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ORIGINAL ARTICLE

Performance in inhibitory control during euthymia is not related to past suicide attempts in individuals with bipolar disorder

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Abstract
Background and objectives: Individuals with bipolar disorder have an elevated risk of suicide. One hypothesis is that deficits in inhibitory control may play a significant part in suicidal behavior. However, the relationship between inhibitory control and suicide behavior in bipolar disorder is still unclear. This study aims, therefore, to investigate the effects of inhibitory control with other clinical variables on the likelihood that individuals with bipolar disorder have had previous suicide attempts.
Methods: 96 euthymic individuals with bipolar disorder were recruited and underwent a clinical interview. Inhibitory control was measured through the Stroop Color-Word Test. A logistic regression model was conducted to investigate the effects of multiple hospitalizations, age of disease diagnosis, family history of severe mental disorders, sex and inhibitory control performance, controlling for age and estimated intellectual functioning.
Results: The model revealed statistically significant main effects of multiple hospitalizations, female sex and family history of psychiatric disorders. Unexpectedly, inhibitory control performance was not a significant predictor, even after designing a new model excluding the clinical variables.
Conclusions: Current inhibitory control performance was not related to the likelihood of previous suicide attempts in individuals with BD, reinforcing the evidence of major effects of clinical

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risk factors. It may play an indirect role in suicidal behavior, however, as it may be related to greater illness severity, which, in turn, may be related to more severe episodes and increased suicidal behavior.

Introduction

Bipolar disorder (BD) is a chronic mood disorder outlined by episodes of mania, hypomania, and intertwined or alternated by episodes of depression.[1] Individuals with bipolar disorder (BD) have an increased mortality rate compared to the general population[2] and a decrease in life expectancy estimated in about 9 to 14 years.[3] One factor associated with disease mortality is death by suicide. People with BD have higher suicide deaths, with rates being as much as 14-fold higher.[4] It is predicted that 25% to 50% of individuals with BD will attempt suicide at least once in their lifetime, and 8% to 19% are likely to die by it.[5]

One hypothesis to better understand suicidal behavior could be that executive function deficits play a significant role in suicide attempts. A key element of executive functioning is inhibitory control, which is the ability to manage thoughts, behavior, emotion and attention in order to override an internal drive or external lure.[6] One aspect of inhibitory control is self-control, which may be viewed as one end of a ''tug of war'' between two potential behaviors, with the other end consisting of sudden, immediate actions.[7] Deficits in executive functioning, especially inhibitory control, are possible explanations as to why some individuals are incapable of emotional self-restraint and suppression of impetuous acts, such as a suicide attempt. A significant portion of suicide attempts has been described as impulsive.[8] Furthermore, individuals with BD have been shown to display impairments in inhibitory control.[9] Finally, while performing inhibition tasks, individuals with BD presented neural abnormalities in brain regions associated with task performance.[10] Thus, individuals with BD who attempt suicide may be unable to override the urge to end their lives, ignoring long-term results.

Individuals with major depression who attempted suicide have displayed deficits in inhibitory control.[11] Impulsivity has also been associated with attempt severity in BD.[12] Likewise, a recent study found that self-reported motor impulsivity predicts a history of suicide attempts in BD and major depression.[13] Contrastingly, individuals with BD who did not attempt suicide scored higher in self-reported scales, while low scores in individuals who did were associated with higher lethality.[14] The relationship between executive function deficit and suicide in BD had a smaller effect in some samples.[15] In another study, impulsivity and suicide attempts were related in patients with major depression, but not BD.[16] Thus, although there is some evidence on the relationship between inhibitory control and suicide attempts, its role in BD is still unclear. For this reason, further studies are needed to better understand the mechanisms of suicidal behavior in this population.

This study aims, therefore, to investigate the effects of inhibitory control performance during euthymia, in addition to other clinical variables, on the likelihood that individuals with BD had previous suicide attempts.

Methods

Participants

This was a cross-sectional study part of a larger project focusing on cognition of individuals with BD from southern Brazil. We included 96 participants with BD recruited from the Bipolar Disorders outpatient facility from Hospital de Clínicas de Porto Alegre, Brazil, between October 2015 and September 2018. Inclusion criteria were: 1) DSM-5 diagnosis of BD, 2) age of 18 years or older, and 3) euthymic state confirmed by Hamilton Depression Rating Scale (HAM-D)[17] scores <7 and Young Mania Rating Scale (YMRS)[18] scores <7. Exclusion criteria were: (1) any medical or clinical condition affecting neuropsychological performance, (2) substance abuse, and (3) eletroconvulsive therapy within the past year. Patients were receiving pharmacological treatment according to the program's protocols. Our study was conducted in accordance to the latest declaration of Helsinki. All participants signed a consent form, and the project was approved by the local ethics committee (Project 15-0298). Patient anonymity was preserved at all times.

Clinical and cognitive measures

Clinical information was collected through an interview and patient records. Subjects' functional outcome was measured through the Functioning Assessment Short Test (FAST), which evaluates general functioning,[19] which consists of 24 items evaluating 6 functioning domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time). Afterwards, patients were submitted to a cognitive evaluation. Estimated IQ was assessed through the Wechsler Abbreviated Scale of Intelligence (WASI) two-subtest form, through the vocabulary and matrix reasoning subtests.[20] Inhibitory control was assessed through the Stroop Color-Word Test–Interference score.[21] This test consists of three trials of 45 s each: a Word trial, where subjects are required to read a list of written color words (''blue'', ''pink'', and ''green''), in black ink, as fast as possible; a Color trial, where participants are asked to report the color of neutral text (''XXXXX''), colored with blue, green, or pink ink, as fast as possible; and a Color-Word trial, where subjects are presented to a list of written colors (e.g. ''blue'') colored

in a different ink (e.g. red), having to report the ink color instead of the actual word. This test requires inhibitory control, as subjects need to ignore their primary automatic drive (to read the actual word) and override it with an arbitrary task. The interference score is calculated by deducting the predicted Color-Word score, based on the previous Color and Word Scores, from the raw Color-Word score.[21] This is made in order to remove the processing speed component of the trial and isolate the inhibitory control measure.

Statistical analysis

Statistical analysis was completed in SPSS v20. We first described participants' clinical and demographic characteristics. Regarding hospitalizations, we created a dichotomic variable for multiple hospitalizations. Individuals with three or more hospitalizations were classified as having numerous hospitalizations, whereas individuals with two or fewer were placed on the other end of the category. This was made in order to identify cases with several admissions and, thus, greater illness severity. Then, we compared variables of subjects who did or did not attempt suicide through Student's t-test or Chi-squared test. Afterwards, we conducted logistic regressions to predict participants' history of suicide attempts. The first model included the variables of multiple hospitalizations, family history of psychiatric disorders, age at diagnosis, sex, and inhibitory control performance, controlling for age and estimated IQ. Finally, we designed a second model with only IC performance, controlling for age, sex, and estimated IQ. Significance was set at $p < .05$, 2-tailed.

Results

Clinical and sociodemographic characteristics and comparisons between subjects who attempted suicide and subjects who did not are presented in Table 1. Among the individuals that had history of suicide attempts, the mean number of suicide attempts was 2.10 ($\pm$1.22).

Characteristics related to the history of suicide attempts

A logistic regression was performed to ascertain the effects of multiple hospitalizations, age of diagnosis, family history of severe psychiatric disorders, sex, and inhibitory control performance, controlling for age and estimated IQ, on the likelihood that participants had previous suicide attempts. The model was statistically significant (χ^2 (7) = 27.120, $p < .001$) and explained 35.40% (Nagelkerke R^2) of the variance in suicide attempts, correctly classifying 70.50% of cases. In our model, numerous hospitalizations, the presence of a family history of severe psychiatric conditions and female gender were associated with increased likelihood of having attempted suicide. Inhibitory control performance presented no significant effects (Table 2).

However, once the effect of the clinical variables could be limiting the results related to inhibitory control performance, we performed another model excluding these main effects. A new logistic regression was then made to verify the effect of inhibitory control, controlling for age, sex, and estimated IQ, on the likelihood that participants had attempted suicide. Despite that, the logistic regression model was not significant (χ^2 (4) = 6.313, $p = .177$). Inhibitory control performance, therefore, was not a predictor of previous attempts (Fig. 1).

Discussion

In this study, we investigated the relationship between inhibitory control and history of suicide attempts in BD. Individuals who attempted suicide consisted of nearly half of our sample and displayed greater illness severity, with earlier estimated onset, increased number of hospitalizations, increased family history of psychiatric disorders, and worse functioning. Multiple hospitalizations, female gender and family history of psychiatric disorders were significant predictors in attempted suicide, whereas performance in inhibitory control was not. Inhibitory control was not associated with past suicide attempts even after designing a new model without other clinical variables. Hence, our results indicate that suicide attempts are related to clinical characteristics of the disease and not to inhibitory control performance. However, our findings bring light into the unclear role of this ability the suicidal behavior of BD, as it may be viewed as an indirect contributing factor to illness severity, which could lead to suicide attempts, thus potentially performing a secondary role in suicidal behavior.

The variable in our model with the highest effect size was multiple hospitalizations. Patients are much more likely to be hospitalized if they display suicide risk, as it is one of the standard guidelines in suicide risk management.[22] Furthermore, prior hospitalizations have been established as a significant predictor for future attempts.[23] Additionally, individuals recently discharged from psychiatric care show a subsequent risk for suicide.[24] In another study, 28% of patients hospitalized for an attempt tried it again within the next ten years, and another 4% eventually died by it.[25] It is expected, therefore, that previous hospitalizations would predict past and future suicide attempts. The second variable with the highest odds ratio was female sex. This result follows other studies which have identified female sex in BD as a risk factor.[26,27] Such results accompany the tendency described in general suicide literature, in which women attempt suicide more than men.[28] This was observed in our sample, where nearly 80% of the group with previous suicide attempts consisted of women. Finally, our last significant predictor was family history of severe psychiatric disorders. This finding is supported by other studies that have found associations between suicide attempts in BD and psychiatric family history.[29–31] Additionally, a family history of psychiatric conditions reflects a robust genetic factor and possible stressful life events for individuals, further backing its effect.

Age at diagnosis was not a significant predictor. We decided to use the age at diagnosis variable instead of age of onset, as our data regarding age of onset may not have been reliable, since it mainly relied on individuals' recollection, whereas age at diagnosis could be verified through patient records. Research has indicated long delays between age at onset and age at diagnosis of BD, suggesting a lengthy period where individuals did not receive proper treatment and could, therefore, display more adverse illness courses.[32]

Table 1 Clinical and socio-demographic characteristics of individuals with bipolar disorder.

	Individuals with bipolar disorder ($n = 96$)	Participants according to history of suicide attempt		
		Individuals who attempted suicide ($n = 47$)	Individuals who did not attempt suicide ($n = 49$)	Group comparisons
Age [mean(SD)]	48.42 (±13.50)	47.94 (±13.49)	48.88 (±13.64)	$t(94) = .340$; $p = .735^{\#}$
Sex (female) [n (%)]	66 (68.80%)	37 (78.72%)	29 (59.18%)	$\chi^2(1) = 4.263$; $p = .039^{\dagger}$
Marital status [n (%)]				$\chi^2(3) = 1.507$; $p = .681^{\dagger}$
Single	32 (33.30%)	18 (38.30%)	14 (28.57%)	
Married	42 (43.80%)	19 (40.43%)	23 (46.94%)	
Divorced	16 (16.70%)	8 (17.02%)	8 (16.33%)	
Widowed	6 (6.30%)	2 (4.25%)	4 (8.16%)	
Years of education [mean(SD)]	10.58 (±3.79)	10.32 (±3.56)	10.84 (±4.01)	$t(94) = .667$; $p = .506^{\#}$
Work status [n (%)]				$\chi^2(6) = 2.098$; $p = .910^{\dagger}$
Employed	23 (24.00%)	9 (19.15%)	14 (28.57%)	
Unemployed	19 (19.90%)	10 (21.28%)	9 (18.37%)	
Receiving government aid due to illness	47 (49.00%)	25 (53.19%)	22 (44.90%)	
Retired	7 (7.30%)	3 (6.38%)	4 (8.16%)	
Bipolar disorder type I [n (%)]	88 (91.70%)	42 (89.36%)	46 (93.88%)	$\chi^2(1) = .640$; $p = .424^{\dagger}$
Estimated age at disease onset [mean(SD)]	26.62 (±11.87)	23.18 (±10.36)	29.71 (±12.38)	$t(91) = 2.742$; $p = .007^{\#}$
Estimated illness duration [mean(SD)]	21.48 (±13.68)	24.07 (±14.00)	19.16 (±13.09)	$t(91) = -1.746$; $p = .084^{\#}$
Age at diagnosis [mean(SD)]	32.75 (±12.36)	30.73 (±11.92)	34.65 (±12.60)	$t(91) = 1.536$; $p = .128^{\#}$
Years of treatment [mean(SD)]	15.34 (±9.87)	16.58 (±9.80)	14.19 (±9.91)	$t(91) = -1.169$; $p = .245^{\#}$
Number of hospitalizations [mean(SD)]	4.20 (±4.97)	5.48 (±5.62)	2.91 (±3.88)	$t(90) = -2.547$; $p = .013^{\#}$
Multiple hospitalizations (>2) [n (%)]	47 (49.00%)	32 (69.57%)	15 (32.61%)	$\chi^2(1) = 12.571$; $p < .001^{\dagger}$
Family history of severe mental disorders [n (%)]	69 (71.90%)	39 (84.78%)	30 (61.22%)	$\chi^2(1) = 6.624$; $p = .010^{\dagger}$
Lifetime suicide attempts [n (%)]	47 (49.00%)			
Hamilton Depression Rating Scale [mean(SD)]	3.58 (±2.26)	3.81 (±2.27)	3.37 (±2.26)	$t(94) = -.954$; $p = .343^{\#}$
Young Mania Rating Scale [mean(SD)]	1.44 (±1.90)	1.49 (±1.70)	1.39 (±2.11)	$t(94) = -.260$; $p = .795^{\#}$
Functioning Assessment Short Scale [mean(SD)]	25.34 (±13.34)	29.81 (±12.60)	21.06 (±12.73)	$t(94) = -3.383$; $p = .001^{\#}$
Estimated IQ[a] *[mean(SD)]*	86.66 (±17.40)	85.08 (±18.54)	88.21 (±16.26)	$t(93) = .874$; $p = .385^{\#}$
Stroop Color Word Test–Interference [mean(SD)]	48.57 (±8.91)	47.61 (±10.20)	49.49 (±7.45)	$t(94) = 1.030$; $p = .306^{\#}$
Medications [n (%)]				
Lithium	29 (32.58%)	11 (26.83%)	18 (37.50%)	$\chi^2(1) = 1.146$; $p = .284^{\dagger}$
Anticonvulsants	63 (70.79%)	31 (75.61%)	32 (66.67%)	$\chi^2(1) = .855$; $p = .355^{\dagger}$
Atypical antipsychotics	54 (60.67%)	27 (65.85%)	27 (56.25%)	$\chi^2(1) = .855$; $p = .355^{\dagger}$
Typical antipsychotics	6 (6.74%)	3 (7.32%)	3 (6.25%)	$\chi^2(1) = .040$; $p = .841^{\dagger}$
Clozapine	10 (11.24%)	3 (7.32%)	7 (14.58%)	$\chi^2(1) = 1.171$; $p = .279^{\dagger}$
Benzodiazepines	13 (14.61%)	7 (17.07%)	6 (12.50%)	$\chi^2(1) = .371$; $p = .543^{\dagger}$
Antidepressants	22 (24.72%)	12 (29.27%)	10 (20.83%)	$\chi^2(1) = .845$; $p = .358^{\dagger}$

SD: Standard deviation; # Independent samples *t*-test. † Chi-square test.

[a] Estimated IQ: Intelligence Quotient assessed by Wechsler Abbreviated Scale of Intelligence (WASI) two-subtest form.

Table 2 Model 1 – clinical characteristics and inhibitory control performance on the likelihood that individuals with bipolar disorder had previous suicide attempts, controlling for age and intellectual performance.

	Odds ratio	95%CI Lower	95%CI Upper	*B*	S.E.	Wald	*p*
Multiple hospitalizations (>2)	5.673	1.892	17.013	1.736	.560	9.595	.002
Sex	4.831	1.483	15.736	1.575	.602	6.834	.009
Psychiatric family history	3.324	1.090	10.139	1.201	.569	4.456	.035
Age at diagnosis	.976	.921	1.035	−.024	.030	.639	.424
Stroop Color-Word Test – Interference	.962	.902	1.025	−.039	.033	1.431	.232
Age	.985	.931	1.041	−.016	.028	.298	.585
Estimated IQ	.999	.970	1.029	−.001	.015	.004	.948

IQ: Intellectual performance assessed by Wechsler Abbreviated Scale of Intelligence (WASI) two-subtest form.

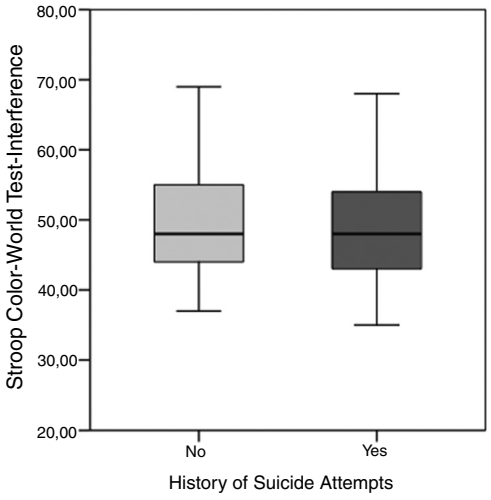

Figure 1 No difference in inhibitory control performance assessed by Stroop Color-Word Test between individuals with bipolar disorder who did and did not have history of suicide attempts.

This occurred in our sample, with results showing a mean gap of 6 years between estimated onset and diagnosis.

In our sample, nearly half of individuals with BD had attempted suicide. While it may seem like a high proportion, this is not unprecedented in the literature.[5,33] Additionally, since our sample consisted of patients from a tertiary hospital, it is possible that some of these individuals display a higher illness severity, which could contribute to a higher prevalence of suicide attempts.

The clinical characteristics from subjects who attempted suicide may be indicators of a worse illness trajectory, which is consistent with the staging model for neuroprogression in BD, which establishes a framework of progressive clinical, biological and cognitive impairments in BD.[34] Thus, individuals with BD tend to display greater impairments over time, with overall greater illness severity. In our sample, subjects who attempted suicide displayed worse functional outcomes. These clinical variables have previously been associated with illness severity in BD.[30,35,36] This suggests that these individuals may be in advanced illness stages, and reinforces the idea that suicide attempts are an important outcome that should be carefully considered in clinical interventions.

Our findings regarding inhibitory control were corroborated by some studies, albeit not all. Generally, inhibitory control performance is impaired across mood disorders.[37,38] Regarding inhibitory control and suicide behavior, studies have found a positive association.[39–41] Contrastingly, studies have also found no association.[42,43] There may be various reasons for these conflicting results. Different instruments were used across studies, from the classic Stroop test to modified versions of it and self-report scales. This may be particularly confounding, as different tests and variations may differ in what they are actively measuring. For instance, a study found no association between the Stroop Test and the Barratt Impulsiveness Scale.[44] Similarly, self-report scales may not be as reliable, as they depend on high levels of insight and metacognition.[45] It is also worth noting that the study with the largest BD sample reported negative results regarding inhibitory control and suicide attempts.[43] Additionally, some studies included individuals with major depression with those with BD or did not include BD at all. Therefore, it is challenging to draw absolute conclusions from past results.

Such contradictory findings in the literature regarding inhibitory control may explain its lack of significance in our sample and may help to establish cognition as a secondary and complex role in suicidal behavior. It may also reflect a limitation of the Stroop Test to evaluate real clinical deficits regarding suicidal behavior in BD. Moreover, we assessed subjects' inhibitory control during euthymia. Subjects' performance may have been different if measured in moments of suicidal ideation or soon after an attempt. Despite that, inhibitory control has been found to be impaired regardless of the current clinical state.[46]

That is not to say that inhibitory control should not be taken into account when planning clinical interventions, since impairments in inhibitory control are associated with several harmful outcomes, such as higher body mass index,[47] poorer eating behaviors[48] and substance abuse.[49,50] It is also a predictor of health, wealth, and safety even 30 years after measurement.[51] Poor inhibitory control, thus, may lead to increased life complications, which in turn may lead to a worse illness trajectory, which may contribute to more severe episodes and increased suicidal behavior. This, then, may set inhibitory control as an indirect factor in suicidal behavior.

We have replicated a negative-finding study which found no association between inhibitory control and suicide attempts in BD.[43] However, other negative results may have been shelved and unpublished due to publication bias.[52,53] Publication bias may enforce researchers to adjust and reshape results as positive lest their studies are rejected, which may drive the field toward inaccurate outcomes.

Negative results, thus, are essential in order to maintain scientific transparency and avoid misleading conclusions.

One significant limitation in our study is that measures were taken during euthymia, and our data of age of onset may not have been reliable. Further limitations were that this was a cross-sectional study with no healthy controls comparison. We also did not control for medication effects, although no differences in psychopharmacological treatment among groups were found.

In conclusion, we found that inhibitory control performance was unrelated to previous attempts in individuals with BD, reinforcing the evidence of significant effects of clinical risk factors. However, while it may not be directly related to suicide attempts, it may contribute to worse outcomes, which in turn may lead to greater illness severity and increased suicidal behavior. Our results help to support the concept of suicide as a remarkably complex behavior, of which mental health professionals should be constantly alert to. Future studies are, therefore, necessary so as to investigate cognitive predictors in order to better understand and prevent suicidal behavior.

Ethical consideration

Our study was conducted in accordance to the latest declaration of Helsinki. All participants signed a consent form, and the project was approved by the local ethics committee (Project 15-0298).

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Conflict of interest

The authors have no conflict of interest to declare.

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