TITLE:

"Brain Circuitry Associated with the Development of Substance Use in Bipolar Disorder and Preliminary Evidence for Sexual Dimorphism in Adolescents" by Lippard, Elizabeth; Mazure, Carolyn; Johnston, Jennifer; Spencer, Linda; Weathers, Judah; Pittmann, Brian; Wang, Fei; Blumberg, Hilary (Manuscript # jnr-2016-Apr-6685)

AUTHORS:

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Comment: major revisions

Feedback: the authors explore the neurodevelopmental basis of the comorbidity between substance use disorders (SUDs) and mood disorders. They approach this research question by investigating the association of regional gray matter volume (GMV) with subsequent substance use problems in adolescents with bipolar disorder (BD), and examine these associations for females and males. The most compelling result of this study is that GMV was associated with future substance use; while in males, lower rostral prefrontal GMV was associated with future use. Findings indicate GMV development is associated with risk for future substance use problems in adolescents with BD, with results implicating GMV development in regions subserving emotional regulation in females and regions subserving executive processes and attention in males.

I commend the authors for exploring the neurodevelopmental changes associated with A/SUD comorbidity to BD as it is indeed a novel topic. Further focusing on adolescence and gender is interesting as they are known risks for developing specific affective, behavioral, addiction disorders. The design has, however, a few limitations that limit the generalizability of these findings. Further, more thought could be given to potential reasons for observing differences in GMV between females/males and whether cognitive processes related to hot cognition (emotional regulation) vs cold cognition (attention) may develop at a different speed between males and females. I appreciate the contribution of this study to psychiatry and would support the publication of this manuscript pending major revisions.

1. I would explore a bit further the reasons for studying tobacco as one of the substance use disorders observed in youth with BD. What is the prevalence of tobacco use among BD compared to other psychiatric populations or even healthy controls? Do the authors expect to changes in brain volume related to alteration in the glutamatergic system? Or could the authors report other potential clinical/functional changes that may derive from tobacco use.
2. Could the authors report difference sin GMV between males and females regardless of substance use (before and after the follow-up period). Wouldn’t this provide a measure of neurodevelopment?
3. The authors report the lack of comparison group as a limitation in the discussion. I am, however, curious to know the reason for not including a comparison group in the first place. Could they place clarify?
4. Could the authors report which differences in development one could expect between the ages of approx. 17 and 23 in males and females?
5. How does sexual development affect 1. Brain development, 2. Age of higher risk for SUD development; in males and females?
6. Were participants contacted/ followed-up over the 6-year period between the 2 scans? I am surprised that no other questionnaires were administered such as clinical scales, stress event, trauma questionnaires etc. could you please clarify?
7. How did the authors check for medication adherence over time? And how participants dropped out or discontinued the study?
8. How were participants recruited?
9. Did author exclude participants with neurological disorders?
10. Could the authors add a table summarizing information on clinical measures such as onset of BD, number of mood episodes, age of first medication, age of substance use diagnosis, CDRS, YMRS (if available), BD subtypes, BIS, education years, IQ
11. Could authors explain the selection of the CRAFFT cut-off score?
12. A figure (histogram? boxblot) would be extremely useful to better understand the most relevant clinical and neuroimaging results
13. Did the authors calculate correlations or regression analyses to check relationships between clinical and GMV measures?
14. Previous studies suggest that in healthy individuals, right posterior insula plays an important role in awareness and self-attribution of mental phenomena, contributing to the emergence of a sense of self (Craig, 2002; Farrer et al., 2003). Did the authors give some thought to potential gender differences in the role of insight in substance use?
15. Since the regions listed by the authors do refer to rather “hot cognition” in females and “cold cognition” in males would they have explanations for this? do they think that that is dependent on differences in neuro/cognitive development? Please address this in the discussion.
16. In table 1 Please provide a list of the substances used by participants after the 6-year follow-up period

Minor points

-please provide a reference for CRAFFT and explain that is stands for the key components in the questions: Car, Relax, Alone, Forget, Friends, Trouble