**Association of thalamic hyperactivity with treatment resistant depression and poor response in early treatment for major depression. A resting state fMRI study.**

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**Comment: Accept pending revisions**

By applying fractional ALFF the authors aimed to identify potential alterations in spontaneous neuronal activity associated with TRD. The authors also performed correlational analyses between HRSD scores and fALFF values in brain regions with differing activity for patients with and without TRD. The results suggest that increased right thalamic fALFF values are characteristic of TRD patients. The percent change in the HRSD was negatively correlated with fALFF values in non-TRD patients. TRD patients also show increased fALFF values in the IFG, IPL, and vermis compared to non-TRD and HC.

These findings provide novel and important insights into the neural mechanisms underlying treatment response in TRD patients. Pending a few revisions this study deserves to be published as it will assist the development of future research focusing on the understanding of the neural basis of progression of subclinical depressive symptoms, prevention and treatment strategies in severe cases of depression

**My comments**

-The authors should consider mentioning in the title that this is a resting state fmri study using fALFF or investigating the amplitude of low frequency oscillations. This would add significance and appeal to the manuscript.

-I would encourage the authors to highlight the reliability and clinical relevance of both resting fMRI and f/ALFF. Examples of ways to expand the introduction/conclusion would be to mention that:

1. Resting fMRI has been shown to be related to cognitive performance. How could this relate to mood regulation/ reactivity for instance?

2. In rsfMRI the brain regions are compared to each other to determine if there are synchronized changes of activation over time. Because of their common behavior, these regions are believed to be functionally connected but do not need to be structurally connected.

3. Connect the current findings to the concept of default mode network as this network of brain regions becomes active when participants are at wakeful rest and disengage otherwise.

-A number of methods have been developed for analyzing rs-fMRI data. Independent component analysis (ICA) and region of interest (ROI)-based FC are the two most common approaches used in rs-fMRI studies. How does the methodology used in this study compare to previous resting fMRI studies in the mood spectrum disorders.

-Previous studies mention that the increased specificity to the gray matter signal for f/ALFF compared to ALFF may suggest favoring the former, but doing so would reduce test-retest reliability. Thus reporting both measures is recommended. Could the authors explain why they did not report ALFF?

-could the authors describe the entire imaging protocol, i.e. what kind of sequences, duration of the scanning session.

-Did the authors consider correlating fALFF to the MSM score (severity of treatment resistance in the TRD group) to determine if there was a linear/non-linear connection between the two measures.

-page 10: “DPARSF”: please explain this acronym and provide reference.

-In the discussion the authors should highlight the importance of the reported altered brain circuits in terms of cognitive and emotional function.

-The clinical relevance of these findings in terms of preventive intervention and personalized treatments should be discussed.

-Future research directions in terms of diagnosis, prevention treatments could be discussed too.

-Minor comment: I noticed a few typos and grammar mistakes. Please proofread before resubmission.