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Influence of Cognitive Reserve on Neuropsychological Functioning in Bipolar Disorder:

Findings from a Five-Year Longitudinal Study

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Keywords: Bipolar Disorder, Cognitive Reserve, Clinical Neuropsychology

Abstract

Objectives: The present study examines the five-year longitudinal course of cognitive functioning in a large sample of well-characterized patients with Bipolar Disorder (BP), compared to healthy

controls (HC), and the influence of cognitive reserve factors (e.g., education and IQ) on cognitive change over time.

Methods: Participants included 159 individuals diagnosed with BP and 54 HCs recruited as part of a longitudinal naturalistic study of BP who had completed neuropsychological testing at the time of their enrollment and again 5 years later.

Results: Overall relative rate of change did not differ between the BP and HC groups. 46.5% of the BP group and 37% of the HC group showed evidence of decline on at least one measure over time. T-test analyses did not find differences between BP "decliners" and "non-decliners" in cognitive reserve variables. However, we found that higher baseline intellectual ability was associated with more stability in cognitive test scores over time for the BP group. Results of linear regression modeling revealed that lower verbal IQ and education were related to increased cognitive decline in specific domains in the BP group.

Conclusion: The BP group did not demonstrate accelerated cognitive decline over 5 years compared to the HC group. Our results explore the influence of cognitive reserve on preservation of specific cognitive abilities over time in BP. Although the trajectory of cognitive change over time was similar between BP and HC, higher overall intellectual ability may be a protective factor against cognitive decline, particularly for BP patients.

Introduction

It has been well established that individuals with bipolar disorder (BP) typically achieve lower neuropsychological test scores compared to healthy controls (HC) across a number of cognitive domains, including attention, memory, psychomotor speed, and executive functioning (1-4). However, few studies have examined if and how these cognitive deficits change over time. Past studies have found that older individuals with BP tend to have more functional impairment, neurocognitive impairment, and higher rates of dementia (5-7). These findings lead to the assumption that individuals with BP may be at increased risk for cognitive decline, and therefore suffer a progressive, accelerated neurodegeneration over time (8, 9). Further, previous cross-sectional work by our group (10) has demonstrated an additive effect of aging and cognitive burden on health-related quality of life, as well as evidence of an age by BP diagnosis interaction in terms of performance on emotion processing, processing speed, and executive functioning tasks. These findings highlight the importance of studying cognitive changes in aging individuals affected by BP.

Although relatively sparse, a number of recent articles have proposed that progression of cognitive symptoms over time may not differ between individuals diagnosed with BP and healthy control subjects (11-13). In a recent review article examining longitudinal and cross-sectional research on the trajectory of neuropsychological dysfunction among those with BP, Strejilevich and colleagues (13) concluded that evidence does not support progressive neurocognitive decline over time. They noted, however, that many of the studies to date had methodological limitations such as small sample size and brief neuropsychological batteries. In other recent work, Gildengers and colleagues (11) explored longitudinal neuropsychological performances in BP over two years and found that, although individuals with BP tended to score lower on cognitive measures overall, the change in scores did not differ compared to healthy controls, suggesting that BP was not related to an accelerated rate of cognitive decline as was previously assumed. Similarly, Santos and colleagues analyzed the longitudinal course of BP cognitive trajectory over a longer time period and again found that BP participants demonstrated a similar cognitive trajectory over time compared to controls, despite performing at lower levels on neuropsychological testing. Again, these findings suggest that having a BP diagnosis was not associated with progressive neurocognitive decline. Further, this work reported that the clinical symptom course of BP (measured by number of mood episodes) was unrelated to cognitive performance over time, indicating that cognitive deficits in BP tend to be stable, following a course similar to those without a significant psychiatric condition. Although compelling, data was obtained via a small sample size of 80 BP participants, and further exploration with larger samples and over longer periods of time is needed to better evaluate this hypothesis. As normative age-related changes can be notable and highly variable, a null effect of disease by age is likely underpowered with smaller samples over shorter periods of time. Overall, analysis of neurocognitive change in BP is a relatively new area of study, and most work done in the area has been cross-sectional in nature, utilizes small sample sizes over a short follow-up time interval, and has used a brief incomprehensive test battery.

While patterns of cognitive dysfunction across BP mood states have been found in executive functioning, psychomotor speed, attention, and memory (4), there is a large amount of heterogeneity in cognitive profiles and presentations (9), with patient's ranging from no impairment to substantial impairment (14, 15). Many individual differences in cognitive impairment lead to questions regarding possible environmental, experiential, or social factors that influence the development and change of neurocognitive performance over time. Cognitive

reserve (CR) is an important factor that could be contributing to this variability in neuropsychological performances in those with BP. The theory of CR asserts that some individuals have more resilient brains than others and can sustain higher levels of pathology or damage before exhibiting significant behavioral symptoms. This is thought to be due to accumulation of more efficient, larger, or stronger neural networks (16-19). Because CR cannot be easily quantified, proxy measures such as pre-morbid intellectual ability, education, occupational attainment, and leisure activity have been used as surrogate variables and are established as standards of CR measurement in literature (20).

CR has most frequently been adopted in research on acquired or neurodegenerative conditions, such as Alzheimer's disease, traumatic brain injury, and vascular disease (21-28); however, CR has only recently been applied to neuropsychiatric disorders, such as schizophrenia, post-traumatic stress disorder, and BP, to help explain variability in symptom severity and neuropsychological correlates (1, 29, 30). In one of the few studies examining CR in BP, Forcada and colleagues (31) found that BP participants with lower neuropsychological functioning (in verbal and visual memory and executive functioning) also tended to have lower psychosocial functioning, education, occupational attainment, and leisure activities compared to the control group (31). Similarly, in 2015, Anaya and colleagues (32) studied the relationship between CR variables and BP neuropsychological functioning in a large sample of 200 participants. They reported that higher CR was indeed associated with better cognitive functioning in processing speed, working memory, verbal and visual memory, executive functioning, and attention. Therefore, preliminary support exists for the importance of premorbid characteristics in the severity of cognitive and functional impairment in bipolar disorder (33), although to this point, no longitudinal study has explored how CR factors may influence change in neurocognitive ability over time with a longitudinal research design.

Clearly, examining potential CR effects of neuropsychiatric conditions is difficult, as the accumulation of CR is probably related to the clinical symptoms themselves (29). Clinical symptoms that are present at an earlier age and severe enough to interfere with daily functioning can significantly impact the patient's ability to complete advanced schooling, obtain steady high-level employment, or partake in other enriching experiences (34, 35). While careful consideration should be taken, discovery of psychosocial moderators of neuropsychological change over time may have a significant impact on treatments and early interventions among individuals with BP symptoms. CR may be an important factor to consider, given its implications

in other neurocognitive conditions. Detection of a CR effect on neurocognitive change over time may provide important insights into cognitive resiliency and how to achieve it.

The present study examines the five-year longitudinal course of cognitive functioning in a large sample of well-characterized patients with BP, and the influence of CR factors on any changes in cognitive functioning over time. First, we hypothesized that group differences would exist between groups in terms of neuropsychological test scores, consistent with previous literature. Secondly, based on some of the limited evidence, we expected that differences would not exist between BP and HC in terms of change in neuropsychological test scores over 5 years, and thus show a similar cognitive trajectory. Secondly, we predicted that individuals with higher CR, as measured by intellectual ability and educational level, would experience less cognitive decline over time compared to individuals with low CR in a sample of patients with BP, similar to findings that suggest that CR is a mediator variable between brain injury/pathology and clinical outcomes. We also explored the effect of age on changes in cognitive test scores over time and expected that age would have a small but significant effect on changes on neuropsychological test scores over time; specifically, that older individuals would demonstrate a larger negative change in scores compared to younger participants. Additionally, we aimed to identify individuals who showed a significant decline in test scores ("decliners") over time and explored if any CR or clinical variables were associated with decline. Again, we hypothesized that low CR would be associated with higher rates of decline over the 5-year span.

Methods

Participants

All participants were recruited from the Prechter Longitudinal Study of Bipolar Disorder, a large-scale naturalistic study of bipolar disorder conducted at the University of Michigan in Ann Arbor, MI (36, 37) and approved by the University of Michigan institutional review board. For the present study, 159 individuals with Bipolar Disorder (Type I, II, or NOS), and 54 healthy individuals without a history of psychiatric illness (Healthy Control; HC) were used based on having five years of longitudinal data available by July 2015. Two-hundred eighty two participants were eligible for 5 year testing but did not complete it due to attrition or other factors (see Results section for analyses comparing those who completed 5 year testing and those who did not). Individuals were excluded from the longitudinal study if they had a history of diagnosed schizophrenia, active substance dependence, or history of significant neurological disease at the

time of study entry. HC participants were excluded from the study if they met diagnostic criteria for a DSM-IV-TR disorder at any time during the 5 year study timeframe, as assessed by biennial clinical interviews (n=11). Participant data was not used if evidence of substantial intellectual impairment (IQ <70) was present (n=1). Individuals with history of developmental disorder were also screened out at the initial interview. Mood states during the neuropsychological assessment were also documented at the time they entered the study. At baseline, 54.1% of the BP group was euthymic, 36.5% were considered depressed, and 8.8% were considered to be in a hypo/manic state. All the HC were in the euthymic state. Among the BP sample, separate chi-square analyses showed that mood state at the time of testing (i.e. depressed, manic, or euthymic) was not significantly related to overall decline, $\chi^2(2, N=158)=1.10$, $p=.578$, or the number of tests participants declined on, f(2)=.289, $p=.75$. Further, baseline test performances ($p>.05$) were not different among the specific mood states, other than measure of visuospatial functioning (RCFT Copy), f(2)=5.39, $p=.005$. Change in cognitive performance was not related to change in depression (Hamilton Depression Rating Scale(38), HDRS) or mania symptoms (Young Mania Rating Scale(39), YMRS) from baseline to year 5 (all $p>.05$). Further, results ANOVA analyses showed that mood state at the time of testing was unrelated to change in cognitive performance across all tests. Thus, those with current mood symptoms were included to increase sample size.

Clinical Assessment

All participants completed an initial psychodiagnostic interview with an experienced clinician using the Diagnostic Interview for Genetic Studies (DIGS; (40)). Psychiatric diagnoses were then determined through best estimate consensus processes in which two MD/PhD level clinicians independently evaluated information obtained from the DIGS and other available data (e.g. available medical records, self-report forms). Educational achievement and other demographic variables were obtained through the DIGS interview. Also, information regarding presence of cerebrovascular disease/risk factors and historical clinical information (e.g., number of mood episodes, presence of psychosis, suicide history, etc) were obtained through the DIGS. The Hamilton Depression Rating Scale (HDRS) (38) and the Young Mania Rating Scale (YMRS) (39) were used to assess mood state at the time of testing. The HDRS has 17 items and scores range from 0-50, indicating overall depressive symptomatology. The YMRS has 11 items and scores range from 0-60, indicating overall mania symptomatology. Each participant's medication classes and composite load score were determined with methods adapted from other groups (41-46), in which higher scores represent a larger medication burden.

Cognitive Reserve Variables

Proxies for CR in our study included education and premorbid intellectual functioning as measured by the vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence (see *Neuropsychological Assessment* below). Years of education was used as a continuous variable. Higher educational attainment and standardized IQ scores were considered to be reflective of higher cognitive reserve.

Neuropsychological Assessment

All participants completed comprehensive neuropsychological testing at the time of their entry into the longitudinal study (baseline) and again five years later (year 5), administered by trained research associates and supervised by neuropsychologists on the team. The neuropsychological test battery was based on previous work by Langenecker et al. (37) and captured neurocognitive abilities in the areas of attention, memory, language, processing speed, executive functioning, and motor speed. The test battery has also been used in a number of other published articles investigating neuropsychological abilities among individuals with BP (10, 47-51), addressing separate questions about the disorder in cross-sectional analyses. Scores from seven neuropsychological tests were selected that emphasize major areas of cognitive dysfunction among individuals with BP. These included The California Verbal Learning Test-II (verbal memory: CVLT-II, long delay free recall) (52), Rey-Osterrieth Complex Figure Test (visuospatial integration and visual memory: RCFT; copy, immediate, delay) (53), Purdue Pegboard (motor speed/dexterity: Pegboard; dominant and non-dominant hand speed) (54), Wisconsin Card Sorting Test (executive functioning: WCST; total correct) (55) , Stroop Color and Word Test (attention/executive functioning: Stroop; Color-Word interference subtest) (56), Controlled Oral Word Association Test (phonemic verbal fluency: COWAT; FAS administration) (57), Animal Fluency (semantic verbal fluency: Animals) (57), and Trail Making Test A & B (psychomotor speed and executive functioning: TMTA & TMTB). The Wechsler Abbreviated Scale of Intelligence (overall intellectual ability: WASI) (58) was administered during the baseline evaluation to provide information regarding overall intellectual ability (resulting in an estimated full scale IQ score); however we used the Vocabulary scaled score from the WASI as the measure of intelligence as this has shown to be robust to neurological illness(59, 60).

Data Analyses

Analyses were completed using IBM Statistical Package for Social Sciences (Version 21) and Statistical Analysis System. T-Tests or chi-square tests were used to determine demographic

differences between the BP and HC groups. Raw scores were converted to Z-scores based on mean HC group scores at baseline and year 5. Paired t-test analyses were used to compare BP and HC in terms of their neuropsychological test scores at baseline, and again at year 5. Change scores were created by calculating the difference in Z scores between baseline testing and year 5 testing. Next, we identified decliners (n= 120) as individuals with change scores at least 1.5 standard deviations below the HC mean on any of the cognitive tests. Below 1.5 SD was chosen as a cut-off to represent a clinical change in functioning. Those who did not demonstrate decline of >1.5 SD were considered non-decliners (n=104). T-test analyses of the decliners and non-decliners were completed to further assess for differences among groups in terms of CR variables. We used chi-square and t test analyses to compare the BP decliners and non-decliners on clinical variables including cerebrovascular risk factor/disease variables. Finally, variable regression models were used to determine the relationship between changes in test scores over the five year period, as well as the influence of CR variables. As previously noted, CR variables included in our analyses were education and IQ.

Results

There were no significant differences between the BP and HC groups in terms of education, age, gender, handedness, WASI full-scale IQ or WASI vocabulary standard score at study entry. Descriptive statistics are presented in Table 1.

We compared participants who completed 5 year re-testing (completers; n=283) to those in the entire sample of individuals who had been enrolled long enough that five year testing could have been completed, (non-completers; n=282) to contextualize this sample in terms of attrition. The completers had similar full scale IQ (p=0.27) and education (p=0.19) as non-completers but were more likely to be older (M(SD)=38.97(13.13) vs. M(SD)=35.90(14.11); t(237)=-2.68, p=.01) and male (p=.0009).

Next, when examining differences between groups for neuropsychological test scores at baseline testing and year 5 testing, the BP group showed significantly lower scores on 7 of 13 test scores at baseline, and 6 of 13 test scores analyzed at year 5 as compared to the HC group. Please see Table 2.

To provide an indicator of overall relative change, change scores were created by calculating the difference in Z scores for all neuropsychological tests between baseline testing and year 5 testing. See Figure 1. Change scores for the neuropsychological test variables did not differ between the BP and HC groups, with the exception of a visuospatial skills (RCFT copy) and the delayed visual memory score (RCFT delay), which revealed an improvement in performance for BP, but not HC (t=-2.07; p=.04 & t=-2.70, p=.007; see Table 3). Immediate visual memory (RCFT immediate) showed a trend toward significance, t=-1.97, p=.05.

Individual participants were considered a "decliner" if they obtained a change score that was at least 1.5 standard deviation below the mean HC change score on one or more neuropsychological test (i.e. if they demonstrated more change in test scores over 5 years than was typical for the HC sample). Individual HC means and standard deviations were used to calculate change scores for each test score, at each time point. "Non-decliners" included individuals with change scores within the HC range, based on the HC change score mean (i.e. those who did not change more drastically than the average HC over the 5 year time frame).

Decliners included 74 individuals from the BP group (46.5% of the BP group), and 20 individuals from the HC group (37% of the group). Among the whole group of decliners, there were no significant differences between the groups in terms of age, education, WASI vocabulary (estimated verbal IQ) or gender. Within the BP group only, decliner status was not associated with any of the demographic or CR variables. However, we found that the decliners in the BP group had significantly lower overall IQ scores than those in the BP non-decliner group (p<.001).

Those in the decliner group included a majority who declined on at least one cognitive test (n=53, 71.6%), 20.3% declined on 2 tests (n=15), 4.1% declined on 3 tests (n=3), 2.7% declined on 4 tests (n=2) and 1.4% declined on 6 tests (n=1). Within the HC group only, decliner status was associated with education with the decliner group having less education than the non-decliners (p=.005, decliners education=14.8(2.4), non-decliners education=16.5(1.8)). Out of the HC who declined, the majority declined on one cognitive test (n=13; 65%), 20% declined on two tests (n=4) and 15% declined on 3 tests (n=3).

Although not the main analyses, we examined clinical, illness variables between decliners and non-decliners among just the individuals with BP. See Supplemental Table 1. There were no illness features that were significantly different between the decliner and non-decliner groups.

Further, there were no differences between the decliners and non-decliners in terms of the presence of cerebrovascular disease or cerebrovascular risk factors. There also was no difference in total medication load when comparing BP decliners to BP non-decliners. When considering the entire sample (HC, BP), the results continued to be non-significant.

Finally, the changes in neuropsychological performance over 5 years were analyzed at a posthoc level with linear regression modeling. The BP and HC groups were analyzed separately to evaluate the influences of IQ and education. Regression models showed that within the HC group, age and baseline verbal IQ influenced change in semantic verbal fluency performance (Animals). Specifically, education influenced semantic fluency (parameter estimate=0.11, p=0.02) and with every 10 point increase in IQ, change in semantic verbal fluency scores decreased by 0.08 (*parameter estimate*= -0.08; *p*=0.02). Further, baseline verbal IQ influenced change in interference control (Stroop parameter estimate=-0.94, p=.02) such that for every 10 point increase in IQ, change in interference decreased by 0.94. Age and education influenced visuomotor attention (TMTA; parameter estimate age=0.03, p=0.004; parameter estimate education=-0.13, p=.03) and fine motor dexterity (parameter estimate age=-0.03, *p*=0.008; parameter estimate education=0.17, *p*=.02. Within the BP group, regression analyses indicated that lower IQ score was associated with significantly decreased verbal memory task (CVLT long delay free recall; *parameter estimate*= -0.06; *p=*0.01). Lower education was found to be related to attenuated decline on a visuospatial functioning (RCFT Copy; *parameter estimate=-0.10; p=0.04*) and simple visuomotor attention (TMTA parameter estimate=-.07, p=.048). Age at the time of testing was also included in a regression analyses as a covariate, and results indicate that age was related to change on specific measures (see Table 4).

Discussion

The results of this study yielded several notable findings regarding change in cognition over 5 years in individuals diagnosed with BP, compared to control subjects, as well as important insight into potential cognitive reserve factors, particularly in those with BP using a large sample size and longitudinal study design. First, we re-demonstrated that baseline neurocognitive deficits exist among those with BP compared to HC, consistent with previous literature (37). Specifically, we showed that significantly lower scores were obtained by individuals with BP in terms of visuospatial ability, immediate and delayed visual memory, bilateral motor speed, attention, executive functioning, and psychomotor speed (at baseline year 5, or both time points). Next, we found that change in neurocognitive performance over time did not differ between the

BP and HC groups (with one exception, which showed slightly improved performance for BP in delayed visual memory). More broadly, we did not find evidence for accelerated decline in the 5 year time frame for BP, consistent with an interpretation of additive, but not compounded or accelerated, effects of age and BP (61). When we identified individuals who demonstrated a significant decline on at least one cognitive measure, we found that decline was significantly associated with lower overall intellectual scores compared to those who did not decline within the BP group only. This finding was not replicated within the HC decliner group. However, we did not find a difference between the BP decliners and BP non-decliners in terms of our cognitive reserve variables (WASI Vocabulary and education). This finding suggests that overall IQ may be protective for general cognitive decline in BP, but not traditional cognitive reserve variables as expected.

Instead, we found verbal IQ (WASI Vocabulary) and education were related to changes in specific cognitive domains. Specifically, we found that intellectual ability was related to change in performance on visuospatial ability, simple visuomotor attention, and verbal memory in the BP group, three particularly important skills in everyday life. Overall, findings supported our hypotheses which indicate that there does not seem to be evidence of accelerated cognitive decline in BP, and that CR variables were related to change in select areas of cognition. The overall lack of cognitive decline could represent a stable cognitive endophenotype in bipolar disorder and warrants future exploration (47, 62).

Overall, our sample was highly educated and intelligent, with IQ scores well in the average and high-average ranges, which may account for why we did not find change in more of the cognitive domains assessed. Additionally, a longer period of time, beyond 5 years, may be necessary to detect more significant cognitive change within the groups. Since our cohort was relatively young (mean age= 41.6), longer studies and analysis of older individuals with BP is warranted. It is possible that older individuals with BP do experience accelerated cognitive decline and that our sample was too young to detect this.

Our finding that those with a bipolar diagnosis did not experience an increased decline over 5 years is in support of a growing body of new literature (11, 13, 63), and also contradictory to previous work that has claimed BP is associated with significant neurocognitive decline (5-9, 64). However, our study utilized a large sample of participants with BP and longitudinal methods, which may increase the specificity and generalizability of our findings to BP groups, given the

typical high rate of variability between patients. Overall, this finding is important to consider in treatment planning and support for middle-aged and older adults with BP, as these individuals may start at a lower cognitive level, and with a similar pattern of decline, may reach the point of dementia at an earlier age. Specifically, the BP group tended to have lower baseline neuropsychological scores compared to HC, and that a "normal" decline in cognition associated with age may lead to more significant functional deficits as they may reach an objectively more impaired cognitive level, which might translate into higher levels of occupational disability as well (14).

Our study makes a significant contribution to the existing literature in that it applies the concept of CR to BP, a highly unique condition with a complex constellation of neuropsychological symptoms and mood difficulties. Our findings suggest, to some degree, that higher intellectual abilities earlier in life may be related to preserved cognitive abilities in BP, while traditional cognitive reserve variables, including verbal IQ and education, have a selective effect on in visual spatial ability and verbal memory. It is possible that CR may provide the same kind of preservation and/or accommodation of neurocognitive difficulties in BP as that demonstrated in stroke, TBI, dementia, or other conditions affecting cognition. To our knowledge, this is the largest study utilizing a longitudinal design following patients for 5 years that exists in current literature. Although other studies have explored the relationship between CR variables and neuropsychological performance in BP, or change in neuropsychological test scores for BP over time, this is the first study to our knowledge to integrate both features.

While the current study has a number of strengths, there are a few limitations that may reduce the generalizability of our results and should be considered for future studies. In particular, this study utilized participants taking a variety of psychotropic medications and participating in psychosocial treatments for BP and with comorbid conditions, as is common in naturalistic studies of this kind. It is possible that specific medications, such as lithium, had an effect on neurocognitive functioning in our study, but since we did not detect significant differences between change in BP and HC groups over time, it is unlikely that medications were related to a significant decline in cognition. Please see supplemental table 1 which illustrates the total medication load BP participants reported at the time of their initial assessment. Secondly, the particular neuropsychological test battery utilized in our study was selected for ease of administration and comprehensiveness across cognitive domains known to be affected in BP (65). Administration time and participant fatigue generally precluded a longer or more comprehensive

test battery. Finally, we included BP participants in various mood states in our analyses (euthymic, depressed, manic), and acute mood symptoms may have influenced overall performance on testing. However, our preliminary analyses did not find a relationship between decline and mood state, and therefore seems unlikely that mood at the time of testing significantly influenced our findings. Future work may focus on further characterizing the BP participants who showed evidence of decline over our 5 year time frame. Use of additional statistical methods (i.e. cluster analyses, etc.) may provide evidence of decliner subtypes, offering more precise ways to identify those in need of future supports. Other factors such as substance abuse, history of traumatic brain injury, illness duration, or cardiovascular risk are also important considerations for future research, although these were beyond the scope of our current work.

It is possible that our findings were influenced by test-retest variability in our sample. However, our decision to use a cut-off of 1.5 standard deviation change score makes it likely that our findings reflect meaningful differences, particularly as we utilized standard neuropsychological measures that are widely accepted in the field and report strong test-retest reliability.

In summary, the present study demonstrated that neurocognitive deficits exist among individuals with BP, though there is generally a high degree of heterogeneity and variability among patients. These deficits seem to be present early in the disorder, but do not progress at a more rapid rate than that experienced by a "normally" aging healthy adult sample with no psychiatric illness. Further, higher intellectual ability may selectively preserve cognitive abilities over time, particularly for individuals with BP and an above-average IQ. Traditional CR factors (WASI Vocabulary, education) were only partially influential for decline. We would like to emphasize that it is quite difficult to examine cognitive reserves variables in this population, as the accumulation of cognitive reserve may be directly impacted by the presentation of disruptive psychological symptoms at a young age.

Our findings provide valuable insight for providers and family members working with patients experiencing BP cognitive symptoms. Specifically, cognitive training groups or other rehabilitation treatments may be quite beneficial for some BP subgroups, and perhaps less necessary for others. Overall, our findings highlight the importance of intellectual engagement in those suffering from neuropsychiatric illness, which may provide some defense against functional decline with age. This is only a speculation based on a small, but growing, body of literature, however, and significantly more research is needed in this area for continued understanding of the

relationship between premorbid intellectual ability, neurocognitive symptoms of bipolar disorder, and functional decline over time.

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Table 1: Demographic variables, Mean and Standard Deviation

	Bipolar I, II, NOS: M(SD)/%	Healthy Control: M(SD)/%	Value (t or chi square)	p
Demographics				
Education	15.33(2.32)	15.85(2.17)	1.44	0.15
Gender (F)	74%	63%	2.20	0.14
Age	40.70(12.03)	36.78(14.88)	-1.95	0.05
Right Hand Dominance	86.1%	86.8%	0.02	0.90
WASI Vocabulary SS	12.65(2.74)	12.40(2.99)	-0.55	0.59
Clinical Variables				
HDRS (Baseline)	8.92(6.18)	1.14(1.53)*	-8.96	0.000*
HDRS (Year 5)	8.26(5.54)	1.85(3.29)*	-8.02	0.000*
YMRS (Baseline)	2.70(3.43)	0.34(0.71)*	-4.94	0.000*
YMRS (Year 5)	3.27(4.06)	0.93(2.67)*	-3.96	0.000*

*significantly different at p <.05. WASI= Wechsler Abbreviated Scale of Intelligence; SS= scaled score; HRDS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale

Table 2: Independent t-test results comparing neuropsychological test scores for BP and HC groups at baseline and year 5 visits.

Measure	Bipolar I, II, NOS: M(SD); Raw Score	Healthy Control: M(SD); Raw Score	T Value	Pr > |t|
Visuospatial Integration and Visual Memory				
RCFT Copy				
Baseline	32.07(3.31)	33.19(2.52)	2.29	0.023*
5 Year	33.55(3.41)	33.75(2.66)	0.39	0.70
RCFT Immediate				
Baseline	18.82(7.06)	22.72(5.87)	3.66	0.000*

5 Year	21.65(7.37)	24.84(7.53)	2.72	0.007*
RCFT Delay				
Baseline	18.43(6.82)	22.53(5.87)	3.95	0.000*
5 Year	21.56(7.51)	23.82(6.89)	1.95	0.052
Verbal Memory				
CVLT Total Learning				
Baseline	52.94(10.64)	54.53(11.03)	0.93	0.35
5 Year	51.39(11.51)	52.54(13.62)	0.60	0.55
CLVT Short Delay				
Baseline	11.25(3.18)	11.79(3.15)	1.09	0.28
5 Year	11.03(3.66)	11.43(3.91)	0.67	0.50
CVLT Long Delay				
Baseline	11.67(2.99)	12.23(2.97)	1.18	0.24
5 Year	11.56(3.60)	11.59(4.11)	0.05	0.96
Motor Dexterity				
Peg Dominant				
Baseline	14.43(1.87)	15.62(2.20)	3.86	0.000*
5 Year	14.57(2.30)	15.96(2.37)	3.78	0.000*
Peg Non-Dominant				
Baseline	13.36(1.88)	14.65(1.58)	4.54	0.000*
5 Year	13.68(2.23)	15.02(2.17)	3.83	0.000*
WCST correct				
Baseline	70.17(13.46)	71.29(11.38)	0.49	0.62
5 Year	69.27(10.89)	68.87(10.26)	-0.24	0.81
Stroop				
Baseline	0.74(7.03)	4.16(8.86)	2.88	0.004*
5 Year	2.79(7.09)	6.56(6.88)	3.39	0.001*
COWAT				
Baseline	41.84(13.07)	42.51(10.56)	0.34	0.74
5 Year	39.06(13.28)	42.22(12.75)	1.53	0.13
Animals				
Baseline	20.52(5.90)	41.84(13.07)	0.53	0.60
5 Year	18.13(5.82)	19.67(4.97)	1.74	0.08

TMT A				
Baseline	30.70(11.75)	27.26(12.68)	-1.81	0.07
5 Year	29.16(11.15)	24.06(10.51)	-2.95	0.004*
TMT B				
Baseline	78.48(44.00)	59.64(27.74)	-2.90	0.004*
5 Year	80.26(40.68)	60.11(27.07)	3.36	0.001*

* significant at p=<.05. RCFT copy= Rey Complex Figure Test Copy; RCFT Immediate= Rey Complex Figure Test Immediate memory; RCFT Delay= Rey Complex Figure Test Delay memory; Peg dominant= Perdue Pegboard speed dominant hand; Peg Non-Dominant= Perdue Pegboard speed non-dominant hand; CVLT Total Learning = California Verbal Learning Test Total Learning; CVLT Short Delay = California Verbal Learning Test Short Delay Free Recall; CVLT Long Delay = California Verbal Learning Test Long Delay Free Recall; WCST= Wisconsin Card Sort Test, total correct; Stroop= Stroop Color/Word Interference Total; COWA= Controlled Oral Word Association Test; Animals= Semantic Fluency, Animals; TMTA= Trail Making Test A; TMTB= Trail Making Test B.

Table 3: Independent t-test comparing change scores among BP and HC groups

Measure	Bipolar I, II, NOS: M(SD)	Healthy Control: M(SD)	Pr > |t|
Visuospatial Integration and Visual Memory			
RCFT Copy	0.37(1.24)	0.00(0.79)	0.39*
RCFT Immediate	0.24(0.96)	-0.04(0.71)	0.05
RCFT Delay	0.37(0.92)	0.00(0.70)	0.007*
Verbal Memory			
CVLT Total Learning	0.06(0.72)	0.00(0.88)	0.64
CVLT Short Delay	0.08(0.85)	0.00(0.81)	0.52
CVLT Long Delay	0.20(0.78)	-0.01(0.81)	0.11

Motor Speed/Dexterity			
Peg Dominant	-0.04(0.76)	-0.01(1.13)	0.80
Peg Non-dominant	0.21(0.93)	0.00(0.98)	0.16
Executive Functioning			
WCST correct	0.07(1.75)	-0.08(1.51)	0.61
Stroop	-0.16(1.00)	0.00(0.85)	0.31
Verbal Fluency			
COWAT	-0.57(2.08)	-0.10(1.90)	0.14
Animals	-0.04(0.71)	-0.22(1.09)	0.28
Psychomotor Speed/Executive Functioning			
TMT A	0.22(0.87)	0.01(1.07)	0.17
TMT B	0.08(1.28)	0.09(0.74)	0.94

* significant at p=<.05. RCFT copy= Rey Complex Figure Test Copy; RCFT Immediate= Rey Complex Figure Test Immediate memory; RCFT Delay= Rey Complex Figure Test Delay memory; Peg dominant= Perdue Pegboard speed dominant hand; Peg Non-Dominant= Perdue Pegboard speed non-dominant hand; CVLT Total Learning = California Verbal Learning Test Total Learning; CVLT Short Delay = California Verbal Learning Test Short Delay Free Recall; CVLT Long Delay = California Verbal Learning Test Long Delay Free Recall; WCST= Wisconsin Card Sort Test, total correct; Stroop= Stroop Color/Word Interference Total; COWA= Controlled Oral Word Association Test; Animals= Semantic Fluency, Animals; TMTA= Trail Making Test A; TMTB= Trail Making Test B.

Table 4: Regression results showing the significant effect of age on neuropsychological test scores in our sample (All participants)

Measure	Group	DF	Parameter Estimate	Standard Error	T Value	Pr > |t|
Visuospatial Integration and Visual Memory						
RCFT Copy	BP	1	0.015	0.008	1.77	0.08
	HC	1	-0.003	0.008	-0.35	0.73
RCFT Immediate	BP	1	0.009	0.006	1.39	0.17
	HC	1	0.001	0.007	0.10	0.93
RCFT Delay	BP	1	0.004	0.006	0.64	0.52
	HC	1	0.003	0.007	0.44	0.66
Verbal Memory						
CVLT Total Learning	BP	1	0.003	0.005	0.67	0.50
	HC	1	0.004	0.008	0.45	0.66
CVLT Short Delay	BP	1	-0.004	0.006	-0.70	0.48
	HC	1	0.004	0.008	0.58	0.56
CVLT Long Delay	BP	1	0.002	0.005	0.33	0.74
	HC	1	0.010	0.008	1.29	0.20
Motor Speed/Dexterity						
Peg Dominant	BP	1	-0.016	0.005	-3.12	0.002*
	HC	1	-0.027	0.010	-2.78	0.008*
Peg Non-dominant	BP	1	-0.012	0.006	-1.90	0.06
	HC	1	-0.019	0.009	-2.18	0.03*
Executive Functioning						
WCST correct	BP	1	0.009	0.012	0.75	0.46
	HC	1	0.018	0.015	1.17	0.25
Stroop	BP	1	0.001	0.007	0.13	0.89

	HC	1	0.013	0.008	1.78	0.81
Verbal Fluency						
COWAT	BP	1	-0.040	0.013	-2.99	0.003*
	HC	1	-0.005	0.019	-0.41	0.78
Animals	BP	1	-0.004	0.007	-0.57	0.57
	HC	1	0.003	0.007	0.52	0.61
Psychomotor Speed/Executive Functioning						
TMT A	BP	1	0.015	0.006	2.51	0.013*
	HC	1	0.025	0.008	3.05	0.004*
TMT B	BP	1	0.011	0.009	1.21	0.23
	HC	1	0.000	0.007	-0.02	0.98

* significant at p=<.05. RCFT copy= Rey Complex Figure Test Copy; RCFT Immediate= Rey Complex Figure Test Immediate memory; RCFT Delay= Rey Complex Figure Test Delay memory; Peg dominant= Perdue Pegboard speed dominant hand; Peg Non-Dominant= Perdue Pegboard speed non-dominant hand; CVLT Total Learning = California Verbal Learning Test Total Learning; CVLT Short Delay = California Verbal Learning Test Short Delay Free Recall; CVLT Long Delay = California Verbal Learning Test Long Delay Free Recall; WCST= Wisconsin Card Sort Test, total correct; Stroop= Stroop Color/Word Interference Total; COWA= Controlled Oral Word Association Test; Animals= Semantic Fluency, Animals; TMTA= Trail Making Test A; TMTB= Trail Making Test B.

Figure 1: Neuropsychological Test Score Means at Baseline and 5 Year for BP (z scores)
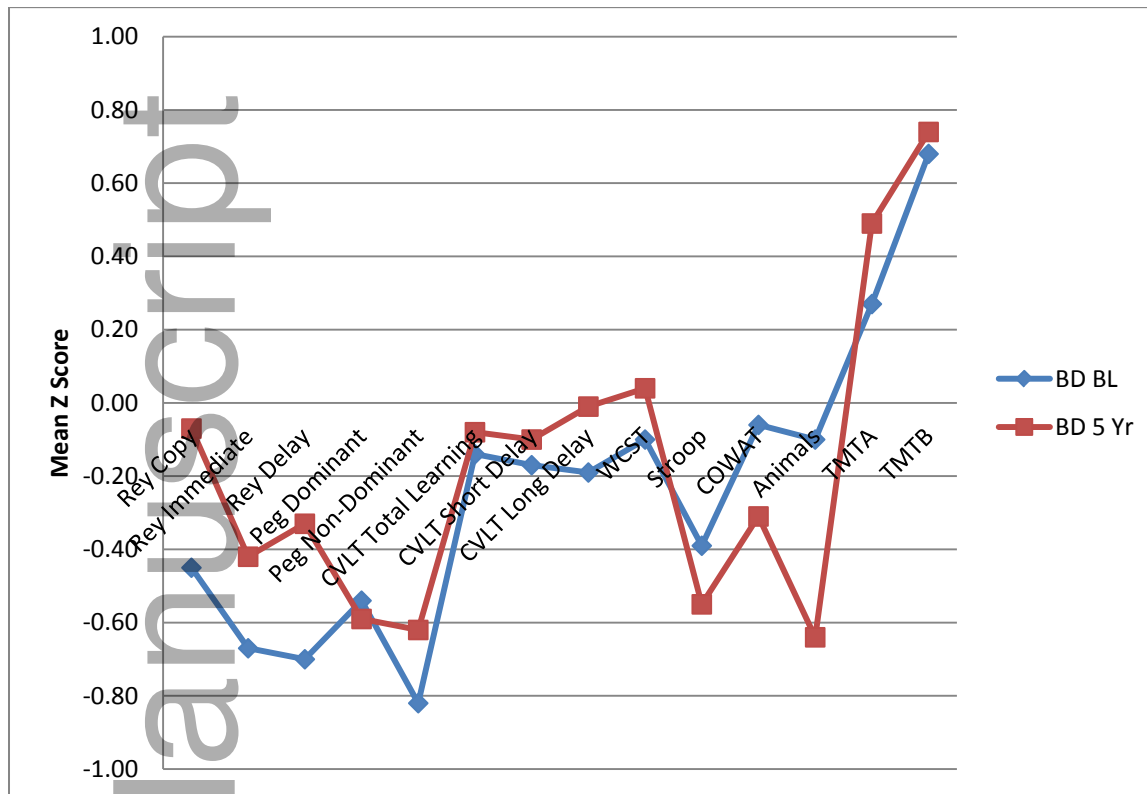
Legend: All HC are set to z score of 0. RCFT copy= Rey Complex Figure Test Copy; RCFT Immediate= Rey Complex Figure Test Immediate memory; RCFT Delay= Rey Complex Figure Test Delay memory; Peg dominant= Perdue Pegboard speed dominant hand; Peg Non-Dominant= Perdue Pegboard speed non-dominant hand; CVLT Total Learning = California Verbal Learning Test Total Learning; CVLT Short Delay = California Verbal Learning Test Short Delay Free Recall; CVLT Long Delay = California Verbal Learning Test Long Delay Free Recall; WCST= Wisconsin Card Sort Test, total correct; Stroop= Stroop Color/Word Interference Total; COWA= Controlled Oral Word Association Test; Animals= Semantic Fluency, Animals; TMTA= Trail Making Test A; TMTB= Trail Making Test B.