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Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls

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Neurocognitive deficits are evident both in established schizophrenia and bipolar disorder (BP). However, it has been suggested that schizophrenia, but not BP, is characterized by neurodevelopmental abnormalities that can lead to cognitive deficits at the earliest stages of the illness. The aim of this meta-analytic review was to compare neurocognitive deficits in first-episode BP (FEBP) with healthy controls and first-episode schizophrenia (FES) patients. The current meta-analysis included a total of 22 adult studies and involved comparisons of 533 FEBP patients with 1417 healthy controls and 605 FEBP and 822 FES patients. FEBP patients were significantly impaired in all cognitive domains (d = 0.26–0.80) and individual tasks (d = 0.22–0.66) investigated. FES patients significantly underperformed FEBP patients in most cognitive domains (d = 0.05–0.63) and on individual tasks (d = 0.13–0.77). Neuropsychological impairment, which is comparable to chronic BP, was evident in FEBP. Similar to chronic patients, cognitive functions in FEBP lie intermediate between FES and healthy controls. Neurodevelopmental factors are likely to play a significant role not only in schizophrenia but also in BP.

Key words: bipolar disorder/ cognition/mania/ psychosis/schizophrenia

Introduction

Cognitive dysfunction is a common and robust feature of schizophrenia.[1–3] Bipolar disorder (BP) is also associated with cognitive deficits in a number of domains including executive functions, attention, and memory that persist in remission.[4] In chronic samples, cognitive dysfunction is less severe in BP than schizophrenia but the magnitude of cognitive differences between schizophrenia and BP are modest.[5,6]

However, it is argued that cognitive deficits in BP and schizophrenia might have very different trajectories. In schizophrenia, there is general consensus that cognitive and intellectual deficits are evident early in neurodevelopment, including childhood, well before the onset of psychosis.[7–10] It also seems that many of the cognitive deficits observed in chronic patients are also seen in first-episode schizophrenia (FES).[11,12] Neurodevelopmental abnormalities play a major role in these deficits.[13–16]

In contrast to the findings in schizophrenia, a number of studies have suggested normal, at times superior, cognitive abilities, and school achievement in children and adolescents who develop adult BP.[17,18] It has been suggested that developmental cognitive abnormalities might be specific to schizophrenia.[9,19] It was also hypothesized that patients with BP only develop cognitive deficits during the course of illness as a result of neurodegenerative changes and that cognitive deficits would be absent or very modest in first-episode BP (FEBP)[20,21]; whereas in schizophrenia it is proposed that cognition is impaired before the onset of the illness and at first-episode which might be a key difference between BP and schizophrenia.

Recently, a number of neuropsychological studies comparing FEBP with healthy controls and FES were conducted. Some of these studies have supported the hypothesis of relative preservation of cognitive abilities in FEBP and specificity of such deficits to schizophrenia.[22] On the other hand, many others have not supported the preserved cognition argument in FEBP casting doubt on the hypothesis that cognitive deficits in BP develop during the course of the illness. A recent meta-analysis found that cognitive function is significantly impaired in FEBP in comparison to healthy controls.[23] However, it is not possible to know whether the severity of these findings are comparable to chronic BP as the meta-analysis of Lee et al[23] reported effect sizes only for broad cognitive domains rather than for individual tasks. More importantly, it is not

known if cognitive differences between FES and FEBP are large unlike modest differences in chronic patients. No previous meta-analysis has compared the cognitive functions of FEBP and FES. Therefore, a meta-analytic review of the literature is warranted in order to examine overall outcome of studies investigating cognitive deficits in FEBP in comparison to schizophrenia and healthy controls. Our aim was to conduct a meta-analysis of cognitive abilities in FEBP in comparison to healthy controls and FES. We hypothesized that cognitive deficits will also be evident in FEBP samples and differences between FEBP and FES, as in chronic samples, would be modest.

Methods

Study Selection

We followed MOOSE and PRISMA guidelines in conducting this meta-analysis.[24,25] A literature search was conducted using the databases Pubmed, PsycINFO, ProQuest, and Scopus to identify relevant studies (January 1990 to July 2014). At the first step of the search, combinations of the following keywords were used: first-episode, recent onset, bipolar disorder, mania. All studies (over 500) identified by this strategy were screened for the use of neurocognitive assessments. Reference lists of published reports were also reviewed for additional studies. This step was followed for checking eligibility of the studies identified after screening. Inclusion criteria were studies that: (1) examined cognitive abilities after a FEBP (within a maximum of 2 years); (2) Compared FEBP with healthy controls and/or patients with FES spectrum disorder; (3) reported sufficient data to calculate the effect sizes and standard errors of the cognitive measures. We contacted the authors for unreported information when needed and additional information was received from three authors (see acknowledgments). Lopez-Jaramillo et al[26] (which was included in Lee et al)[23] was not included as the average duration of illness in this study was 13 years. In the case of multiple reports based on overlapping samples, the study with the largest sample size was selected for inclusion in the main meta-analysis. Data from additional reports were only used for calculation of effect sizes of individual tasks or cognitive domain data that were not included in the main study or calculation of effects size for the euthymic state.[27–29] A total of 25 studies (21 main studies)[22,27–50] were selected for the current meta-analysis (table 1) (see supplementary figure for a flow chart of the study selection process). However, 3 of these studies were based on pediatric samples that had very significant general intelligence deficits compared to adult samples (see below) and therefore were excluded from further analyses.

Adult FEBP vs Healthy Controls

About 15 studies involving 533 FEBP patients and 1417 healthy controls were included. The groups did not differ in the percentage of females included (BP 51.3 %; healthy controls, 55.7 %), and did not differ significantly in age (d = 0.12, CI = −0.07 to 0.31, Z = 1.23, P = .22).

Adult FEBP vs FES

Fourteen studies involving 605 FEBP patients and 822 FES patients were included. The vast majority of FES patients had a diagnosis of schizophrenia but a small subset of these patients had diagnoses of schizoaffective or schizophreniform disorder. The percentage of females was significantly higher in the FEBP (50.5 %) than FES group (34.1 %), and FES patients were significantly younger than FEBP patients (d = 0.17, CI = 0.02–0.32, Z = 2.26, P = .02).

Statistical Analyses

Meta-analyses were conducted when at least 3 independent studies reported on a given measure. Individual cognitive tests were grouped into broader cognitive domains based on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), except for calculation of verbal fluency score separate from processing speed. Cognitive domains included were processing speed, verbal memory, visual memory, attention and vigilance (attention), reasoning and problem solving (reasoning), working memory, and verbal fluency. We classified cognitive tests that were not part of the MATRICS battery under the relevant cognitive domain based on agreement between the 2 authors and factor loadings as reviewed in Nuechterlein et al.[51,52] A global cognitive index, "Global cognition," for each study was calculated by averaging the effect sizes across different domains.

This step was undertaken because there were not sufficient studies to perform meta-analyses for all individual tasks. However, it was also possible to conduct individual task analyses for trail making A and B tests, letter and semantic fluency, list learning and delayed recall (based on similar list learning tasks, see supplementary table for more details), digits span forwards and backwards, letter number sequencing (LNS; only for FEBP vs controls), and Wisconsin Cart Sorting Test (WCST) perseverative errors (only for FEBP vs controls). Most working memory (WM) tests used in the studies included in the meta-analysis were verbal tasks. In addition to the WM domain, a separate effect size was also calculated for verbal WM.

Meta-analyses were performed using MIX software version 1.7 on a Windows platform.[53] Effect sizes were weighted using the inverse variance method. A random effects model (DerSimonian-Laird estimate) was used, as the distributions of effect sizes were heterogeneous for the number of variables. Homogeneity of the distribution of weighted effect sizes was tested with the Q test, and degree of heterogeneity was quantified using the I^2 test. I^2 estimates the percentage of total variation across studies that is due to heterogeneity rather than chance.[54] I^2 values

Table 1. Characteristics of Adult Studies Included in Meta-analysis of First-Episode Bipolar Disorder in Comparison to FES and Healthy Controls

Studies	Sample *N*	Male %	Age (y)	Education	Medications	Psychosis rating	BP state	Mania rating (BP)	Depression rating (BP)
Ayres et al[30]	41 FEBP 98 FES 383 HC	37% 57% 47%	33.5 30.6 32.1	No difference	Most exposed to antipsychotics Many BP on mood stabilizers		Not clear		
Barrett et al[31]	32 FEBP 46 FES 67 HC	50% 70% 58%	36.7 29.0 33.2		91 % of patients on antipsychotics	PANSS positive FEBP:17.4 FES:17.6	Subacute	PANSS excitement: 17.4	BDI:10.0
Bucker et al[32] Torres et al[29] DeFreitas[33]	74 FEBP 98 HC	48% 40%	23.0 22.5	No difference			Mild symptoms: Torres et al, euthymic		
	72 FES 64 FEBP	50% 67%	22.7 21.4	FES<BP		PANSS positive FES:20.5	Euthymic	YMRS:0 (median)	HDRS:3 (median)
Chan et al[34]	40 FEBP 38 FES 37 HC	45% 37% 27%	22.4 21.8 22.4	FES=BP<HC	All but 3 on Antipsychotics 26 BP on mood stablizers	PANSS positive FEBP:8.2 FES:10.7	Euthymic	YMRS:2.4	HDRS:1.1
Daros et al[35]	16 FEBP 24 FES 32 HC	56% 79% 34%	23.6 22.6 25.8	Matched for reading ability	No medications within 3 days of assessment >50% exposed to antipsychotics	PANSS positive FEBP:24.5 FES:22.3	Symptomatic	YMRS:28.2	HDRS:28.5
Demmo et al[36] Hellvin et al[37]	87 FEBP 87 FES 90 HC	45% 43% 58%	29.8 30.1 30.1	No difference					
	34 FEBP 110 HC	44% 45%	31.2 31.1	No difference	28/34 on antipsychotics 18734 lithium or mood stabilizers	PANSS positive FEBP:11.6	Some symptomatic	YMRS:2 (median)	IDS-C:14 (median)
Dickerson et al[38]	60 FEBP 56 FES 312 HC	35% 82% 34%	26.5 23.1 28.6	FES<BP<HC	107/116 on antipsychotics 65% BP on lithium	PANSS positive FEBP:19.9 FES:20.5	Symptomatic		CDS:7.6
Fleck et al[39] Lebowitzet al[28] Larson et al[27]	21 FEBP 48 HC	52% 42%	25.7 28.2	No difference	Most on antipsychotics and mood stabilizers		Manic or mixed but Larson et al: Euthymic	YMRS:21.7	HDRS:16.0
Gruber et al[40]	26 FEBP 20 HC	73% 75%	24.4 25.3	BP<HC	<2 weeks treatment		Not clear Within 2 weeks of manic admission		
Hill et al[41]	22 FEBP 30 FES 41 HC	59% 80% 59%	22.7 23.0 24.9	No difference	Half antipsychotic naive, others brief exposure	PANSS positive FEBP:23.5 FES:23.6	Symptomatic		HDRS:29.1
Hirayisu et al[42]	24 FEBP 20 FES 22 HC	75% 80% 91%	23.6 27.3 24.5		Most on antipsychotics Short duration		Manic		
Minzenberg et al[44]	26 FEBP 73 FES 54 HC	62% 81% 52%	20.6 21.6 20.1	FES<HC	86% FES and FEBP 58% on antipsychotics and 57% mood stabilizer	SAPS FEBP:7.9 FES:9.2	Euthymic or mildly symptomatic		
Mojtabai et al[45]	72 FEBP 102 FES	50% 69%	30.5 30.2	FES<BP		SAPS FEBP:0.3 FES:0.7	Stable but mildly symptomatic		
Nehra et al[46]	16 FEBP 20 HC	50% 60%	28.4 38.7	BP<HC	13/16 antipsychotics 7/16 mood stabilizers		Euthymic	YMRS:1.4	HDRS:1.4

Table 1. Continued

Studies	Sample *N*	Male %	Age (y)	Education	Medications	Psychosis rating	BP state	Mania rating (BP)	Depression rating (BP)
Owoeye et al[47]	73 FEBP 73 FES	52% 74%	30.9 32.6			PANSS positive FEBP:16.3 FES:17.4	Symptomatic		
Thomas et al[49]	11 FEBP 38 FES 16 HC			No difference			Acute manic		
Zanelli et al[22]	37FEBP 65 FES 177 HC	41% 65% 44%	28.1 26.5 37.2	FES<BP=HC			Symptomatic		

Note: FEBP, first-episode bipolar disorder; FES, first-episode schizophrenia; HC, healthy controls; PANSS, the positive and negative syndrome scale; YMRS, Young Mania rating scale; HDRS, Hamilton depression rating scale; SAPS, Scale for Assessment of Positive Symptoms.

between 0 and 0.25 suggest small magnitudes of heterogeneity, while I^2 values in the range 0.25 and 0.50 suggest medium magnitudes, and those >0.50 indicate large magnitudes. Tau squared (τ^2), an estimate of between study variance was used as measure of heterogeneity in the random-effects model. Publication bias was assessed by inspecting funnel plots and fail-safe *N* tests. The Fail Safe *N* test involves computing a combined *P* value for all studies included in the meta-analysis, and calculating how many additional studies with a zero effect (average *Z* of zero) would be necessary to create a nonsignificant *P*.[55]

Meta-regression analyses were conducted for age, gender (male ratio in FEBP and ratio of males in FES vs FEBP), in FEBP control and FEBP-FES comparisons whenever at least 6 studies reported these variables. Meta-regression analyses were also conducted for dichotomized variables of mood state (euthymic vs noneuthymic) and substance abuse (excluded vs not-excluded) and education (matched and not-matched) in FEBP-control comparisons. Meta-regression analyses (weighted generalized least squares regressions) were conducted using SPSS. Meta-regression analyses performed with a random effects model were conducted using the restricted information maximum likelihood method with a significance level set at $P < .05$.

Results

Cognitive Deficits in FEBP

The magnitude of IQ deficits in pediatric samples was large ($d = 1.26$) and the difference between adult and pediatric samples was highly significant ($Q_{bet} = 23.05$, $P < .001$). Therefore, as mentioned above, the pediatric studies were excluded from further analyses.

Healthy controls significantly outperformed euthymic adult FEBP patients in all cognitive domains (range of $d = 0.31$–0.80) as well as current ($d = 0.45$) and premorbid ($d = 0.26$) IQ (table 2; figure 1).

The distribution of effect sizes was heterogeneous for IQ and verbal and visual memory, fluency, and reasoning domains (I^2 = 61–68.3 %). However, the magnitudes of this heterogeneity were small (range of $\tau^2 = 0$–0.11) for all domains in the random effects model. Heterogeneity of IQ was driven by 2 studies with very large effect sizes. The IQ deficit in FEBP patients was smaller ($d = 0.27$, CI = 0.11–0.44, $Z = 3.29$, $P = .001$) and distribution of effect sizes were homogeneous (Q test = 2.33, $P = .80$) in a re-analysis of IQ differences without these 2 studies.

The funnel plots did not show evidence of publication bias in any of the cognitive domains and the trim and fill method did not suggest a different effect size for any of the variables. The fail-safe *N* number was between 15 and 352. Task-specific analyses indicated that healthy controls performed significantly better than FEBP patients on all cognitive tasks ($d = 0.22$–0.66).

In meta-regression analyses, gender, education, age, state (euthymic vs noneuthymic), and exclusion of drug use had no significant effects on global cognition.

Cognitive Deficits in FEBP and FES

FEBP patients significantly outperformed FES patients in processing speed ($d = 0.33$), verbal fluency ($d = 0.50$), verbal memory ($d = 0.47$), and working memory ($d = 0.35$) but not reasoning, sustained attention, and visual memory. FEBP patients also outperformed FES patients in current ($d = 0.63$) and premorbid ($d = 0.50$) IQ (figure 2; table 3). The distribution of effect sizes was homogeneous except for IQ, processing speed, global cognition, and working memory (I^2 = 48.8–67.9 %). Magnitudes for heterogeneity were small (range of τ^2 = 0–0.07) in the random-effects model. The funnel plots did not show evidence of publication bias in any of the cognitive domains and the trim and fill method did not suggest a different effect size for any of the variables. The fail-safe *N* number was between 4 and 80 for the variables where significant between-group differences were found. In individual task analyses, FEBP patients significantly outperformed FES patients on all cognitive tasks other than digit span forwards ($d = 0.18$) and

Table 2. Mean Weighted Effect Sizes for Cognitive Differences Between Patients with First-Episode Bipolar Disorder and Healthy Controls in Adult Only Samples

Test	Study *N*	FEBP	HC	*D*	95 % CI	*Z*	*P*	*Q* test (*P*)	τ^2	I^2	Fail safe *N*
Premorbid	7	207	500	0.26	0.10–0.42	3.17	.001	0.73	0	0	15
IQ	8	275	615	0.45	0.19–0.71	3.43	<.001	0.007	0.09	63.6	58
PS	8	291	494	0.61	0.39–0.84	5.31	<.001	0.07	0.05	47.2	107
TMT A	5	146	283	0.66	0.25–1.06	3.20	.001				
TMT B	4	146	283	0.57	0.23–0.91	3.32	<.001				
Stroop	3	156	135	0.47	0.23–0.72	3.83	<.001				
Fluency	9	354	926	0.36	0.17–0.55	3.65	<.001	0.06	0.04	47	54
Letter	8	280	828	0.30	0.05–0.55	2.35	.02				
Category	5	181	358	0.39	0.–0.77	1.96	.05				
Verbal memory	6	312	785	0.63	0.39–0.86	5.27	<.001	0.02	0.05	61.9	111
Learning[a]	4	220	410	0.50	0.14–0.87	2.70	.007				
Delayed[a]	4	220	406	0.56	0.27–0.84	3.78	<.001				
Reasoning	7	268	785	0.31	0.05–0.56	2.36	.02	0.01	0.07	62	23
WCST per	5	157	510	0.33	−0.16 to 0.82	1.31	.19				
WM	9	344	906	0.34	0.20–0.47	4.83	<.001	0.42	0	0.6	43
Verbal WM	8	300	821	0.32	0.17–0.42	4.25	<.001				
Digit Span F	5	205	603	0.22	0.05–0.40	2.47	.01				
Digit Span B	6	217	615	0.49	0.31–0.66	5.54	<.001				
LNS	3	116	312	0.35	0–0.70	1.94	.05				
Spatial WM	3	114	157	0.38	0.06–0.71	2.32	.02				
Visual memory	5	170	420	0.51	0.16–0.86	2.87	.004	0.01	0.11	68.3	29
Attention	3	107	155	0.80	0.54–1.06	6.09	<.001	0.96	0	0	22
Global	15	533	1417	0.54	0.41–0.66	8.42	<.001	0.23	0.01	19.5	352

Note: *D*, Cohen's D; FEBP, first-episode bipolar disorder; HC, healthy controls; PS, processing speed, TMT, trail making test; WCST, Wisconsin Card Sorting Test; WM, working memory.
[a]List learning task.

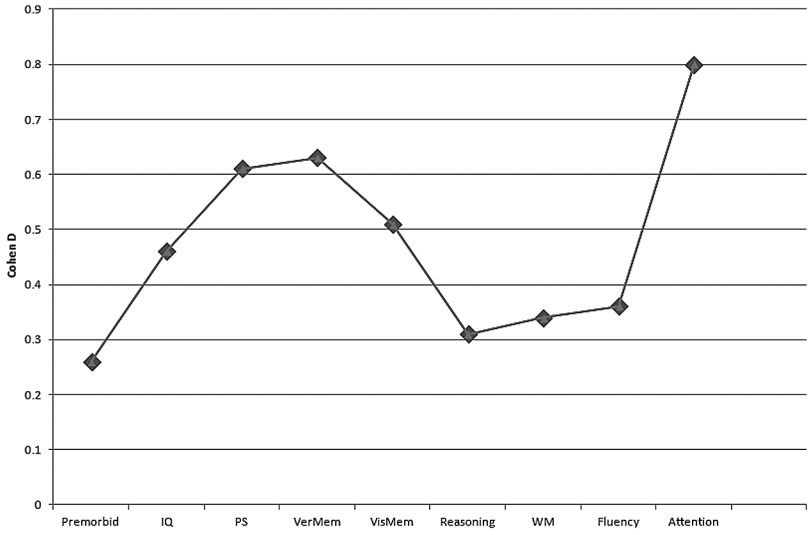

Fig. 1. Cognitive deficits in FEBP in comparison to healthy controls.

backwards (d = 0.13). The only significant finding in the meta-regression analyses was the relationship between age of FES patients and cognitive differences between FES and FEBP. Between-group differences in working memory (Z = 2.79, P = .005) were more significant in studies that included younger FES patients.

Discussion

The current meta-analysis includes 22 main studies and involved comparisons of 545 FEBP patients with 1611 healthy controls and 644 FEBP with 878 FES patients. FEBP was associated with widespread impairment in cognitive functions. Cognitive impairment was generally

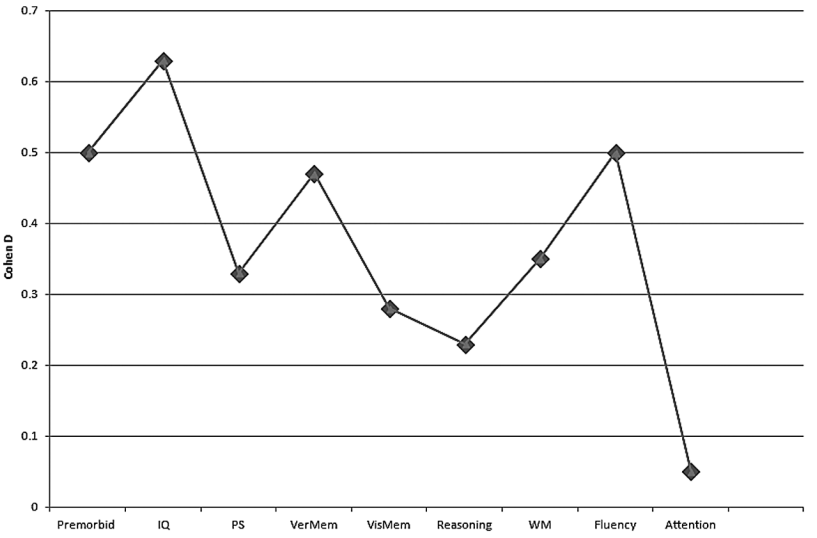

Fig. 2. Cognitive deficits in FES in comparison to FEBP.

more severe in FES in comparison to FEBP. However, cognitive differences between patient groups were modest.

In comparison with controls, FEBP patients were significantly impaired in all cognitive domains and individual tasks investigated. Medium effect sizes were noted for most of the cognitive variables. However, the effect size for sustained attention was large and the number of measures including premorbid IQ, reasoning, fluency and working memory had small effect sizes. These findings are consistent with the recent meta-analysis of Lee et al,[23] however this meta-analysis, unlike Lee et al,[23] also investigated individual cognitive tasks including trail making A and B tests, stroop interference, letter and category fluency, digit span backwards and forwards, LNS, and continuous performance test (CPT). The severity of cognitive impairment in FEBP was mostly comparable to findings in a previous meta-analysis of patients with established BP.[4,56] Only a few measures had relatively small effect sizes in FEBP compared with chronic BP: WCST, trail making B, working memory, and fluency tasks had small to medium rather than medium to large effect sizes. However, such indirect comparisons have limited value, requiring longitudinal studies. Thus far, few studies have directly compared cognitive functions in multiepisode and first-episode (or single episode) patients with BP.[26,28,37,46] These studies gave inconsistent findings and can be considered as providing evidence of no change or only limited progression of cognitive deficits as patients have recurring episodes. Moreover, such findings can reflect the sample differences rather than progression as chronic samples naturally include a higher percentage of patients with severe illness. The limited longitudinal neuropsychological studies in BP do not provide evidence of cognitive decline after onset of illness.[57,58] Overall, these findings suggest that most cognitive deficits are already evident after the first manic episode. However, as indicated, the available studies are small and further work should explore evidence for progressive changes.

While most of the studies in the meta-analysis included symptomatic patients, similar findings in the euthymic samples suggest that cognitive deficits in FEBP persist in remission. This finding suggests that most of the cognitive impairment in FEBP, like in chronic samples, is not explainable by the effect of mood symptoms. Similar to Lee et al,[23] younger age of illness onset in FEBP was not associated with more severe cognitive deficits in adult samples. However, the limited variance of mean age of onset in adult studies can mask a possible relationship between younger onset of illness and cognitive deficits in FEBP. In fact, findings of the few available pediatric FEBP studies clearly suggest that early onset of illness is associated with more severe cognitive deficits. This finding is not surprising as early onset in BP has been associated with poor prognosis.[59] Such a finding might be interpreted as consistent with the notion that earlier age of onset may impact on maturational trajectories of certain abilities during critical developmental phases.[60–62] Alternatively, severe premorbid cognitive abnormalities might be a susceptibility factor for early onset of BP.

Comparison of Cognitive Abilities in Schizophrenia and BP During the Early "Phases" of Illness

In chronic samples, previous meta-analyses compared cognitive abnormalities in schizophrenia and BP.[5,6] Both meta-analyses found that cognitive impairment is significantly more severe in schizophrenia but between-group differences were modest, suggesting that there is a significant overlap between schizophrenia and BP. Our current meta-analysis suggested that this is also true for FEBP. Moreover, findings of this meta-analysis do not suggest that between-group differences (schizophrenia vs BP) for cognitive impairment are more pronounced in FE

Table 3. Mean Weighted Effect Sizes for Cognitive Differences Between Patients with First-Episode Bipolar Disorder and Schizophrenia

Test	Study *N*	FEBP	HC	*D*	95 % CI	*Z*	*P*	*Q* test (*P*)	τ^2	I^2	Fail safe *N*
Premorbid	7	412	316	0.50	0.30–0.69	4.97	<.001	0.15	0.03	36.8	61
IQ	6	318	215	0.63	0.36–0.91	4.49	<.001	0.05	0.06	67.9	59
PS	6	413	266	0.33	0.08–0.59	2.59	.009	0.03	0.06	58.9	21
TMT A	3	197	131	0.45	0.23–0.68	3.91	<.001				
TMT B	3	197	131	0.47	0.14–0.80	2.76	.006				
Digit symbol	3	254	196	0.71	0.36–1.06	4.01	<.001				
Fluency	7	510	355	0.50	0.33–0.66	5.93	<.001	0.26	0.01	22.0	80
Letter	5	300	242	0.42	0.24–0.60	4.66	<.001				
Category	3	182	146	0.77	0.0–1.53	1.98	.05				
Verbal memory	7	458	374	0.47	0.28–0.65	4.97	<.001	0.13	0.02	39.5	69
Learning[a]	5	356	282	0.59	0.40–0.78	5.95	<.001				
Recall[a]	5	356	282	0.38	0.20–0.55	4.30	<.001				
Reasoning	2	121	97	0.23	−0.09 to 0.56	1.42	.16	0.24	0.01	26.3	
WM	8	456	318	0.35	0.11–0.59	2.84	.005	0.02	0.07	59.2	35
Verbal WM	8	456	318	0.33	0.08–0.57	2.60	.009				
Digit span F	4	251	184	0.18	−0.03 to 0.38	1.70	.09				
Digit span B	6	319	217	0.13	−0.04 to 0.31	1.48	.14				
Visual memory	4	243	163	0.28	−0.05 to 0.60	1.68	.09	0.05	0.06	66.2	4
Attention	2	68	33	0.05	−0.38 to 0.47	0.56	.83	0.62	0	0	
Global	14	822	605	0.28	0.12–0.44	3.54	<.001	0.02	0.04	48.8	74

D, Cohen's D, FEBP, first-episode bipolar disorder; HC, healthy controls, PS, processing speed; TMT, trail making test; WCST, Wisconsin Card Sorting Test; WM, working memory.
[a]List learning task.

(d = 0.05–0.63) than in chronic samples (d = 0.26–0.67).[6] Effect sizes for differences between FES and FEBP were small to moderate. Between-group differences for processing speed, working memory, verbal memory, and fluency deficits were significant but moderate suggesting that cognitive differences between schizophrenia and BP are quantitative rather than qualitative. Differences between FES and FEBP for IQ were relatively large (medium effect size). Also, in individual task analyses, effect sizes for a difference between FES and FEBP were relatively larger (medium effect size) for 2 variables (digit symbol and category fluency), while for all other measures the magnitude of between group differences were small. However, effect sizes for deficits in IQ, digit symbol and category fluency are among the very largest in chronic schizophrenia and differences between schizophrenia and BP for these tasks are relatively large in both FE and chronic samples. General intellectual abilities play a role in relative differences between schizophrenia and BP not only in established illness but also at the onset of the major psychoses.[31] The current meta-analysis has not found evidence of significant change in the pattern of neuropsychological differences between schizophrenia and BP over time after first-episode. These findings are not supportive of the hypothesis that cognitive impairment at the beginning of illness is evident in schizophrenia but not in BP.

While FE studies fail to support specificity of early cognitive deficits to schizophrenia, it might be argued that cognitive deficits can develop during prodromal periods of BP before onset of the first-episode. Therefore, studies investigating cognitive deficits in at-risk subjects prior to the first-episode are important to test the hypothesis of specificity of early cognitive deficits to schizophrenia. To date, few studies have compared cognitive deficits in subjects at risk for BP. However, one study suggested that premorbid deficits in UHR subjects that develop schizophrenia and BP might be similar to each other.[63] More studies investigating the cognitive differences between schizophrenia and BP before the first-episode would be very informative. These findings do not exclude the possibility that there might be subgroups of BP who have no neurodevelopmental cognitive deficits as premorbid studies suggest that not only impaired cognitive functioning but also above-average academic achievement predicts BP.[18,64]

This study has a number of limitations. Studies included in this meta-analysis were based on medicated patient samples. Therefore, it was not possible to explore the potential effects of medications on cognitive impairment in FEBP and cognitive differences between FEBP and FES. Also, we were not able to investigate the effects of BP subtypes on our findings (BP I vs BP II; Psychotic vs nonpsychotic BP) due to the lack of FE studies comparing such groups. This subject requires further investigation in future studies as BP I and history of psychosis have been associated with relatively more severe cognitive impairments in established BP.[65–67] Another consideration in interpreting the findings of this analysis is the relationship between global cognition and between-group differences for other cognitive domains. For example, in Barrett et al,[31] while there were significant differences between

FES and FEBP, there were no significant cognitive differences between subgroups of FES and FEBP patients matched for IQ. In the current meta-analysis, many studies were not matched for IQ, with significant group differences apparent between FEBP, FES, and healthy controls. IQ differences may reflect true differences, or may represent potential problems in sample matching that would influence the findings in other cognitive domains. Thus, in neurodevelopmental conditions, like bipolar disorder and schizophrenia, matching for general intelligence on the one hand can mask true cognitive deficits that are strongly associated with IQ, while not matching can overestimate such deficits. Further, lack of comprehensive data across various domains in many studies, as well as limited studies investigating longitudinal changes, were further limitations of our findings.

Conclusion

As a conclusion, the evidence showing that cognitive deficits are already evident at FEBP suggests that neurodevelopmental factors play an important role in the development of cognitive deficits not only in schizophrenia but also in BP. Future studies investigating premorbid trajectories of cognitive functions in BP from childhood to first-episode are important to clarify potential differences and similarities of developmental trajectories of BP and schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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