Reviewer's report

Title: Multimodal functional and structural neuroimaging in major depressive disorder before and after treatment with duloxetine

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Reviewer: Katherine L Narr

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Summary: This study from an established group addresses an important topic, i.e., whether a 12-week trial of duloxetine (an SNRI) in patients with major depression correlates with neuroplastic processes related to treatment and clinical outcome. Though not compared directly, investigators also sought to address whether such effects were compatible with effects observed for more widely studied SRI treatments in major depression. Duloxetine effects on brain structure and function were examined using a multimodal imaging battery including two fMRI activation tasks (emotional faces and emotional Stroop) previously shown to elicit changes in BOLD-response in association with the processing of emotion; resting-state fMRI to address changes in intrinsic, spontaneous neural activity and structural MRI to examine changes in morphology. The sample included 30 untreated patients in an acute depressive episode at baseline, who were subsequently assessed at 1-week, 8-weeks and 12-weeks while receiving duloxetine (slightly fewer subjects were included for analysis of each imaging modality due to early termination or random loss of data). A passive, demographically similar control group (n=25) was assessed at the same time points — considered a strength of the study since change across time could also be assessed unrelated to any manipulation.

Though there was no group by time interactions for comparisons of resting state networks, results showed significant changes in functional connectivity in the anterior default mode network (DMN) with treatment and no change in controls. Within patients, decreased connectivity was observed between the DMN and prefrontal areas (dorsolateral, premotor and inferior frontal) while correlated activity between the DMN and primary and secondary auditory and visual cortex was decreased. Healthy controls showed increased connectivity with time between the DMN and posterior cingulate, fusiform and superior medial frontal gyrus, premotor cortex and parietal lobule. For the emotional Stroop task, an initial increase in posterior cingulate activation was shown to “normalize” with treatment. That is, a decrease of activity in parahippocampal, precuneus and posterior ACC during the processing of negative relative to neural words and a complementary baseline effect of group in the precuneus and posterior ACC were observed. However, contrary to expectations, no change across diagnostic group or group by time interaction was observed for amygdala activation for the emotional faces task. However, in follow-up analysis (of intensity of expressions?), a significant change in activation was observed for the cingulate/precuneus. No differences were observed across group or time for
structural measures of the anterior cingulate, amygdala or hippocampus. Examining relationships with clinical outcome, reduced baseline activity in the orbitofrontal cortex was shown to predict response.

Though this is an interesting study and the methodological approach appears generally sound, there some required clarifications and several ways the authors could improve the readability (and potential impact) of this longitudinal investigation.

Minor Essential Revisions:

1. The results in the abstract do not capture the extent of the analyses performed or the main findings. The conclusion statement that “multimodal functional and structural neuroimaging correlates demonstrated complementary effects of treatment” is inaccurate since no changes in structure were observed. The statement that the specificity of SNRI effects requires further investigation may be true, but interpretation of the current results are considered more important.

2. Though the background is to the point, the methods section is not well organized. It would be most informative to include a figure showing the workflows and dependent measures for each imaging modality, also including the statistical models used for each (in addition to the current Supplementary Figure 1, which shows the study design for treatment and acquisition). Sub-headings for the methods associated with each modality would also help.

3. Freesurfer automatic volumetric segmentation was used to extract volumes of the hippocampus, amygdala and anterior cingulate. The authors do not mention whether these segmentations were individually checked and corrected. It would be relevant to include intraclass correlations for repeated measurements obtained from the control participants as these were not expected to change over time and would provide a good indicator of the reliability for automatic segmentation.

4. The autoregressive model with reference to the activation studies should be at least mentioned in the main text of the article, as this is the key part of this analysis.

5. The paper by Sexton et al., has nothing to do with ICA so the citation on page 9, line 182, is incorrect.

6. At least for me, it is not clear how each time point within subject was used to generate the subject-specific contrast maps. If all time points were included, what is the justification that within-subject effects would be linear? This section (starting at line 191, page 10) is difficult to parse.

7. By contrast, in the following paragraph on page 10, it is stated that the primary outcome for the emotional faces task was difference in signal change between baseline and week 12 for the left and right amygdala. Is this also the case for the resting state analysis? It would be helpful if the authors could make clear which time points were compared for each modality.
8. The MRI measures used to assess relationships with mood scores should be listed explicitly. Were these relationships tested for each of the clinical scales separately? These measures are no doubt correlated, but what of correction procedures for these multiple analyses (currently not clear how many were performed).

9. For the structural analyses, was brain volume included as a covariate?

10. The discussion might also benefit from the inclusion of sub-headings and better organization and the inclusion of a cumulative interpretation.

11. There are some typographical errors in the reporting of imaging parameters (missing decimal places) in the Supplementary materials. Also the headings of the Supplementary tables could be more specific so as not to have to flip back and forth from the main article to understand which effects are being reported.

In sum, though this study is viewed as a potentially important contribution, the methods and results presentation detract from the impact. This should be readily addressable on revision.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.