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## Longitudinal cognitive trajectories and associated clinical variables in youth with bipolar disorder

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### Abstract

**Objective**—There is substantial interest in delineating the course of cognitive functioning in bipolar (BP) youth. However, there are no longitudinal studies aimed at defining subgroups of BP youth based on their distinctive cognitive trajectories and their associated clinical variables.

**Method**—Cognitive functioning was measured in 135 participants from the Course and Outcome of BP Youth (COBY) study using several subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Youth were prospectively evaluated three times on average every 13.75 months over 2.5 years. Clinical and functional outcomes were assessed using the Longitudinal Interval Follow-Up Evaluation (LIFE).

**Results**—Latent class growth analysis identified three longitudinal patterns of cognitive functioning based on a general cognitive index: class 1, “persistently high” (N=21; 15.6%); class 2, “persistently moderate” (N=82; 60.74%); and class 3, “persistently low” (N=32; 23.7%). All classes showed normal cognitive functioning when compared with the CANTAB normative data.

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#### Disclosure of Interests

All other authors declare that they have no conflicts of interest.

After adjustment for confounders, youth from class 3 had a significantly greater percentage of time with overall, manic, and depressive syndromal symptoms than youth in the other two classes. Also, after adjustment for confounders, youth from class 3 had significantly poorer global, academic, and social functioning than youth from class 1.

**Conclusions**—BP youth showed normal overall cognitive functioning that remained stable during the follow-up within each class. However, 24% of BP youth showed relatively poorer cognitive functioning than the other BP youth. This subgroup had poorer mood course and functioning, and may benefit from cognitive remediation and early management with evidence-based pharmacological treatments.

### Keywords

cognitive functioning; children; adolescents; bipolar disorder; longitudinal studies

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### Introduction

There is a need to understand the longitudinal course of cognitive functioning in youth with bipolar disorder (BP)<sup>1,2</sup>. Specifically, it is unclear whether BP youth exhibit either cognitive decline, stable/unchanged cognitive trajectory, or cognitive improvement as they transit into adulthood<sup>3</sup>. By elucidating this issue, we could obtain more evidence about what mechanism of cognitive dysfunction might be associated with academic or social dysfunction<sup>4,5</sup>. Additionally, longitudinal studies of cognitive performance in BP patients may highlight critical windows of cognitive development that may be amenable to novel treatments, such as computer assisted cognitive remediation or cognitive enhancing medications<sup>6</sup>.

To our knowledge, only three studies have evaluated longitudinal cognitive functioning in youth with BP. Pavuluri and colleagues<sup>7</sup> compared 26 youth with BP-I and 17 healthy controls (HC) (mean age: 11 years old) at baseline and 3 years later using the Trail Making Test, the Digit Span Subtest from the Wechsler Memory Scale, the California Verbal Learning Test, several subtests from the University of Pennsylvania Computerized Neuropsychological Battery, and the Cogtest. BP youth exhibited deficits in attention, executive functions, working memory, verbal memory, visual memory, and visual-spatial perception at baseline and again 3 years later. At 3 years, BP youth showed less developmental progress in executive functions, and verbal memory than HC youth, even when outcomes controlled for changes in mood state and treatment with stimulants. Whitney and colleagues<sup>8</sup> studied 35 youth with BP-I and 25 HC (mean age: 15 years old). At baseline, BP youth exhibited bias away from positive valence stimuli (adjectives such as friendly, helpful, lucky, and nice), which persisted over a 1-year period, independent of mood state, medication exposure, and psychiatric comorbidities. Finally, Lera-Miguel and colleagues<sup>9</sup> compared 20 youth with BP (90% BP-I, 10% BP-II) and 20 HC who were assessed at baseline (mean age: 16 years old) and 2.5 years later using several neuropsychological tests including, but not limited to, the Wechsler Intelligence Scale, the Wechsler Memory Scale, and the Stroop Test. Adjusting for changes in mood severity over time, BP youth improved more than HC in verbal reasoning, working memory, processing speed, visual-motor skills, and visual memory. However, among BP youth, scores in executive functions did not improve and remained lower than HC performance at follow-up.

Psychotic symptoms and treatment with lithium at baseline, but not psychiatric comorbidities, were associated with poorer performance in executive control tasks in BP youth.

While the above mentioned studies are important and included both BP and HC groups, they have the following limitations: 1) small sample sizes; 2) inclusion of youth predominantly diagnosed with BP-I; 3) following the sample only one time; 4) no consideration of the relationship between cognitive functioning and mood symptoms over time; and 5) most studies did not adjust for the effects of time-varying factors such as treatment, symptom severity, mood polarity, comorbid disorders, or Intelligence Quotient (IQ).

Using the Cambridge Neuropsychological Test Automated Battery (CANTAB)<sup>10</sup>, we previously found that BP youth with BP-I/II (n= 92) participating in the Course and Outcome of BP Youth (COBY) study had specific deficits in cognitive flexibility at intake relative to youth with BP-Not Otherwise Specified (BP-NOS) (n= 28)<sup>11</sup>. In addition, comparison of the COBY BP I/II with HCs (n= 55) recruited through the Longitudinal Assessment of Manic Symptoms (LAMS) study, showed that across all BP subtypes, BP participants had impairments in sustained attention and information processing for emotionally valenced words.

The goal of this study was to extend COBY's prior baseline findings by evaluating the longitudinal course of cognitive functioning and its relationship with the mood trajectory and psychosocial functioning in COBY youth using Latent Class Growth Analysis (LCGA). LCGA has not been used to assess the longitudinal cognitive functioning of either adults or youth with BP, but it has been successfully utilized to evaluate cognitive trajectories in patients with schizophrenia, dementia, and major depression<sup>12–14</sup>. Particularly, LCGA may help us identify potential subgroups at greater risk for cognitive dysfunction and their associated clinical variables. Thus, in this study we aimed to evaluate: 1) whether there are several distinctive cognitive trajectories among BP youth; 2) the baseline and longitudinal factors associated with distinctive cognitive trajectories (e.g., demographic variables, IQ, exposure to medications, BP subtype, age of BP onset, psychiatric comorbidities); and 3) the relationship between these distinctive cognitive trajectories, mood course (percentage of time in euthymia, and sub/syndromal mood symptoms of different polarities), and psychosocial functioning (global, academic, social) over time.

## Method

### Participants

The methods for the COBY study have been described in detail elsewhere<sup>15–17</sup>. Briefly, 446 youth aged 7–17 years with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) BP-I or -II or an operationally defined BP-NOS were recruited at Brown University, University of California Los Angeles, and the University of Pittsburgh. Age of BP onset was defined as the onset of a DSM-IV mood episode or an episode fulfilling the COBY's modified DSM-IV BP-NOS. BP-NOS was defined as a distinct period(s) of abnormally elevated, expansive or irritable mood, plus: (1) at least two DSM-IV manic symptoms (three if the mood is irritable only) that were clearly associated with the onset of

abnormal mood; (2) clear change in functioning; (3) mood and symptoms present for a significant part of the day (minimum of 4 hours); and (4) a minimum of four days (not necessarily consecutive) meeting these mood, symptom, duration, and functional change criteria over the participant's lifetime. Youth diagnosed with these operationalized criteria for BP-NOS in COBY have shown similarly poor functioning, comorbid disorders, risk for suicidality and substance abuse, and family history of mania, as those with BP-I<sup>17</sup>. Moreover, they are at high risk to convert into BP-I and II<sup>16</sup>. To date, 29% of the youth with BP-NOS at intake converted into BP-I or II by the time of the last cognitive assessment. BP youth were enrolled independent of current mood state or treatment status. Youth with schizophrenia, mental retardation, autism, and mood disorders secondary to substances, medications, or medical conditions were excluded from the study.

BP youth were recruited from outpatient clinics (84.4%), inpatient units (4.4%), advertisements (6.7%), and referrals from other physicians (4.4%) from October 2000 through July 2006. The CANTAB was administered for the first time to 203 youth, on average 53 months after the initiation of the COBY study. For the current analyses, only participants who had at least one additional administration (N=135) are included. Participants who were included in the current study were not significantly different from those excluded (N=68) in terms of demographic characteristics, age at BP onset, duration of mood illness, BP subtype, number of hospitalizations, exposure to medications, lifetime psychiatric comorbidities, and cognitive functioning at the first CANTAB assessment ( $p > 0.05$ ).

BP youth included in the current study were evaluated using the CANTAB at three time points (T1, n=135; T2, n=135; and T3, n=82). On average each CANTAB was administered every  $13.7 \pm 7.1$  months over a period of 2.5 years (range 12–90 months).

Demographic and clinical characteristics at T1 are presented in Table 1.

## Instruments

**Clinical Assessments**—At intake psychiatric disorders were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL)<sup>18</sup>.

History of physical and sexual abuse was evaluated at intake using the specific questions from the PTSD section of the KSADS-PL<sup>18</sup> (separately to caregivers and children). Also, history of abuse was obtained using a medical history questionnaire.

Parents were also interviewed about their first and second degree psychiatric family history using the Family History Screen (FHS)<sup>19</sup>.

Socioeconomic status (SES) was ascertained using the 4-factor Hollingshead scale<sup>20</sup>.

The Petersen Pubertal Developmental Scale (PDS) and their equivalent Tanner stages were used to evaluate and categorize pubertal stages<sup>21</sup>.

Longitudinal changes in psychiatric symptoms were assessed using the Longitudinal Interval Follow-Up Evaluation (LIFE) and tracked on a week-by-week basis using this instrument's Psychiatric Status Rating (PSR) scales<sup>22,23</sup>. These scales use numeric values that have been operationally linked to the DSM-IV criteria. For mood syndromes (depression, mania, hypomania, mixed) scores on the PSR scales range from 1–2 for no symptoms, to 3–4 for varying levels of subsyndromal symptoms and impairment, to 5–6 for meeting full criteria with different degrees of severity or impairment. Comorbid conditions were scored on the PSR scales using a 1 to 3 rating scale (with 3 signifying threshold criteria, 2 signifying subthreshold criteria, and 1 signifying minimal or no symptoms), or on a 1 to 6 point scale (with 5–6 signifying threshold criteria, 3–4 signifying subthreshold criteria, and 1–2 signifying minimal or no symptoms). Comorbid conditions included the presence of psychotic symptoms (hallucinations and/or delusions) and psychiatric comorbidities such as substance use disorders, attention deficit hyperactivity disorder (ADHD), disruptive disorders, any anxiety disorder (panic disorder, separation anxiety disorder, agoraphobia, specific phobia, social phobia, generalized anxiety disorder, anxiety disorder NOS), posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD).

Exposure to medications during the entire follow-up period was ascertained using the Psychotropic Treatment Record of the LIFE. In addition, clinicians asked youth about their use of medications and substances 24 hours prior to each CANTAB testing. Youth who endorsed illicit substance use within 24 hours of the cognitive assessment were excluded from participation.

Longitudinal changes in global functioning were assessed through the Children's Global Assessment Scale (C-GAS) or the Global Assessment of Functioning (GAF) for youth 22 years old or older<sup>24,25</sup>. In addition, we used the Psychosocial Functioning Interview (PSF) of the LIFE to assess academic and psychosocial relationships (with parents, siblings, partner, and friends). Data were encoded using a 1 to 5 scale (with 1 signifying high level of functioning, and 5 signifying severe impairment).

To test potential effects of mood status on cognitive performance, mood severity two days prior to the CANTAB was assessed using the Mania Rating Scale (MRS)<sup>26</sup> and the Depression Rating Scale (DRS) section of the K-SADS-P<sup>27</sup>. Also, at the time that the CANTAB was administered, general intelligence (IQ) was evaluated using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scales of Intelligence (WASI)<sup>28</sup>.

**Cognitive Testing**—The CANTAB contains a suite of the world's most validated and sensitive computerized neuropsychological tests of cognition including: memory, executive function, attention, decision making, and social cognition. Since the COBY study did not include a HC group, we only included those cognitive tasks for which CANTAB provided a z-score based on normative data from the CANTAB. The following CANTAB subtests were used:

**Intra/Extra-dimensional Set Shift (IDED)**: This set-shifting task mirrors the Wisconsin Card Sorting Task (WCST). Stimuli are presented in pairs during 9 stages, each of which

requires the participant to successfully complete 6 trials in a maximum of 50 attempts, or else the test is discontinued. Participants use feedback during trial-and error learning to determine which of two stimuli shapes is rewarded—e.g., purple square rather than purple circle. Stage 2 reverses the stimulus/reward association—e.g., purple circle rather than purple square. White line designs are added as distracters during stage 3–9. However, during stages 3–7, reinforcement depends only on shape, with line design being irrelevant. Stage 6 is known as the “intra-dimensional shift” because new line/shapes replace the old, but choice of the correct shape continues to determine reinforcement. Stage 8 is the “extra-dimensional” shift because it is the first stage when the previously irrelevant construct—e.g., white line design—is rewarded. Outcome data include stages completed, errors, and trials for each stage, for all trials before the ED shift (e.g., stages 1–7 “pre-ED shift”), and those at and after the ED shift. Outcome measures are related to executive functions such as abstract reasoning and categorization (e.g., completed stage trials), and cognitive flexibility/reversal learning (e.g., ED-shift errors).

**Pattern Recognition Memory (PRM):** Participants first view 12 shapes one at a time, and then, pairs of shapes are presented, one novel and one previously presented. Participants must identify the previously presented, rather than novel, shape within the pair. Outcome data include number and percentage correct and mean latency to correct responses. It assesses visual pattern recognition memory.

**Spatial Memory Span (SSP):** This test of working memory is modeled after the Corsi Block Test<sup>29</sup>. Participants watch squares on the screen change colors one at a time from white to a different color. Participants then touch the squares on the screen in the same sequence in which they changed colors. The number of blocks increases from 2 to 9 across trials. Outcome data include length of memory span, total errors (e.g., number of times the participant selected an incorrect box), and total usage errors (i.e., number of times the participant selected a box not in the sequence being recalled).

**Rapid Visual Information Processing (RVP):** A white box appears in the center of the computer screen, inside of which digits from 2 to 9 appear in pseudo-random order at the rate of 100 digits per minute. Participants are asked to press a button whenever they detect a specified target sequence—e.g., “press the button when you see 2–4–6”). Outcome data include  $A'$  [signal detection theory measure of sensitivity to errors, regardless of error tendency—e.g., how good the participant is at detecting target sequence (range 0.00–1.00)],  $B'$  [signal detection measure of strength of trace required to elicit a response—i.e., tendency to respond regardless of whether target sequence is present or not (range –1.00 to 1.00)], and probability (e.g., change of making specific response) of hits, misses, false alarms, and rejections. This subtest is an analogue of the Continuous Performance Test (CPT) and measures sustained attention<sup>30</sup>.

## Procedure

Each university’s Institutional Review Board approved the study, and assent and consent were obtained from youth and parents, respectively. All assessments were completed by research staff trained to reliably administer the above noted interviews, and presented to

child psychiatrists/psychologists who confirmed the diagnoses and the longitudinal mood ratings<sup>16</sup>.

## Statistics

First, raw scores on the cognitive outcome measures at each time point were compared with the CANTAB normative data to calculate z-scores. As referred to by other CANTAB reports<sup>31</sup>, outliers beyond  $\pm 3.0$  z-scores were curtailed to values of +3.0 or -3.0. The number of outliers for any cognitive measurement did not exceed 6% at any time. Similar to Pavuluri and colleagues<sup>6</sup>, standardized domain scores were then calculated for executive functions, sustained attention, working memory, and visual memory by combining z-scores within each of the four CANTAB subtests. Internal consistencies (Chronbach  $\alpha$ ) of scores comprising each cognitive domain were always greater than 0.87. As reported by other studies<sup>7, 32–34</sup> a general cognitive index was calculated by averaging the four cognitive domain scores for each subject per time point.

Second, using LCGA youth were clustered into several classes based on the trajectory of their general cognitive index from T1 to T3. Using the SAS Trajectory procedure (TRAJ)<sup>35</sup>, the number of classes was determined by selecting the model with a minimum value of Bayesian information criterion, a minimum of 20 participants per class, and clinical interpretability of the classes obtained. Scores in MRS/DRS and IQ were not included as covariates in the LCGA because preliminary analyses using linear mixed models did not indicate significant differences between time points in these variables ( $p > 0.05$ ).

Third, univariate analyses using analyses of (co)variance and chi square tests were performed to compare the clinical variables between LCGA classes. Variables at T1 were: demographics, age at onset of BP, duration of mood illness, history of sexual/physical abuse, first/second degree family history of depression/(hypo)mania. Longitudinal variables were: BP subtype at the last assessment, exposure to each medication class during the follow-up (present or absent), psychiatric comorbidities at T1 and during the follow-up (present or absent), number/duration of hospitalizations at T1 and during the follow-up, percentage of follow-up time with sub/syndromal mood symptomatology in general and for each polarity specifically, and global/academic/social functioning during the follow-up (average scores). Medications were grouped by class (antipsychotics, antidepressants, lithium and anticonvulsants, benzodiazepines, stimulants, and atomoxetine). To avoid type I error, multiple-univariate analyses were adjusted using the false discovery rate (FDR) as described by the Benjamini–Hochberg procedure<sup>36,37</sup>. Post-hoc pairwise comparisons were adjusted using the Bonferroni correction.  $P$ -values were based on 2-tailed tests with  $\alpha=0.05$ .

## Results

### Latent Class Growth Analysis

LCGA identified three longitudinal patterns of cognitive functioning based on the general cognitive index: class 1, “persistently high” (N=21; 15.6%); class 2, “persistently moderate” (N=82; 60.74%); and class 3, “persistently low” (N=32; 23.7%). Within these classes, z-scores on the general cognitive index across time points ranged from -0.45/-0.59, 0.10/0.17,

and 0.57/0.69, respectively. As illustrated in Figure 1, youth in the three classes showed stable cognitive functioning across time points. There were no between-class differences in the duration of follow-up, number of cognitive assessments, and time elapsed between cognitive assessments ( $p > 0.05$ ). Analyses of all CANTAB subtests (IDED, PRM, SSP, and RVP) using LCGA showed the same pattern as described for the general cognitive index (persistently high vs. persistently moderate vs. persistently low). A secondary analysis including the whole sample of BP youth ( $N = 135$ ) also showed stable, normal cognitive functioning on the general cognitive index and each CANTAB subtest.

### Clinical Characteristics

As shown in Table 2, at T1 there were no significant between-class differences in demographic variables, age at onset of BP, duration of mood illness, history of sexual/physical abuse and first/second degree family history of depression/(hypo)mania ( $p > 0.05$ ).

Regarding the longitudinal data, youth in class 3 had significantly greater prevalence of ADHD than those in class 1 and 2. These differences remained significant after controlling for multiple-univariate analyses. There were no between-class differences in the exposure to any type of psychopharmacological treatment, BP subtype, and number/duration of hospitalizations ( $p > 0.05$ ).

### Percentage of Time with Syndromal and Subsyndromal Mood Symptoms

During the follow-up, youth with persistently low cognitive functioning (class 3) had significantly greater percentage of time with syndromal mood symptoms than youth in class 1 and 2 (see Table 3). Specifically, youth in class 3 had significantly greater percentage of time with manic and depressive syndromal symptoms than those in class 1 and 2. Between-class differences in overall, manic, and depressive syndromal symptoms remained significant after controlling for ADHD comorbidity ( $p > 0.05$ ). These differences remained significant after controlling for multiple-univariate analyses.

### Global, Academic, and Social Functioning

As noted in Table 4, youth with persistently low cognitive functioning (class 3) had significantly poorer global, academic, and social functioning than youth in class 1 during the follow-up period. Specifically, they showed more impaired relationships with friends than those in class 1. Between-class differences in these variables remained significant after controlling for ADHD, and the percentage of time with overall, manic, and depressive syndromal mood symptoms ( $p > 0.05$ ). These differences remained significant after controlling for multiple-univariate analyses.

### Discussion

To the best of our knowledge, this is the first study aimed at delineating distinctive cognitive trajectories in BP youth and their associated clinical variables. Our main findings were: 1) Three overall cognitive trajectories were identified in BP youth: persistently high, moderate, and low cognitive functioning; 2) In comparison with the CANTAB normative data, all classes had z-scores which are considered above the cutoff levels ( $z < -1.00/-1.5$ ) for



cognitive impairment<sup>38</sup>. However, BP youth in class 3 had relatively low general cognitive functioning; and 3) After controlling for multiple comparisons and confounders, youth with persistently low cognitive functioning had greater prevalence of ADHD comorbidity and greater percentage of time with total, manic, and depressive syndromal symptoms than youth in the other two classes. Also, they showed poorer global, academic, and social functioning than youth with persistently high cognitive functioning.

We found that the three classes showed stable course of cognitive functioning over time. This finding is in accordance with longitudinal studies including large samples of euthymic and non-euthymic adults with BP<sup>3,39</sup> and two longitudinal cognitive studies in BP youth<sup>7,8</sup>. In contrast, another longitudinal study among BP youth showed improvement in working memory over 2.5 years<sup>9</sup>. However, this latter study included a small sample (N=20) and, with the exception for the effects of lithium at intake, it did not control for the effects of pharmacological treatment during the follow-up. Overall, our and the above studies suggest that BP youth do not experience a cognitive worsening over time, and preliminarily, do not support the “hypothesis of neuroprogression”<sup>39</sup>. Notwithstanding, further longitudinal studies with larger samples and longer duration of follow-up are warranted to ensure the lack of cognitive decline in BP.

The current study also showed that the three classes had normal cognitive functioning on the general cognitive index and on each of the specific cognitive domains. These results are in contrast to cross-sectional and longitudinal studies in BP youth. These studies showed cognitive impairments in verbal/visual-spatial memory, processing speed, working memory, or social cognition, even as ascertained by the CANTAB<sup>1</sup>. Specifically, one longitudinal study in BP youth, which also used similar average cognitive scores as the one used in this study, found stable impairments in all cognitive domains over time<sup>7</sup>. It is possible that divergences between the results of these studies and the current research may be explained by the fact that we used a normal group derived from the CANTAB normative data rather than a HC group. Also, prior longitudinal studies in BP youth included small sample sizes and they did not adjust for the presence of confounders (e.g., treatment other than stimulants, comorbid disorders other than ADHD)<sup>7-9</sup>.

Our study also showed that the presence of ADHD comorbidity was associated with poorer overall cognitive functioning over time. This result is in contrast with those findings from other longitudinal<sup>8,9</sup> and cross-sectional studies in BP youth<sup>1</sup>, which reported no effects of ADHD comorbidity on those cognitive domains included in our general cognitive index (e.g., sustained attention, working memory, executive functions). Differences with prior studies may be accounted for by the fact that we used a large sample size of youth fully covering the bipolar spectrum disorders.

We also found that poorer overall cognitive functioning was associated with poorer global, social, and academic adjustment over time. Our finding is similar to other cross-sectional studies in BP youth<sup>4,40</sup>, but in contrast with one longitudinal study which showed that poorer executive functions were not associated with math difficulties in BP-I youth<sup>6</sup>. However, unlike our study, this longitudinal research measured math difficulties as a categorical variable (yes/no) reported by parents. Other longitudinal studies among adults

with BP are in line with the association between cognition (mainly executive functions) and functioning. Tabares-Seisdedos and colleagues found that a worsening of executive functions in 43 BP-I adults predicted poorer global functioning over one-year follow-up<sup>41</sup>. Similarly, Bonnin and colleagues showed that a decrease in executive functions among 32 adults with BP-I and BP-II predicted greater functional maladjustment over four-year follow-up<sup>42</sup>. The central role of executive functions on functional outcomes is supported by the fact that these cognitive domains refer to the capacity to think or change an idea before acting, increasing the ability to deal with new learning, situations, and people. Because of this potential link between cognition and functioning, the use of cognitive remediation therapy may be indicated for BP youth<sup>6</sup>.

Consistent with another longitudinal study<sup>44</sup>, we found an association between poorer cognitive functioning and poorer mood course. Also, cross-sectional studies reported that worse cognitive functioning among BP patients with greater number of mood episodes, particularly manic<sup>44,45</sup> had worse cognitive functioning. The pernicious relationship between cognitive function and BP illness may be explained by the fact that both clinical variables may imply similar brain regions, particularly in the prefrontal and anterior cingulate cortex and the subgenual region<sup>46</sup>. Hence, improving cognitive impairments could be an indirect strategy to ameliorate the mood course among BP youth.

### Limitations

The results of this study need to be taken in the context of the following limitations. First, although we evaluated several key cognitive domains (e.g., sustained attention, and executive functions), other cognitive domains such as social cognition and verbal memory were not assessed<sup>47</sup>. Second, the generalizability of the observations to other populations remains uncertain because most participants were Caucasian, and they were recruited primarily from outpatient settings<sup>48</sup>. Nevertheless, course and morbidity in non-clinically referred adolescents with BP have shown similar results to those found in referred populations<sup>49</sup>. Finally, the average follow-up between CANTAB administrations was only 2.5 years and 53/135 participants at T2 have not yet complete the CANTAB assessment at T3.

### Conclusions

BP youth showed normal overall cognitive functioning, which in each class remained stable during the follow-up. However, about 24% of BP youth showed relatively poorer cognitive functioning than the other BP youth. This subgroup of BP youth had poorer mood course and functioning, and may benefit from cognitive remediation and early management with evidence-based pharmacological treatments.

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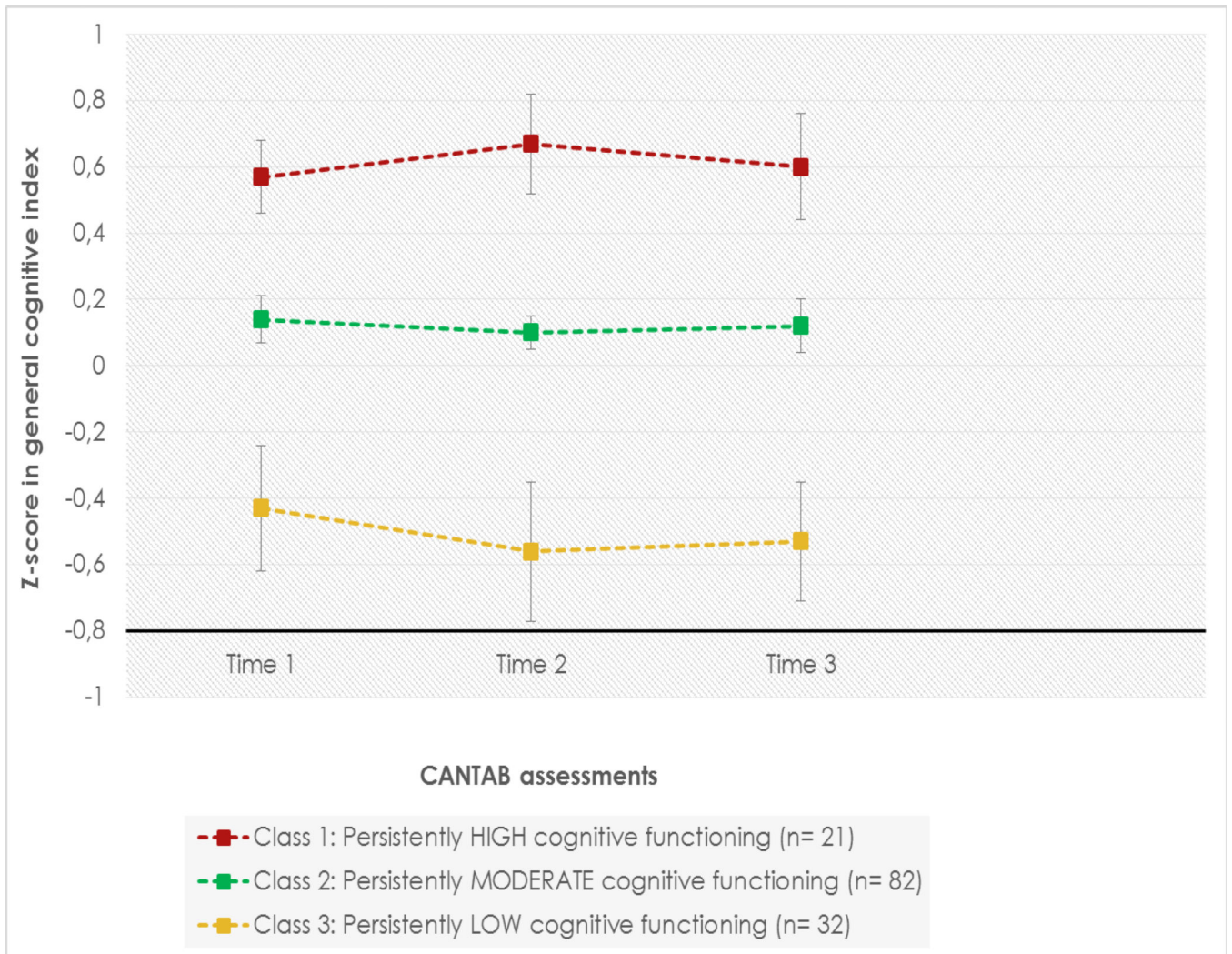
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**Figure 1.** Latent class growth analysis based on z-scores in the general cognitive index at three time points for youth with bipolar disorder. CANTAB, Cambridge Neuropsychological Test Automated Battery

**Table 1**

Demographic and clinical characteristics at CANTAB T1 assessment in youth with bipolar disorder (N= 135).

	<b>N (%)</b>	<b>M (SD)</b>
<b>Age</b>		16.18 (3.28)
<b>Sex (male)</b>	79 (58.5)	
<b>Race (white)</b>	110 (81.5)	
<b>SES</b>		3.27 (1.31)
<b>IQ</b>		104.84 (15.05)
<b>BP subtype</b>		
<b>BP-I</b>	77 (57.03)	
<b>BP-II</b>	16 (11.85)	
<b>BP-NOS</b>	42 (31.11)	
<b>Age at onset of BP (years)</b>		8.3 (3.55)
<b>Duration of mood illness (years)</b>		7.88 (2.76)
<b>First degree family history of depression</b>	92 (68.8)	
<b>First degree family history of (hypo)mania</b>	45 (33.4)	
<b>Second degree family history of depression</b>	88 (65.7)	
<b>Second degree family history of (hypo)mania</b>	45 (33.9)	
<b>Comorbid psychiatric disorders</b>		
<b>PTSD</b>	7 (5.18)	
<b>OCD</b>	16 (11.85)	
<b>ADHD</b>	84 (62.2)	
<b>SUD</b>	9 (6.66)	

ADHD, attention deficit hyperactivity disorder; BP, bipolar disorder; BP-NOS, bipolar disorder not otherwise specified; CANTAB, Cambridge Neuropsychological Test Automated Battery; IQ, Intelligence Quotient; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SES, socioeconomic status; SUD, substance use disorder

Table 2

Clinical characteristics in latent classes of youth with bipolar disorder.

Variables	Class 1- Persistently high cognitive functioning (N = 21)	Class 2- Persistently moderate cognitive functioning (N = 82)	Class 3- Persistently low cognitive functioning (N = 32)	df	Statistics	p values	Effect size (partial $\eta^2/V$ )
	M (SD) / %	M (SD) / %	M (SD) / %				
<b>Clinical data at T1</b>							
Age	16.95 (2.88)	16.61 (1.95)	15.78 (3.63)	2, 132	F= 1.53	0.49	0.05
Sex (male)	76.21	57.14	50	2	$\chi^2= 3.70$	0.15	0.16
Race (white)	85.71	78.04	87.5	2	$\chi^2= 1.65$	0.43	0.11
SES	3.47 (0.93)	3.31 (1.05)	2.99 (1.26)	2, 132	F= 2.71	0.09	0.03
Age at onset of BP (years)	8.29 (4.16)	7.74 (3.32)	7.19 (3.64)	2, 132	F= 3.02	0.19	0.08
Duration of mood illness (years)	8.11 (1.81)	8.28 (2.64)	8.55 (3.02)	2, 132	F= 0.15	0.84	< 0.001
First degree family history of depression	65.9	67.33	70.09	2	$\chi^2= 2.64$	0.24	0.13
First degree family history of (hypo)mania	31.13	33.01	33.77	2	$\chi^2= 1.59$	0.41	0.11
First degree family history of depression	64.8	64.71	66.03	2	$\chi^2= 1.54$	0.49	0.1
First degree family history of (hypo)mania	33.76	35.21	34.65	2	$\chi^2= 1.12$	0.63	0.11
History of sexual abuse	10.9	11.7	11.5	2	$\chi^2= 1.55$	0.47	0.1
History of physical abuse	13.12	13.9	15.25	2	$\chi^2= 1.49$	0.53	0.12
<b>Longitudinal clinical data</b>							
Number of hospitalizations	3.36 (1.54)	3.43 (1.41)	3.79 (1.55)	2, 132	F= 3.15	0.14	0.05
Duration of hospitalizations (weeks)	3.88 (5.19)	3.82 (6.05)	3.99 (5.24)	2, 132	F= 1.95	0.46	0.02
<b>BP subtype</b>							
BP-I	61.90	57.31	71.87	4	$\chi^2= 5.16$	0.27	0.13
BP-II	23.80	24.39	6.25				
BP-NOS	14.30	18.30	21.88				
<b>Psychiatric comorbid disorders</b>							
ADHD	52.38 <sup>3</sup>	65.85 <sup>3</sup>	78.12 <sup>1,2</sup>	2	$\chi^2= 7.01$	0.01 <sup>a</sup>	0.24
Disruptive disorders	47.61	54.87	53.12	2	$\chi^2= 0.33$	0.75	0.05



Variables	Class 1- Persistently high cognitive functioning (N = 21)	Class 2- Persistently moderate cognitive functioning (N = 82)	Class 3- Persistently low cognitive functioning (N = 32)	df	Statistics	p values	Effect size (partial $\eta^2/V$ )
	M (SD) / %	M (SD) / %	M (SD) / %				
<b>OCD</b>	19.04	13.41	12.50	2	$\chi^2 = 0.85$	0.56	0.06
<b>PTSD</b>	9.52	10.97	12.50	2	$\chi^2 = 0.99$	0.58	0.07
<b>Any anxiety disorder</b>	52.38	59.75	71.87	2	$\chi^2 = 4.61$	0.09	0.20
<b>SUD</b>	14.28	7.31	12.50	2	$\chi^2 = 1.39$	0.14	0.12
<b>Psychotic symptoms</b>	14.28	10.97	15.62	2	$\chi^2 = 1.63$	0.26	0.13
<b>Medication exposure</b>							
<b>Antipsychotics</b>	75	63.41	65.62	2	$\chi^2 = 3.38$	0.18	0.15
<b>Antidepressants</b>	33.33	19.51	28.12	2	$\chi^2 = 2.21$	0.33	0.12
<b>Atomoxetine</b>	9.52	8.53	12.50	2	$\chi^2 = 0.41$	0.81	0.05
<b>Stimulants</b>	40	34.14	50	2	$\chi^2 = 3.24$	0.19	0.15
<b>Lithium, anticonvulsants</b>	66.66	50	46.87	2	$\chi^2 = 1.86$	0.39	0.11
<b>Benzodiazepines</b>	0	7.31	12.50	2	$\chi^2 = 2.19$	0.23	0.14

ADHD, attention deficit hyperactivity disorder; BP, bipolar disorder; BP-NOS, bipolar disorder not otherwise specified; IQ, intelligence quotient, OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SES, socioeconomic status; SUD, substance use disorder; T1/3, time point 1/3

<sup>a</sup>Significant *p* value after controlling for multiple-univariate analyses (Benjamini–Hochberg FDR)

<sup>1</sup>Significant difference with class 1 after post-hoc Bonferroni correction

<sup>2</sup>Significant difference with class 2 after post-hoc Bonferroni correction

<sup>3</sup>Significant difference with class 3 after post-hoc Bonferroni correction

Table 3

Longitudinal data on the percentage of time with mood symptoms in latent classes of youth with bipolar disorder.

Variables	Class 1- Persistently high cognitive functioning ( <i>N</i> = 21)	Class 2- Persistently moderate cognitive functioning ( <i>N</i> = 82)	Class 3- Persistently low cognitive functioning ( <i>N</i> = 32)	df	Statistics	<i>p</i> values	Effect size (partial $\eta^2$ )
	M (SD)	M (SD)	M (SD)				
Percentage of time euthymic	51.17 (39.04)	43.26 (33.21)	32.95 (36.75)	2, 132	<i>F</i> = 1.84	0.16	0.03
Percentage of time in any syndromal mood	5.90 <sup>2</sup> (10.63)	10.51 <sup>2</sup> (16.91)	24.46 <sup>1,2</sup> (29.98)	2, 132	<i>F</i> = 7.13	<0.001 <sup>a</sup>	0.10
Mania	0.07 <sup>2</sup> (0.32)	0.48 <sup>2</sup> (2.02)	4.40 <sup>1,2</sup> (13.41)	2, 132	<i>F</i> = 4.40	0.01 <sup>a</sup>	0.06
Hypomania	0.0 (0.0)	2.79 (8.27)	4.80 (12.82)	2, 132	<i>F</i> = 1.81	0.16	0.02
Depression	4.80 <sup>2</sup> (10.02)	6.41 <sup>2</sup> (13.01)	15.02 <sup>1,2</sup> (25.47)	2, 132	<i>F</i> = 3.67	0.01 <sup>a</sup>	0.06
Mixed states	1.02 (4.20)	0.78 (3.96)	0.22 (0.93)	2, 132	<i>F</i> = 0.39	0.67	0.01
Percentage of time in any subsyndromal mood	42.93 (37.41)	46.23 (32.35)	42.59 (35.07)	2, 132	<i>F</i> = 0.19	0.82	0.01

<sup>a</sup>Significant *p* value after controlling for multiple-univariate analyses (Benjamini–Hochberg FDR)

<sup>1</sup>Significant difference with class 1 after post-hoc Bonferroni correction

<sup>2</sup>Significant difference with class 2 after post-hoc Bonferroni correction

<sup>3</sup>Significant difference with class 3 after post-hoc Bonferroni correction

Table 4

Longitudinal data on global, academic, and social functioning in latent classes of youth with bipolar disorder.

Variables	Class 1- Persistently high cognitive functioning ( <i>N</i> = 21)	Class 2- Persistently moderate cognitive functioning ( <i>N</i> = 82)	Class 3- Persistently low cognitive functioning ( <i>N</i> = 32)	df	Statistics	<i>p</i> values	Effect size (partial $\eta^2$ )
	M (SD)	M (SD)	M (SD)				
Global functioning (CGAS)	60.90 <sup>3</sup> (9.45)	59.60 (13.19)	51 <sup>1</sup> (8.02)	2, 132	<i>F</i> = 4.30	0.01 <sup>a</sup>	0.07
Academic functioning (PSF)	2.63 <sup>3</sup> (1.55)	3.08 (1.35)	3.49 <sup>1</sup> (1.43)	2, 132	<i>F</i> = 4.57	0.01 <sup>a</sup>	0.06
Global social adjustment (PSF)	3 <sup>3</sup> (0.70)	3.11 (0.79)	3.47 <sup>1</sup> (0.71)	2, 132	<i>F</i> = 4.41	0.01 <sup>a</sup>	0.06
Relationship with biological parents (PSF)	3.05 (1.35)	2.89 (1.45)	3.38 (1.49)	2, 132	<i>F</i> = 1.23	0.29	0.01
Relationship with step-parents (PSF)	3 (1.41)	3.10 (1.33)	3.50 (1.22)	2, 132	<i>F</i> = 0.23	0.79	0.01
Relationship with siblings (PSF)	3.11 (1.31)	3.21 (1.17)	3.48 (1.18)	2, 132	<i>F</i> = 0.75	0.47	0.01
Relationship with partner (PSF)	1.80 (0.83)	2.25 (1.00)	2.78 (1.09)	2, 132	<i>F</i> = 1.63	0.21	0.10
Relationship with friends (PSF)	2.27 <sup>3</sup> (1.35)	2.87 (1.11)	3.03 <sup>1</sup> (1.17)	2, 132	<i>F</i> = 4.76	0.01 <sup>a</sup>	0.07

CGAS, Children-Global Assessment Scale; PSF, Psychosocial Functioning Scale from the Longitudinal Interval Follow-Up Evaluation (LIFE)

<sup>a</sup>Significant *p* value after controlling for multiple-univariate analyses (Benjamini–Hochberg FDR)

<sup>1</sup>Significant difference with class 1 after post-hoc Bonferroni correction

<sup>2</sup>Significant difference with class 2 after post-hoc Bonferroni correction

<sup>3</sup>Significant difference with class 3 after post-hoc Bonferroni correction