Author's response to reviews

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

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Author's response to reviews: see over
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Professor Andrew Leuchter  
Associate Editor  
Mood Disorders

Dr. Alice Murray  
Executive Editor  
BMC Psychiatry

Dear Professor Leuchter:

Thank you for the thoughtful reviews of our manuscript “Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine”.

We have addressed each of the Reviewers’ comments and have made substantial revisions to the manuscript. We hope that the revised manuscript is acceptable for publication in BMC Psychiatry.

Sincerely yours,

Cynthia H. Y. Fu
Reply to Reviewers

Manuscript: “Multimodal functional and structural neuroimaging in major depressive disorder before and after treatment with duloxetine”

Reviewer: Professor Thomas Frodl

Reviewer’s report:
This is a very interesting paper by a highly respected group in the field. The sample of 32 currently not yet treated patients with MDD is large for such a study and the longitudinal control arm (healthy controls) is novel. Interestingly, the default mode network connectivity increased while increased posterior cingulate cortex activity during the emotional stroop task decreased. OFC connectivity predicted response to therapy. The paper has several strengths, in particular the sample size and longitudinal design and adds to the current knowledge about depression and response.

I have some minor suggestions:
There is a missing literature link to an earlier publication of this kind on venlafaxine and mirtazapine treatment using fMRI in untreated patients with depression (Frodl et al. 2011, J Clinical Psychiatry, also Lisiecka et al. 2011/2012, J Psych Res), which further would add to the hypothesis of the current study and also found changes during therapy and predicted therapy response. The current study did follow-up patients for 12 weeks, whereas the previous studies only had a treatment duration of 4 weeks until a second scan was carried out.

We thank Professor Frodl for these suggestions and we have added the references to the manuscript in the Introduction (p 7) and in the Discussion (p 23).

Information on the previous course of depression should be included, e.g. number of previous episodes, previous response to therapy and it should also be indicated if these variables differed between responders and nonresponders to duloxetine.

We have added this information to the Results section (p 16, par 2).

The facial emotional task and the stroop task should be briefly described in the main text of methods as well, since it is not that easy often to access the online material of journals.

We thank Professor Frodl for this suggestion and we have added descriptions of the tasks in the Methods section (pp 9-11).

Please describe the difficulties in data acquisition that leaded to drop outs.

We have added the reasons for the drop outs in the Methods section (p 13, par 1).

The fact that there were no significant time by group interactions in resting state and face task limits the results and this should be discussed as limitation as well. Interesting is that there was a significant group by time interactions in stroop task fMRI.

We agree with Professor Frodl and have included this in the Discussion section as a limitation, and we have expanded our discussion of the group by time interactions in the Stroop task in the Discussion section (pp 21-24).
Reviewer: Professor Katherine L Narr

Reviewer’s report:
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.

We thank Professor Narr for her comments. We have made substantial revisions and clarifications to the manuscript in order to address each of the comments.

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.
We thank Professor Narr for this suggestion and we have modified the Abstract (pp 4-5).

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.

We thank Professor Narr for highlighting this, and we have made substantial revisions to the Methods section in order to clarify the analysis and have added sub-headings, which we hope are acceptable (pp 11-16).

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.

Yes, the segmentations were individually checked, and we have added the quality control assessment to the Methods section (p 13, par 2, lines 287-289). We also thank Dr. Narr for the helpful suggestion, and we have added the intraclass correlations for repeated measurements for the control participants. This analysis confirmed that the measurements were highly reproducible within healthy subjects. The intraclass correlations are presented in the Methods sections (pp 13-14) and in Supplementary Table 1.

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 the analysis.

We have expanded the Discussion (pp 23-24, lines 532-543), in order to address this. We hope this is acceptable to Professor Narr.

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

We agree and have removed this citation.

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.

Please see reply to query 7.

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.
We respond to queries 6 & 7 in the following, as they raise related issues.

The pre-specified primary outcome, as Professor Narr states, was the difference in signal change between baseline and week 12 for the mean of the left and right amygdala. We determined the sample size for the study based on effect size estimates for this primary outcome obtained from our previous work on fluoxetine pre- to post-treatment effects on amygdala activation in patients with depression relative to healthy controls [Fu, Cynthia HY, et al. "Attenuation of the Neural Response to Sad Faces in Major Depression by Antidepressant Treatment: A Prospective, Event-Related Functional Magnetic Resonance Imaging Study." Archives of General Psychiatry 61 (2004): 877-889.].

In addition, we conducted secondary analyses on functional and structural region of interest measurements, as well as whole-brain functional images. For region of interest measurements, we employed mixed model analyses that can account for missing observations. Whole-brain functional analyses (task-related and resting state), however, were only performed using those participants who had completed all the scans, as standard imaging approaches (SPM and FSL) can process only complete data (they are, so far, no validated procedures for missing observations).

For these whole-brain functional analysis using completer data, and based on our previous studies, we sought to investigate the most parsimonious model, ie linear changes in activity over time. We have made significant modifications to the Methods section to try to clarify these points (pp 11-13, lines 244-280), and we hope that the modifications are acceptable.

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 correction procedures for these multiple analyses (currently not clear how many were performed).

We thank Professor Narr for this suggestion. In the Methods section (pp 12-13, lines 252-267), we have explicitly listed the 5 clinical scales (lines 252-254) and 5 region-of-interest outcome measures (lines 254-256) for which a mixed-model repeated measures (MMRM) was fitted. The significant findings of these models are presented in Supplementary Table 2. As these were pre-specified, but secondary analyses, no correction for multiple testing was performed (line 267).

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

The structural data were only analysed as region-of-interest measurements in mixed models. These models did not include total brain volume as covariates. However, the aim of the analysis was to study the intra-individual changes in regional brain volumes over time in MDD patients (the models did include a continuous covariate of the baseline measurement), rather than differences across groups at a given time, for which correction by brain volume would be more relevant.

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

We have made substantial additions and revisions to the Discussion (pp 20-24), which we hope is acceptable to Professor Narr.
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.

We have corrected the typographical errors and have revised the Supplementary Material, which was also raised by the Reviewer, Professor Thomas Frodl. We hope these revisions are acceptable.