oslo, Norway	DSM-IV SZ and BD-I diagnosis			32	37	31		Extensive battery of neuropsychological tests: WCST (Heaton *et al.* 1993); TMT A and B; WAIS-III; Stroop color-word; Grooved Pegboard; AVLT
17	Krabbendam *et al.* 2000	Case-control study Department of Psychiatry, Academic Hospital, Maastricht	DSM-IV SZ and BD-I and BD-II diagnosis		BD-I (296.x) and BD-II (296.89)	22	22	22		GIT (Luteijf & van der Ploec, 1983)
18	Kumar *et al.* 2010	Case-control study South London and Maudsley NHS Trust	DSM-IV SZ and BD-I diagnosis			50	37	93		Full-scale WAIS-R
19	Pradhan *et al.* 2008	Case-control study Department of Psychiatry, Chandigarh, India	ICD-10	F20	F30.2, F31.2 or F31.5	32	48	23		BSB-R (Bhatia, 1955)
20	Wirgenes *et al.* 2010	Case-control study TOP Study, University of Oslo and Oslo University Hospital, Ulleval	DSM-IV SZ and BD-I and BD-II diagnosis			137	144	340		WASI (Wechsler, 1999)
21	Brambilla *et al.* 2011	Case-control study South Verona Community-based Mental Health Service	DSM-IV			19	14	45		Full-scale WAIS-R
22	Cuesta *et al.* 2011	Case-control study University of Barcelona, Spain	DSM-IV			96	65 (BD-I)	76		GCCS
Premorbid and post-onset										
23	Toulopoulou *et al.* 2006	Case-control study The Maudsley Family Study, London, UK	DSM-IV SZ and BD diagnosis			36	39	65	NART	Five-subtest short form of the WAIS-R (Canavan *et al.* 1986)

24	Seidman *et al.* 2002	Retrospective family study Massachussetts, USA	DSM-III-R SZ and BD diagnosis			87	15	94	WRAT-R Reading Standard Score	WAIS-R Vocabulary and Block Design age-scaled score (Wechsler, 1981; Booker & Cyr, 1986)
25	McIntosh *et al.* 2005	Retrospective case-control study Royal Edinburgh Hospital and associated hospitals	DSM-IV SZ and BD-I diagnosis			27 SZ with family history of SZ	27 BD-I from BD family 20 BD-I from 'mixed' family (first- or second-degree relative with SZ)	50	NART	WASI Full-Scale IQ, Performance IQ and Verbal IQ scores
26	Zanelli *et al.* 2010	Population-based, case-control AESOP study	ICD-10	F20	F30.2, F31.2 or F31.5	65	37	177	NART	WAIS-R
27	Barrett *et al.* 2009	Case-control incidence study NIFEPS	ICD-10	F20	F30.2, F31.2 or F31.5	46	32	67	NART	WASI two-test version: vocabulary and matrix reasoning
28	Gogos *et al.* 2009	Case-control study Melbourne, Australia	DSM-IV SZ and BD diagnosis			38	40	43	NART	RBANS

SZ, Schizophrenia; BD, bipolar disorder (BD-I, type I; BD-II, type II); PPVT, Peabody Picture Vocabulary Test; WISC-R, Weschler Intelligence Scales for Children Revised; WRAT, Wide Range Achievement Test; NART, National Adult Reading Test Revised; GLAVAMC, Greater Los Angeles Veterans Administration Medical Center; TOP, Thematically Organized Psychosis; B-SNIP, Bipolar-Schizophrenia Network on Intermediate Phenotypes; WAIS-R, Wechsler Adult Intelligence Scale Revised; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; AVLT, Auditory Verbal Learning Test; GIT, Groningen Intelligence Test; BSB-R, Bhatia's Short Battery of Performance Tests of Intelligence; WASI, Wechsler Abbreviated Scale of Intelligence; GCCS, global cognition composite score; NHS, National Health Service; AESOP, Aetiology and Ethnicity in Schizophrenia and Other Psychoses; NIFEPS, Northern Ireland First Episode Psychosis Study.

[a] Data provided by authors.

All references in this table are listed in the online Supplementary Appendix.

Table 2. *Raw premorbid IQ scores for studies included in the meta-analysis*

	Study	Healthy comparison group			Schizophrenia (SZ)			Bipolar disorder (BD)		
		n	Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.
Prospective studies										
1	MacCabe *et al.* 2008, 2010	713 876	3.24	0.69	493	2.95	0.79	280	3.31	0.79
2	Osler *et al.* 2007	6774	67.7	18	87	64.1	18.6	16	63.8	18
3	Zammit *et al.* 2004	49 215	4.3	1.91	350	3.42	2.02	108	4.03	1.99
4	Cannon *et al.* 2002	531	0.07	0.97	26	−0.42	1.02	16	0.02	0.95
Retrospective studies										
5	Toulopoulou *et al.* 2006	65	111.5	10.69	36	102.88	12.44	39	111.3	11.6
6	Seidman *et al.* 2002	94	101.9	13.4	87	99.4	16.9	15	101.2	13.3
7	Hill *et al.* 2009	41	99.35	7.51	30	93	11.69	22	94.77	14.36
8	Simonsen *et al.* 2011 (psychotic bipolar)	280	106.6	4	102	103.4	4.4	75	105.4	4.5
9	Simonsen *et al.* 2011 (non-psychotic bipolar)	280	106.6	4	102	103.4	4.4	61	106.5	3.7
10	McIntosh *et al.* 2005 (BD-I from BD family)	50	110.8	8.5	27	101.3	12.6	27	111.5	10.9
11	McIntosh *et al.* 2005 (BD-I from mixed family)	50	110.8	8.5	27	101.3	12.6	20	105.9	10.8
12	Zanelli *et al.* 2010	177	106.3	12.63	65	95.58	14.39	37	104.49	12.02
13	Schretlen *et al.* 2007	316	105.2	10.1	106	96.5	10.5	66	103.7	10.9
14	Cannon *et al.* 1997	100	113	8.5	70	105	10.6	28	116	7.6
15	Barrett *et al.* 2009	67	107.74	9.98	46	98.58	11.61	32	103.29	11.88
16	Gogos *et al.* 2009 (male)	21	111	8	24	111	7	16	106	12
17	Gogos *et al.* 2009 (female)	22	112	4	14	106	12	24	109	10
18	Altshuler *et al.* 2004	22	114.37	10.77	20	104.65	10.37	40	115.53	9.51
19	Hartberg *et al.* 2011	192	106.9	4	117	105.9	4.5	121	106.2	4.1
20	Hill *et al.* 2013	295	103.09	13.8	293	93.96	15.52	227	101.35	13.76

BD-I, Bipolar disorder type I; S.D., standard deviation.
All references in this table are listed in the online Supplementary Appendix.

to −0.024, p=0.013) (Fig. 3). Non-significant heterogeneity in effect size between studies was observed (28.99, S.D.=19, p=0.066, I^2=34.5%). SMD for prospective cohort studies was −0.029 (95% CI −0.199 to +0.142, p=0.744) with a non-significant heterogeneity between studies (5.63, S.D.=3, p=0.131, I^2=46.8%); SMD for studies using retrospective measures of intellectual function was −0.147 (95% CI −0.238 to −0.056, p=0.001) with a non-significant heterogeneity in effect size between studies (16.54, S.D.=15, p=0.341, I^2=9.8%).

Publication bias

Egger's test for the meta-analyses did not show evidence of significant publication bias for premorbid cognitive function (−0.019, p=0.824).

Potential effect modifiers

In meta-regression analyses, there were no effects of medications, age at time of assessment, duration of illness, clinical status, source population, year of publication and cognitive test used to measure premorbid intellectual functioning (results, not shown, are available from the authors).

Post-onset intellectual function

A measure of post-onset intellectual function was available from 17 studies. Of these, three were based on a sample of patients in their first episode of illness and 14 used a sample of patients not in their first illness episode. There were 1087 SZ patients, 811 BD patients and 1400 healthy controls from the general population (Table 3).

SZ

SMD in post-onset cognitive function between SZ patients and controls was −1.369 (95% CI −1.578 to −1.160, p<0.0001) (Fig. 4). There was significant heterogeneity in effect size between studies (82.59, S.D.=18, p<0.0001, I^2=78.2%). SMD for studies assessing a sample of SZ patients during their first episode of illness was −1.111 (95% CI −1.423 to −0.798, p<0.0001) with a non-significant heterogeneity in effect size between studies (3.85, S.D.=2, p=0.146, I^2=48%); SMD

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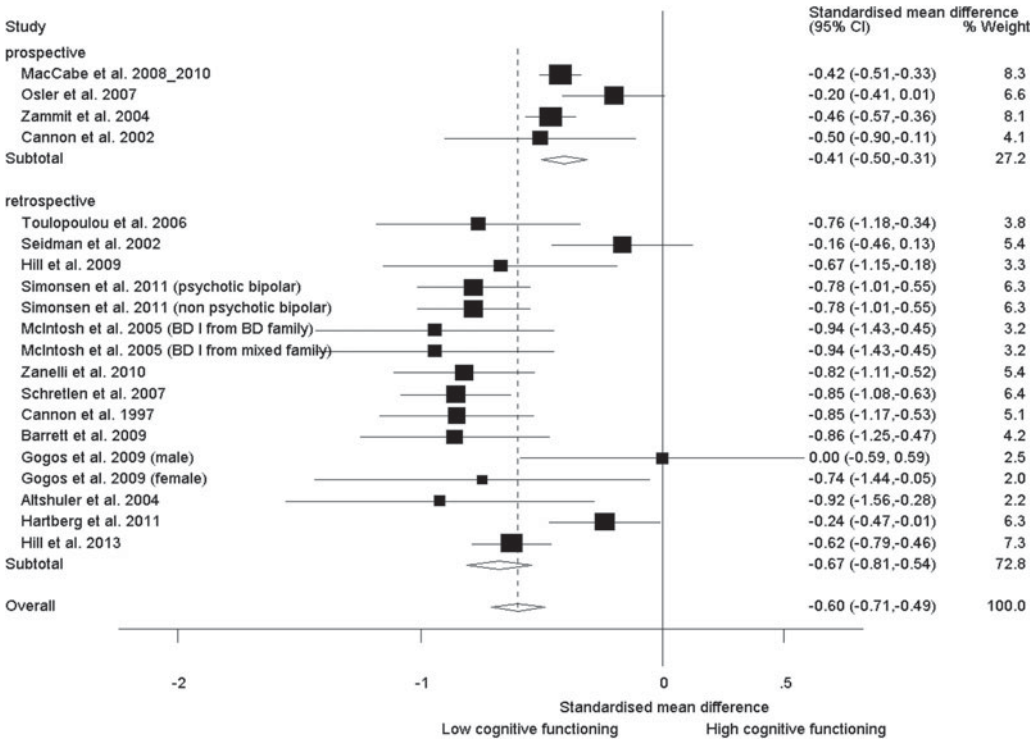

Fig. 2. Forest plot of premorbid cognitive function in schizophrenia (SZ) *versus* healthy comparison group.

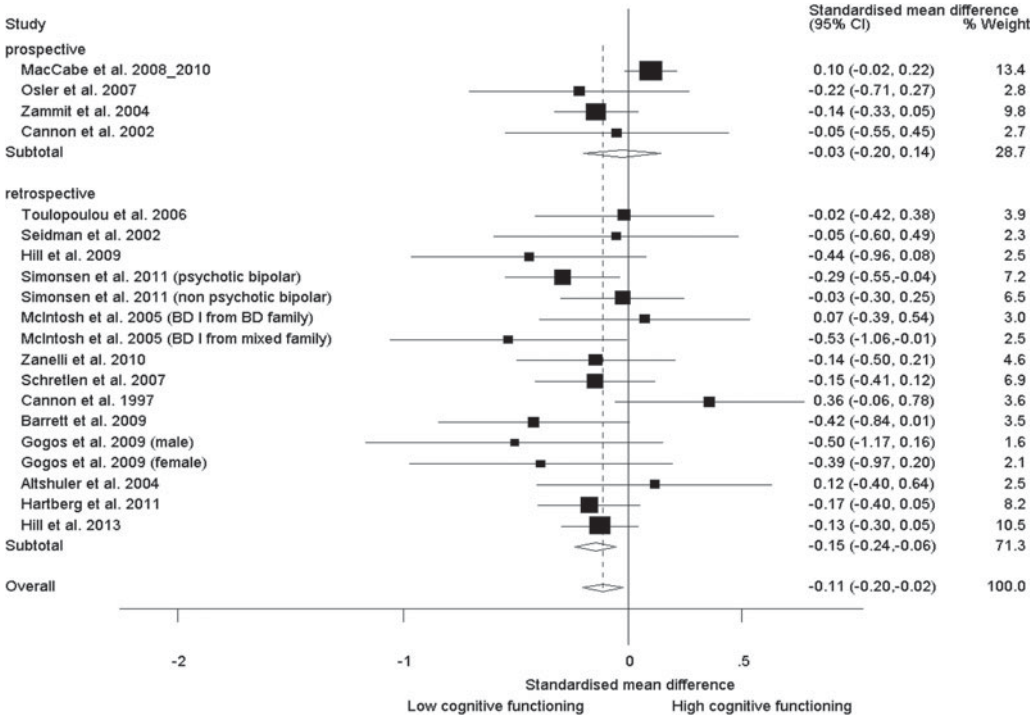

Fig. 3. Forest plot of premorbid cognitive function in bipolar disorder (BD) *versus* healthy comparison group.

for studies that used a sample of SZ patients not in their first episode was −1.432 (95% CI −1.679 to −1.185, $p<0.0001$) with a significant heterogeneity between studies (77.47, S.D. = 15, $p<0.0001$, $I^2=80.6\%$).

BD

SMD in post-onset cognitive function between BD patients and controls was −0.623 (95% CI −0.717

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Table 3. *Raw post-onset IQ scores for studies included in the meta-analysis*

	Study	Healthy comparison group			Schizophrenia			Bipolar disorder		
		n	Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.
First-episode samples										
1	Barrett *et al.* 2009	67	105.72	11.28	46	88.87	13	32	98.81	16.81
2	Zanelli *et al.* 2010	177	102.93	15.15	65	86.23	14.65	37	98.89	16.73
3	Chan *et al.* 2012	37	110.19	6.99	38	101.82	13.53	40	109.8	13.26
Not first-episode samples										
4	Toulopoulou *et al.* 2006	65	107.43	12.29	36	94.3	14.46	39	95.95	13.71
5	McIntosh *et al.* 2005 (BD-I from BD family)	50	114	13.3	27	90	14.2	27	106.7	13.3
6	McIntosh *et al.* 2005 (BD-I from mixed family)	50	114	13.3	27	90	14.2	20	101.6	13.3
7	Seidman *et al.* 2002	94	106.7	14.1	87	96.2	14.5	15	105.9	15.6
8	Laes & Sponheim, 2006	38	110.96	14.94	39	98.79	12.61	27	112.96	14.27
9	Dickerson *et al.* 2004	100	94.9	12.2	229	70.7	15.4	117	85	16
10	Zalla *et al.* 2004	20	106.7	13.9	25	81.4	13.1	37	89.5	14.5
11	Varga *et al.* 2007[a]	31	57	4.43	32	43.5	6.69	37	49.1	6.9
12	Krabbendam *et al.* 2000	22	114.2	13	22	94.6	13	22	102.4	21.4
13	Kumar *et al.* 2010	93	119.83	18.47	50	93.95	16.91	47	118.74	17.7
14	Pradhan *et al.* 2008	23	106.04	15.3	32	92.37	17.24	48	94.17	16.3
15	Wirgenes *et al.* 2010	340	113.58	9.9	171	103.5	13.8	144	107.7	12.3
16	Gogos *et al.* 2009 (male)	21	102	13	24	86	13	16	88	15
17	Gogos *et al.* 2009 (female)	22	104	13	14	81	10	24	99	17
18	Brambilla *et al.* 2011	45	104.59	6.61	19	83.39	13.23	14	87	9.44
19	Cuesta *et al.* 2011[b]	76	0.01	0.6	96	−1.16	0.91	65	−1.22	0.93

BD-I, Bipolar disorder type I; S.D., standard deviation.

[a] Overall IQ was calculated from an extensive battery of neuropsychological tests (see Table 1) and converted into *t* scores (mean 50, S.D. = 10).

[b] Global Cognitive Composite Score (GCCS) calculated using: Wechsler Adult Intelligence Scale–III (WAIS-III; Wechsler, 1999) subtests of Arithmetic, Digit Span (total score), Letters and Numbers Sequencing, Symbol Search (total score) and Vocabulary, the Wechsler Memory Scale–III (WMS-III; Wechsler, 2004) subtests of Word list I (total words recalled) and Word list II (total words recalled), the Trail Making Test (Army Individual Test Battery, 1944) part A (time), and categories and percentage of iterative errors on the Wisconsin Card Sorting Test (WCST; Berg, 1948; Heaton *et al.* 1993).

All references in this table are listed in the online Supplementary Appendix.

to −0.529, $p<0.0001$) (Fig. 5). Significant heterogeneity in effect size between studies was observed (97.76, S.D. = 18, $p<0.0001$, $I^2=81.6\%$). SMD for studies assessing a sample of bipolar patients during their first episode of illness was −0.277 (95% CI −0.510 to −0.044, $p=0.020$) with a non-significant heterogeneity in effect size between studies (2.36, S.D. = 2, $p=0.308$, $I^2=15.1\%$); SMD for studies that used a sample of BD patients not in their first episode was −0.691 (95% CI −0.793 to −0.588, $p<0.0001$) with a significant heterogeneity between studies (85.28, S.D. = 15, $p<0.0001$, $I^2=82.4\%$).

Publication bias

Egger's test did not show evidence of significant publication bias for post-onset intellectual function (−1.02, $p=0.441$).

Potential effect modifiers

In meta-regression analyses, there were no effects of medications, age at time of assessment, duration of illness, clinical status, source population, year of publication and cognitive test used to measure post-onset intellectual functioning (results, not shown, are available from the authors).

Discussion

We used a meta-analytic approach to investigate the global intellectual function of patients with SZ and BD, compared to controls, pre- and post-illness onset. To our knowledge, this is the first systematic review and meta-analysis of the literature comparing premorbid and post-onset overall intellectual functioning in

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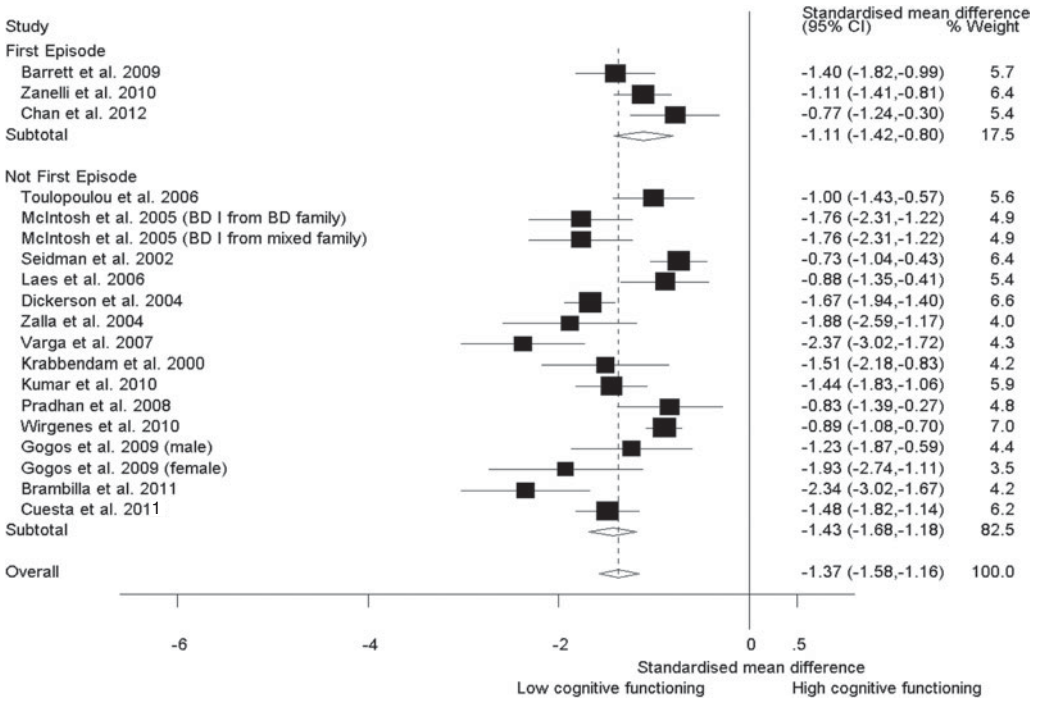

Fig. 4. Forest plot of post-onset cognitive function in schizophrenia (SZ) *versus* healthy comparison group.

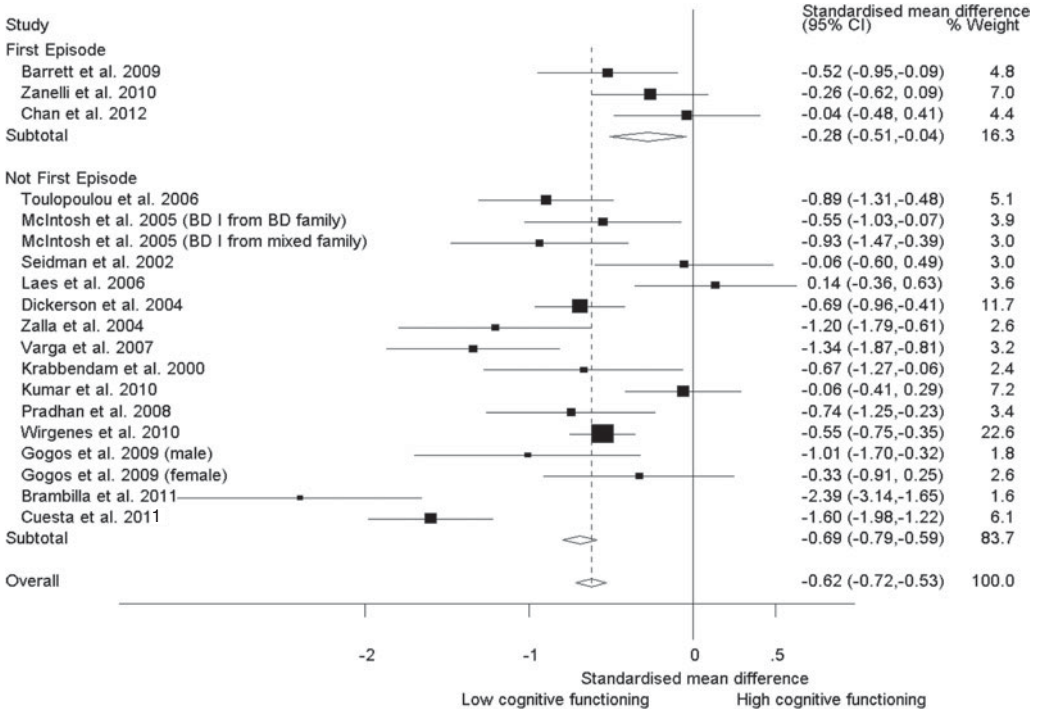

Fig. 5. Forest plot of post-onset cognitive function in bipolar disorder (BD) *versus* healthy comparison group.

SZ and BD. The novelty of our study is that we compared 'like with like' by including only studies comparing cognitive functioning of SZ and BD patients and healthy controls, drawn from the same population and using identical methodology. It could be argued that the studies that include only one or other disorder, of which there are around 150, might have provided information on either one of these disorders' cognitive functioning, relative to healthy controls. However, for the reasons set out earlier, we do not consider that it

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would meaningful to compare the pooled results of all studies of SZ with those of BD, as there are many differences in methodology, cognitive tests and analysis between studies. By restricting to studies that include both disorders, direct comparisons can be made within each study and the resulting differences meta-analyzed.

As we hypothesized, our findings confirm that SZ is characterized by severe post-onset impairment and also shows significant deficits in premorbid cognitive function. BD shows a much smaller premorbid deficit, as measured retrospectively in case-control studies, but no deficit when the analysis is restricted to prospective studies. BD patients suffered a degree of post-onset impairment, much smaller than that found in SZ. Of note, the magnitude of post-onset decline is less in first-episode studies than in chronic patients. This might constitute evidence of continuing intellectual decline following the first episode; however, the number of studies on patients with a first episode of illness included in our meta-analysis is too small to draw any conclusion.

For premorbid intellectual function in schizophrenia, we found a moderate effect size (Cohen's $d = -0.597$). Our results are comparable with previous meta-analytic reviews that found that premorbid intellectual function in these individuals was around one-half of a standard deviation below that of healthy comparison subjects (Aylward *et al.* 1984; Woodberry *et al.* 2008). After illness onset, we found impairment on overall intellectual functioning in both SZ and BD, although the magnitude of the overall difference between premorbid and post-onset cognitive functioning was greater for SZ.

To reduce selection bias, we therefore report separate analyses for longitudinal population-based studies. In fact, case-control studies that assess cognitive functioning retrospectively are liable to selection bias (including through unrepresentative comparison groups) and information bias, whereby the effects of the disorder impair performance on tests, such as the NART, that are designed to estimate premorbid intelligence. The smaller estimates of effect size measured by prospective studies included in our meta-analysis compared to the effect size measured by retrospective studies suggest that such biases were present in those studies that assessed cognitive functioning retrospectively.

Limitations of this meta-analysis include considerable heterogeneity in the methodology of the studies selected, and statistical heterogeneity of effect sizes was detected in many of the analyses. We used a random effects model to allow for this heterogeneity but the results, particularly the overall estimates of differences, should be treated with caution. In particular, the type and number of tests used to estimate the global intellectual function varied considerably between studies. We included studies that used scholastic achievement as a measure of premorbid intellectual function in addition to studies that used non-standard instruments. However, Deary *et al.* (2007) have shown that general cognitive ability (Spearman's *g*) at age 11 correlate with national school examinations (GCSE scores) taken at age 16 (Cohen's $d = 0.69$).

Retrospective studies included in our meta-analysis assessed premorbid cognitive function using the NART or the Reading subtest of the WRAT. The high association of reading ability with general intellectual function and the resistance of reading skill to processes of cognitive deterioration (Nelson & McKenna, 1975) make these two tests a quick and sensitive measure of estimating premorbid intelligence levels.

To assess post-onset intellectual function, 12 of the studies included in our meta-analysis used the full or the short versions of Wechsler scales. Wechsler scales are considered the gold standard for assessing global intellectual function, providing an individual profile of both verbal and non-verbal intelligence. However, given the extensive time needed to administer the complete test batteries, large sample studies typically estimate intellectual function using short forms with two to five subtests whose reliability and validity had been previously demonstrated (Cyr & Booker, 1984; Booker & Cyr, 1986; Canavan *et al.* 1986; Wechsler, 2007).

We focused on overall quantitative measures of intellectual functioning in SZ and BD, so we did not assess whether profiles of cognitive functioning across subtests may have differed between these two disorders. However, previous studies conducted to compare cognitive profiles of SZ and BD have shown that patients with BD suffer from cognitive deficits that are milder but qualitatively similar to those of patients with SZ (Schretlen *et al.* 2007; Stefanopoulou *et al.* 2009).

To assess potential sources of heterogeneity, we conducted a meta-regression for potential biological or environmental factors that might confound the association between cognitive performance and SZ or BD, such as sociodemographic and clinical variables (age at time of assessment, duration of illness, clinical status, and cognitive test used to measure intellectual functioning) and also the influence of medication on cognitive functioning.

Conclusions

Our study shows that SZ and BD are distinguished by premorbid cognitive impairment being found in the former but not the latter in prospective studies.

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This may reflect a neurodevelopmental abnormality in SZ but not in BD. The excess of CNVs or risk alleles in neurodevelopmental genes, which are present in preschizophrenic children, may interact with early environmental stressors, such as obstetric complications or other early hazards (Lodge & Grace, 2011). Indeed, recent evidence (Fromer *et al.* 2014) shows that SZ patients with an excess of CNVs show greater cognitive impairment.

Following the illness onset, both disorders seem to be associated with further cognitive impairment, which is of greater magnitude in SZ than BD. This deficit could be intrinsic to the illnesses but could also be related to other factors such as substance misuse, physical ill-health or the effects of prescribed medications (Zipursky *et al.* 2012). In fact, patients with more severe deficits are over-represented in most clinical settings, and are thus more likely to be recruited into research projects than people with good outcomes. This bias, which has been termed 'the clinician's illusion', means that our data come from that proportion of the post-onset patients who were still in contact with psychiatrists, and that the researchers did not generally sample those patients who recovered after initial onset and were discharged from psychiatric care (Zipursky *et al.* 2012).

To exclude the bias resulting from the 'clinician's illusion' it would be necessary to prospectively follow-up and then examine all those individuals who have an onset of SZ or BD. Studies that include prospective indicators of premorbid intellectual function and post-onset intellectual function in the same individuals, although difficult to conduct, would also advance our understanding of this issue, identifying the potential causes of the deficits.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291714001512.

Declaration of Interest

None.

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