**Ref:** JAD\_2015\_1093

**Title:** Alterations in resting-state brain regional homogeneity in patients with major depressive disorder screening positive on the hypomania checklist 32 (HCL-32): an fMRI Study

This study compared the brain activity of patients with MDD screening positive on the 32-item hypomania checklist (HCL-32) using rs-fMRI. The authors tested 19 MDD patients screening positive on HCL-32 and 18 MDD patients screening negative, together with 24 age- and gender-matched healthy controls (HCs). They compared ReHo maps between the MDD with HCs, and between these two subgroups of patients with MDD. Compared to HCs, patients with MDD showed resting-state brain functional abnormalities in many brain areas, especially in frontal cortex and parietal cortex. Compared to HCL-32(-) patients, HCL-32(+) patients showed significant increase of ReHo in right medial superior frontal cortex (MSFC), left inferior parietal cortex (IPC) and middle/inferior temporal cortex (MTC/ITC), and decrease of ReHo in left postcentral cortex and cerebellum. Further ROC suggested that the features of ReHo in these regions might be used to distinguish between the two subgroups of MDD patients. Conclusions: rs-fMRI measurement of ReHo in the right MSFC, left IPC, left MTC/ITC, left postcentral cortex and cerebellum may be putative biomarkers which differentiate bipolar depression from unipolar depressive disorder.

Overall assessment: I commend the authors for using both an alternative approach based on resting state network to differentiate MDD from bipolar depression and separating MDDs based on their HCL-32 scores as hypomania can lead to misdiagnosis between bipolar depression and MDD. This is new topic that deserves to be addressed and investigated further. I think that the authors need to provide a more in-depth interpretation and critical appraisal of their findings. I also suggested some changes at the structural level. I am sure that these changes will increase the quality and impact factor of this paper.

Comments:

1. Abstract: please add descriptives such as age and gender.
2. Introduction: why is resting state activity interesting or more interesting than task related activity for instance? I noticed that the authors mentioned ALFF at the end of their manuscript. I would suggest that the authors briefly present different methodological approaches in the introduction and explain why they selected/preferred ReHo (and not ALFF for instance, as it is mentioned in the discussion).
3. Add a sentence explaining why it is important to study ReHo (Yao et al. 2009 provides some insight into the significance of ReHo in psychiatry for instance)
4. Methods: Add a reference to ROC in the methods and explain its significance (e.g. e.g. used to study sensitivity and specificity of the ReHo technique to separate clinical groups in this case (e.g. Gao et al. 2014, in BMC Psychiatry describe this well).
5. Age range is vast. How do the authors cope with this, are there usually age-related difference in state brain activity? Please refer to a longitudinal study or cross-sectional study.
6. Would ECT change state related brain activity? By the way ECT stands for “electroconvulsive therapy” not “electronic convulsive therapy” (correct this please)
7. Add reference for the “non-patient version” of the SCID (page 6)
8. Page 7. Please rephrase “all the subjects underwent structure and functional MRI scanning within one week after assessment”. Do the authors mean the neuroimaging investigation was conducted on average within a week from the clinical assessment?
9. Page 9. When talking about ROC the authors should explain the advantages of looking at this measure. They could refer to Liu et al. 2013 if helpful.
10. Please provide comorbidities, number of mood episodes, age of onset and illness duration, types of medication for the participants etc. They could add all this to table 1 if preferred. They could compare HCL-32+ and HCL-32- on these.
11. Page 11. In 3.3. please clarify that the 5 ROIs were the MSFC, IPC, MTC/ITC, prefrontal cortex and cerebellum (if I understand correctly). It is a bit confusing if sentence was left as is.
12. Please provide a description of the HCL 32 (psychometric properties in Chinese, brief description of how/when it was administered)
13. Results: have the authors thought about looking at correlations between clinical status (symptom severity, illness duration etc.) and ReHo. Can they address this here?
14. Page13. Please clarify what “action” refers to. Processing speed? Motor speed?
15. Discussion: Overall please restructure the discussion to better integrate the ReHo findings with 1. Current knowledge of structural and functional abnormalities in MDD, 2. the clinical status of the MDD participants included in this sample (e.g.e.g. how do abnormalities in ReHo could relate to individuals’ HCL scores); do ReHo correlate with cognitive status in general? 4. What could be expected to be seen in BD participants.
16. Please highlight clinical relevance of current findings and future directions (methodologically, clinically etc.)
17. When referring to Fitzgerald et al. 2008 please explain how exactly the cerebellum contributes to depression. The sentence here is vague.
18. Please provide references for the link between cerebellum and muscle tension. I am not sure if discussing the latter is relevant to the current study – could the authors highlight why they talk about this.
19. Page 14. I would have discussed ROC in the first section of the conclusions (not at the end). I would have also highlighted that the RoC confirms t-tests showing differences between the two groups and it is strong evidence that state brain related differences separate the two groups.
20. Overall English is poor and detracts the reader from fully appreciating the importance of the data and the relevance of the manuscript. Thus, the manuscript needs thorough proofreading. I know the authors addressed this in a previous revision but this is not sufficient. Please ask a native speaker or professional help to reformulate/edit the paper. I listed some of these here for your convenience.
    1. “many researches about psychiatric disorders using ReHO method were carried”. Sentence needs to be rewritten.
    2. “did not have this phenomenon” page 13
    3. Overall the abstract limitations section needs to be proofread
    4. Page 12. Please correct “may plays”

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