Author's response to reviews

Title: A investigation of cognitive "branching" processes in major depression

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Author's response to reviews:

Dear Editor

We thank the reviewers for their constructive comments that have significantly improved our manuscript. We respond to the comments and concerns below.

Reviewer 1

1) Minor Essential Revisions:

22.8 (4.9)** – – – – in Table 1 does not make sense, if there are no control data, there can be no significance level.

- The additional asterisks have now been removed.

Reviewer 2

1) My main recommendation is that the authors provide more information and discussion about the issues of power and the size of the effect they are looking for. This is essentially a negative study, which is fine, but it puts the burden on the authors to show that they have enough data to effectively accept the null hypothesis that there are not significant differences in cognitive branching between their patient and control groups. The authors should perform power calculations to support or refute this conclusion. It would probably not be appropriate to use Koechlin et al (1999)’s data as that was obtained from patients with gross frontal lobe dysfunction to perform these calculations, but they could perform power calculations using other neuropsychological tests that have shown differences between depressed patients and controls from one of their references.

- We have now addressed this issue by including a power calculation from one of the key papers already referenced Elliott et al. (1996. Elliott et al. (1996) used a version of the Tower of London task, a test previously shown to be sensitive to
APFC lesions, as described in the introduction of our manuscript. From their report we used the main effect of group shown on page 982, and displayed in Figure 3a. The main effect of group statistic reported in this study was \( F(1,48) = 22.62, P < 0.001 \).

Using the effect sizes calculator from http://www.work-learning.com/effect_size_download.htm (last accessed Aug 27th 2009). We were able to calculate an effect size of 1.38 from the F value. We then used the power and sample size calculator from this web site: http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize (last accessed Aug 27th 2009).

With the effect size of 1.38 from the Elliott et al. (1996) study, we needed to study 9 experimental subjects and 9 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error associated with this test of this null hypothesis is 0.05.

We have added in this information to the discussion section of the manuscript. We welcome this query from the reviewer and we believe the inclusion of this information strengthens the findings of this research.

2) A related point, which should be discussed in greater length in the paper, is the difference in effect size between neuropsychological deficits in patients with frontal lobe damage and patients with depression. In the Discussion section of the manuscript, the authors state, “deficits have been found in cognitive branching with patients with APFC lesions (n=7) [19], arguing against the criticism that this task lacks sufficient to detect group differences”. In the literature, the magnitude of neuropsychological deficits in patients with frontal lobe damage is much larger than that observed in patients with depression. To equate them, as the authors do in that sentence, is misleading. In fact, if the power calculations suggested previously suggest that 11 depressed patients and controls are insufficient to test for a difference that is shown by 7 patients with lesions, this could be a starting point for an interesting discussion comparing the relative differences in neuropsychological deficits between these two patient populations.

- The intention of the discussion here is to describe other studies that have shown impairments in this task rather more than deal with power issues (which are now more explicitly dealt with in the revised manuscript). Therefore we have removed the statement “arguing against the criticism that this task lacks sufficient to detect group differences,” focussing the issues of power upon previous studies and our current study in patients with depression. Indeed, the power calculations do demonstrate that 11 patients and controls are sufficient to test for effect sizes expected from previous work on cognitive control in depression (using the Tower of London task). While we agree with the reviewer that a discussion of the relative differences in neuropsychological deficits between these two patient populations would be interesting we feel it is beyond the scope of this work and
would be too speculative. Hence our decision to tone down the reference to lesion patients instead.

3) In the Conclusion sections of both the abstract and the discussion, the authors state that, “our data argue for a generalized learning impairment underlying cognitive dysfunction in this disorder.” This is the opposite of the conclusion I would take from the study – at least in regards to the authors’ main hypothesis, the study is negative. The conclusion should reflect this.

- We accept the comment from the reviewer that we do not have strong evidence to support the conclusion that the impairment in the depressed group constitutes a generalized learning impairment. Stronger support for this claim would be if the patient group demonstrated reduced accuracy at the beginning of every condition compared to controls that then normalised with practice.

However, the patients did demonstrate a learning impairment on condition 1, and although it is not strong evidence of a generalized learning impairment, it may be evidence of impairment in adjusting to the experimental context. We are more confident of this conclusion and have amended the discussion section to reflect the reviewers concern on this issue.

4) I do not understand why the patients and controls made more errors in the control condition than the apparently more difficult other conditions. Please explain.

- The reviewer is correct in that it appears as though the errors on the control condition should be lower than the other conditions as it is easier in terms of the cognitive control requirements. However, the design of the task is hierarchical in that the simpler conditions are learned before the more complex condition and thus the control condition is presented first. Thus, the impairment in the control condition may reflect impairment in adjusting to the experimental context, as discussed in response to the previous point. The specific processing impairments this represents is however difficult to ascertain from this study alone.

In the control condition, the participants are required to decide whether two successively presented letters were also in immediate succession in the word ‘tablet’. It requires the participant to hold in mind letters from the word ‘tablet’ and to update their memory depending on what letter occurred previously. Therefore this updating process, of whether a target letter matches their expectation or not, and then pressing the correct button, appears to be a sensorimotor skill learning process that becomes more automatic with increasing practice (from runs 1-6). It is however unclear at present from this data, which of the cognitive processes involved, are the specific processes, the patients with depression are impaired on. It could be a number of things, such as the ability to ‘hold in mind’ the letters from the word ‘tablet’, it could be adjusting to the pace of the task, or it could be a problem in dealing with feedback that does not match their expectation and updating their subsequent predictions of what letter will occur next. There is much work to be conducted in future experiments to clarify the nature of the impairment in the control condition. We have recently shown that these
processes can be dissociated behaviourally and neurally in healthy participants
(1), but it is currently unknown which of these specific processes are impaired in
depressed adults.

5) Because you ran the runs sequentially, you cannot separate out the condition
and order effects. You should probably discuss this and how one might perform
future experiments to address this issue.

- We agree with the reviewer that as a result of running the conditions
sequentially we were unable to separate out the condition and order effects. It is
worth noting however that in previous published studies using this task the
learning of each condition is not explicitly recorded. In this study we have
explicitly recorded the learning (across six blocks) and the fixed order of
conditions simplifies the learning procedure considerably as each condition
builds on the previous one. Now that we have shown that these conditions can
be accurately learned in patients with depression, future experiments can be
conducted on pre-trained participants where the conditions are administered in a
counter-balanced order. We have amended the discussion accordingly.

6) At the beginning of the Methods section, it is confusing when you talk about 12
subjects in each group when Table 1 and all of the analyses have 11 subjects in
each group.

- This has now been changed by altering the first line in the methods section to
clarify the number of participants per group. We felt it important to report the
actual number of participants recruited to reflect the reality of the experiment.

References

1. Walsh ND, Phillips ML. Interacting Outcome Retrieval, Anticipation, and