TITLE: Assessment of cognitive functions in bipolar-I disorder: A one-year naturalistic follow-up study

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ABSTRACT: Objective: Available cross-sectional studies have demonstrated cognitive impairments in Bipolar disorder-I (BD-I) during various phases. Very little is, however, known about the longitudinal course of these cognitive impairments across different phases. The purpose of the study was to explore the longitudinal pattern of changes in cognitive functioning in BD-I patients with currently depressed, manic and euthymic. Methods: A total of 180 individuals participated at baseline (131 subjects, 49 healthy controls). Subjects were aged 18-55 years, diagnosed as BD-I (using SCID-I) with formal education ≥5years, IQ > 80 with no psychiatric/medical comorbidity. All three patients groups and control group were assessed at baseline, three, six, nine and 12 months. Clinical assessments were carried out using 17-item Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS) and Brief Psychiatric Rating Scale. All groups were assessed for cognitive functions using Verbal Adult Intelligence Scale, Digit span, Postgraduate Institute Memory Scale, Colour Trails Test- trial 2, Stroop Test and Verbal working memory N-Back Test. Results: Compared to controls, all three patient groups performed poorly on all cognitive measures at baseline and follow-ups. However, manic patients showed improvement over time in delayed recall (p=<0.001), visual recognition (p=0.004) and executive functions (CTT-2-p=0.006; Stroop interference-p=0.002). Euthymic group improved on executive functions, especially interference task (p-<0.001) and working memory (p=0.001) whereas depressed patients improved on measures of executive functions (CTT-2-p=<0.001; Stroop interference- p=0.002). Conclusion: The study adds substantial information on longitudinal course of cognitive impairments in manic, depressed and euthymic individuals, with several clinical and research implications.

Comment: Relevant manuscript focusing on the longitudinal trajectory of cognitive functioning in euthymic, depressed, and manic BD. As the authors mentioned this is indeed the first longitudinal study in a sample of adults with BD, not in early BD stages (as previously examined by Torres et al. 2014), and in different mood states. The fact that this study has been conducted in India is of relevance too since the majority of current studies is biased towards Caucasian populations. I have a few comments and suggestions that I would like the authors to implement in their manuscript. Methodology, specifically in terms of cognitive tests, needs to be more precise, statistical analyses and reporting of results need to be thorough and follow official guidelines, and the discussion should explore important topics such as the interaction between affective symptoms and cognition, potential covariates, and implications for the clinical practice.

-introduction: please discuss the interaction between affective symptoms (even at subthreshold levels) and cognitive performance. This is truly the reason why most studies focus on euthymic populations. This is also the reason why there is still so much debate on whether cognitive impairment is a core deficit or the consequence of current mood state. Please summarize findings on this research question and how did you address this in your study?

-Cognitive tasks: a)how did you select the intelligence items and why didn’t you administer the “WAIS” vocabulary test? It is considered the best estimate of premorbid intellectual functioning. b)Please provide additional information on the “Postgraduate Institute memory scale” (add PGI after mentioning the name of this scale). For clarity purposes I would also consider describing the PGI first and then talk about the digit span (e.g. was the digit verbal or spatial?). c)Add the acronym CTT after mentioning “Colour Trails Test”. Did you administer parts A, B and C? If not why not? d)What are the universal sign language symbols you referred to. Stroop: how did you calculate the interference score? Did participants have a certain amount of time to finish the Stroop task or not? Did you administer the colour, verbal and interference components? E) Overall mention that the cognitive tests were administered in Hindi and that you used a version validated in Hindi. Also mention if what kind of populations these test were validated and report relevant psychometric properties. Overall please provide as much information as you can as it will allow me, and any reader with neuropsychological training, to fully understand what the current cognitive findings mean.

-Analyses: make sure to talk about Bonferroni as a multiple comparison correction and not a type of posthoc analysis. For instance you can say you performed post-hoc tests and then say, “we adjusted for multiple comparisons using Bonferroni corrections”. Also, did you check for correlations between cognitive variables, correlations between affective symptom severity and cognitive variables and cognitive variables and age within each group? If so please report the correlation matrix in your supplementary material or text. Did you have covariates in your analyses? Age usually slows down processing speed (e.g. time-based tasks) and affective symptoms play an important role too.

-when you report your results mentiond df, F, p and partial eta square. For post-hoc results the p values don’t need to be reported but you can say p<.05 or p<.01 for instance. make sure to have all your statistical parameters in table(s) too. please refer to the APA website for some guidelines.Also Blechert et al. 2005’s tables may be used as an example “Are measures of hypomanic personality, impulsive nonconformity and rigidity predictors of bipolar symptoms? BJCP”.

-add subheaders in the results section. For instance, divide text by cognitive domain (e.g. working memory, learning and memory, executive functions, attention). This approach will make it easier for any kind of reader to read and understand your results.

-discussion: please address the following topics: medication (please add to your demographic table what kind of medication participants took), if patients received some sort of follow-up, e.g. counselling or talk therapy (even if just once a month) and if you considered using parallel versions of your tests to reduce learning effect. If you did please talk about this in your methods, if you didn’t please explain why.

-calculate the statistical power of your analyses, comment on effect sizes of your findings, and comment or conduct a discriminant analysis to check which variables would predict group membership (this is generally the best way to follow up on analyses of variance.

-tables: mention F, X2, p values, eta square, N for each analysis, and add timexgroup interaction results for table 4. Also please explain what “Matriculation” is what “lower and higher SES” refer to. It may not be the same for all countries. Also how did you define urban and suburban in Delhi (I assume).

-please add figures representing relevant interactions.

Minor details

-overall proofread and edit your manuscript, there are a few missing words, grammar mistakes, wordy, too long, and “clunky” formulations here and there. Just an example: a little effect of time, a little bit better on page 11 sound a bit colloquial; page 14 contains a few grammar errors (“more of verbal test”,“more number, as compare, atleast in 1 word etc. )

-introduction: instead of saying range of 0% to .6%, why not say that prevalence reaches up to .6%.

-no need to have the last paragraph in bold.