Author's response to reviews

Title: Alertness and visuospatial attention in clinical depression

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Author's response to reviews: see over
Dear Professor Brown,

we herewith kindly ask you to consider the revision of our manuscript “Alertness and visuospatial attention in clinical depression” by Schock et al. for publication in BMC Psychiatry.

As cognitive deficits in psychiatric disorders constitute a substantial burden for the patients, our work attempted to shed light on attention impairments in clinical depression. Reduced alertness as a consequence of sad mood in depressive patients was suggested to elicit visuospatial impairments in the left visual field. We could not confirm a significant visuospatial attention deficit in patients, but alertness and at a trend level sad mood predicted omissions in the left visual field.

We would like to thank the reviewers for their comments and suggestions. Their notes were very useful for us to improve our manuscript regarding its clarity and efficacy. We addressed each of the points raised by the reviewers and modified our manuscript accordingly. Please find below a detailed point wise reply to the issues raised by the reviewers. Furthermore, we highlighted the respective changes in the revised manuscript in yellow.

In the revision of the manuscript, we added reaction time data and analyzed the effect of gender to complete our results. Furthermore, we clarified the suitability of the applied attention tests. The interpretation of the influence of sad mood was critically discussed. Our work was edited by a native speaker to improve the style of written English.

We are confident that these improvements made the manuscript suitable for publication in BMC Psychiatry.

Sincerely yours,

Lisa Schock
Reviewer’s report
Title: Alertness and visuospatial attention in clinical depression
Version: 1 Date: 23 December 2010
Reviewer: Karen Lidzba

Reviewer’s report:
In their study, the authors studied differences in visuospatial attention between patients with depression and healthy controls, and the impact of sad mood and alertness on visuospatial attention. While differences in visuospatial attention between the two groups were not significant, alertness did influence visuospatial attention. The effects of sad mood were very small (non-significant and inconsistent).

The authors showed concern in choosing an appropriate control-group for their patients, which is an important prerequisite for a good neuropsychological study. Also the tests chosen are well established and therefore well interpretable. The findings add to our understanding of the interaction between basic (i.e., alertness) and higher-order (i.e., visuospatial) attentional functions.

I have, however, some major concerns concerning a) the rationale behind the choice of tests, and b) the interpretation of the results.

Major Compulsory Revisions:

Abstract:
1) I am not sure if the trendlevel result for the influence of sad mood on one of the three visuospatial tests is justification enough for the conclusion: “…alertness and – to a lesser extend – sad mood led to left omissions in visuospatial neglect tests”.

The manuscript has been changed accordingly (p.2, ll.10-12).

Background:
2) In the literature, the term “unilateral neglect” seems to be confined to phenomena in the wake of stroke, which lead to clear deficits in daily life. I am not convinced that the term “neglect” can be utilized for the phenomenon of slightly impaired visuospatial attention in the left visual field in the depressed patients of the study. In the hypothesis (p. 4) the authors seem to make a difference between “neglect” and “shift of visuospatial attention”, however, no definitions are provided, and in the rest of the text the terms “neglect” and “visuospatial deficits” seem to be used interchangeably. This issue should be better clarified.

We changed the manuscript accordingly. We use the term “neglect” only when referring to clinical manifestations like impaired navigation in the environment in patients with lesions and differentiate it from “visuospatial impairments”, “deficits”, or “spatial bias” when referring to the laboratory measures (p.2, l.15; p.3, l.3; p.4, ll.19-20; p.8, l.16; p.9, ll.24-25; p.11, l.9; p.12, ll.14,19-20, 24; p.14, l.6).

Methods:
3) What was the rationale behind choosing the three different tests for neglect and visuospatial attention? Furthermore, the “Visual Scanning” test of the TAP is originally not a neglect test, even if it could be interpreted as one in the modification introduced by the authors.
We argue that computerized test batteries measuring different aspects of attention serve as useful instruments for the diagnostic of cognitive deficits. For both test batteries in our study (TAP, Vienna Testsystem) normative data are available and reliability and validity of the tests are documented. Furthermore, the tests have proven themselves as reliable visuospatial attention measures in the clinical setting. With three different tests measuring visuospatial attention we wanted to exclude the possibility of random effects because of a temporary lack of concentration different from clinical attention impairments. The “Visual Scanning” test was used in previous studies to measure subtle impairments in attentional orienting. In the reply to comment 2 of reviewer 2, we discuss this problem further and include references underpinning the argument.

4) WAF neglect-extinction: What was the rationale behind summing the omission errors in the “extinction” and “no extinction” conditions? Would there not be differential effects to be expected?
Summing the “extinction” and “neglect” condition was meant to increase the number of critical events to reach enough power in the results. We are well aware that the clinical picture of extinction can emerge independently of the one of spatial neglect. Extinction, however, is discussed as one aspect of the neglect syndrome and not as reposed on a separable attention component (J. Driver, P. Vuilleumier, Perceptual awareness and its loss in unilateral neglect and extinction, Cognition 2001, 79: 39-88). Therefore, we consider it as methodically reasonable to sum the two conditions possibly tapping into the subtle spatial attention deficits observed in emotion disorders.

5) Have the t-tests also been corrected for multiple comparisons? Did the authors check for interdependence between the three visuospatial tests?
Correction for multiple comparisons was performed by the adjustment of the significance threshold. We mentioned the adjustment of the threshold in the methods section (p.9, ll.3-4). The T-values remain the same values and p-values were interpreted according to the corrected thresholds (p.9, l.25 – p.10, l.2; p.21, Table 2). Since all three tests are expected to measure visuospatial attention, correlation between the measures on a large scale can be expected – particularly if including patients with clinical neglect symptoms. In our relatively small patient sample, there was no significant correlation between the tests. Nevertheless, the conservative Bonferroni-correction would also account for biases in multiple testing.

6) Did the authors use only one item of the BDI as indicator of “sad mood”? Is this item answered with a rating scale, and is the expected variance large enough for the item to show effects in the regression analysis? (Maybe the variance could be added in the results section).
Only one item of the BDI was used as indicator of “sadness”. The variance of this item had a value of .40 which is statistically acceptable for a regression analysis. We chose this item because our hypothesis focused on the influence of negative emotion on attention. The BDI, however, measures the complex syndrome of depressiveness including somatic complaints. In the last paragraph of the discussion, we discussed the restricted effect of sad mood on spatial attention in the present study (p.13, ll.16-25; p.19, ll.22-24).

Results:
8) “However, the scores were compatible with more omissions in the left visual
field - a rightward bias - in the depressive group, opposed to a more leftward oriented bias in the control group in all three tests. This conclusion does seem convincing to me when checking table 2 (and when reading the detailed description of results which follows):

a) In the visual scanning task, patients show a leftward bias, as do the controls; in the neglect task, the "rightward bias" is tiny.

b) Controls show a true leftward bias only in the visual scanning task. In the neglect test, the "leftward bias" is tiny, in the neglect-extinction test there is no bias at all.

We aimed at pointing out that not the absolute values – with reference zero – consistently express more omissions in the left visual field, but the values (left visual field omissions minus right visual field omissions) are consistently higher as compared to the control group. Indeed, only the TAP Visual Scanning shows a negative value in depressive patients. This is consistent with the assumption that the instruction for TAP Visual Scanning task (scan from left to right side) biases the results in terms of shifting the absolute value – as discussed, but the interval between depressive and control group does not change.

We clarified this assumption in the results (p.9, ll.9-11) and discussion section (p.11, ll.9-10).

Discussion:
The authors tend to over-emphasize (in my opinion) non-consistent trend-level effects. The discussion should demonstrate much more caution with regard to the results:

9) The discussion regarding effects of mood has to be much more cautious, as there is only a trend-level effect in only one of three tests. Furthermore, when applying Bonferroni-correction for six tests, trend-level can be assumed at p< (0.1/6) = 0.017. While the effect is in the hypothesized direction, and can therefore be mentioned in the discussion, I find the authors’ conclusions much too confident.

The revised manuscript uses a more careful wording and explicitly re-states the trend-level character of the findings when referring to the mood effect (p.2, ll.10-12; p.11, ll.2,4-5; p.12, ll.16-18; p.13, ll.16-25; p.14, ll.4-5). Omitting this finding, however, would bear the danger of a false negative finding – even though the cleaner finding “only alertness affects visuospatial attention in depression” seems attractive with respect to our theoretical framework. Its limitations however should not be neglected.

10) The absent effect of sad mood on visuospatial attention in the group could perhaps be explained by a low variability within the whole group in the sad mood parameter. This leads to a missing train of discussion: Do the authors assume a specific effect of depression on visuospatial attention, or to they assume an effect of “sad mood”, which should be noticeable also in the non-depressed controls (if the variance is large enough). The same question should be answered with regard to alertness. Only if a continuous, not depression-specific effect is expected, it is feasible to collapse the two groups for the regression analysis.

This remark is partly addressed in the answer to the reviewer’s comment 6. The cited studies in our manuscript universally point out the effect of sadness on visuospatial attention. Accordingly, we phrased our hypothesis. Reduced alertness is, equally, not only found in clinically relevant disorders. Alertness deficits can also result from sleep deprivation in healthy persons (B. Fimm, K. Willmes, W. Spijkers, The effect of low
arousal on visuo-spatial attention, Neuropsychologia 2006, 44: 1261–1268). Therefore, it is justified to assume a continuous and not depression-specific effect. This effect, however, may be even clearer in induced sadness in healthy subjects, because of the complex interplay of symptoms in depressive disorder and intervening covariates.

11) 2nd paragraph: “In our patient sample there was a non-significant albeit consistent trend towards leftsided neglect seen in positive values in the number of omissions in the three neglect tests, i.e. an attentional bias towards the right visual field.”
This is not true, as the effect was noticeable (but nonsignificant) in the WAF, small in the TAP neglect and nonexistent in the TAP Visual scanning. So there is no consistent trend.
The manuscript has been changed accordingly (p.11, ll.9-10).

12) 5th paragraph: “TAP Neglect and WAF Extinction-Neglect revealed effects of alertness and mood”. This is not true, as is even described in the following paragraph.
We agree with the reviewer that this phrasing may sound too confident and changed the manuscript accordingly (p.12, ll.16-18).

13) 7th paragraph: In line with my previously mentioned concerns, this paragraph should focus more on the effects of alertness than on the effects of negative emotion, as is done in the conclusions.
We added an outlook on future studies – which had been represented in the 7th paragraph the reviewer referred to - to the conclusion section (p.14, ll.7-11). Attention deficits as well as their relation to impaired emotion processing were considered.

Minor Essential Revisions:

Background:
1) The paragraph on the functional neuroanatomy of neglect symptoms in depression is not very clear. What, for example, is meant by “concerning clinical implications” in “Concerning clinical implications, more activation in the right hemisphere, especially in frontal regions, seems to be indicator of negative affect.”?
This statement was ambiguous, especially as the citation refers to healthy subjects. The manuscript has been changed accordingly (p.3, ll.11-13).

Methods:
2) Have all participants been included into the regression analysis or only the depressed patients?
Yes, all participants have been included into the regression analysis within a repeated-measures design (p.8, l.25 - p.9, l.2).

Results:
3) Results of regression: This could be more structured with regards to results for the variables “sad mood” and “alertness”.

In the revised manuscript, the results of the regression analysis are listed according to the effects of the factor alertness for the three tests each, followed by the effects of the factor sad mood for the three tests (p.9, l.25 – p.10, l.7).

Minor issues not for publication
The text should be thoroughly reedited with respect to English language.
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
'I declare that I have no competing interests'

Reviewer’s report
Title: Alertness and visuospatial attention in clinical depression
Version: 1 Date: 2 January 2011
Reviewer: Mario Liotti
Reviewer’s report:
This paper extends previous research on attentional deficits in clinical depression by testing a group of 16 patients with clinical depression and 16 matched controls using four computerized tasks of visuo-spatial attention and alertness. While no differences were found in the main dependent variables, alertness performance and sad mood were found to predict more left hemifield omissions.

The hypotheses are clearly stated and the methods appear reasonably sound. However, I have a number of mostly analytical concerns I would like the authors to address before this paper should be accepted for publication.

1) In the light of previous findings reporting VF asymmetries in depression employing RT measures, it is not clear while the 3 visuo-spatial tasks only report omissions. This measure may be not sufficiently sensitive to pick up a mild deficit in spatial orienting/alertness caused by depression. At any rate, since these measures have been reported before, it would be instructive for the readership to see those data, and make sense of the results across RT and omissions. This also make sense in light of the significant RT effect for the alertness task. I would therefore encourage the authors to include their RT results if they have analyzed them.

The manuscript was complemented with reaction time data as suggested by the reviewer (p.6, l.21; p.7, ll.9-10; p.8, ll.1-2, 17; p.9, l.6; p.10, ll.8-15; p.11, ll.11-15). Nevertheless, the interpretability of the reaction time results is restricted in the light of our hypothesis suggesting a relation of alertness and visuospatial deficits. Alertness is a reaction time measure, too, and alertness differences between the two groups – for example seen in higher variance in the depressive group – may be confounded with visual field performance concerning reaction time. Accordingly the RT data reveal in the first place that an accuracy-speed trade-off effect would not explain the findings.

2) The TAP subtest "visual scanning" does not seem to be suitable to pick up a
deficit in attentional orienting, given the fact that there is no central fixation and the subjects were instructed to start their scanning always from the top left, which would in fact would compensate for a tendency to preferentially orient attention toward the right or away from the left. Therefore it seems that the present version of the task may be more useful for neglect rehabilitation (pulling attention to the neglected side) than to diagnose a left hemifield deficit.

Indeed, the low specificity of the Visual Scanning task may be reflected in the results. Depressive patients show a slight bias in the leftward direction, which they do not show in the two other tests. This finding may be due to the instruction given to scan from left to right side. Considering the difference between omissions in the depressive group and in the control group, however, the interval seems to be constant. Attention was shifted to the left according to the instruction for the task but still less pronounced as compared to the control group. In conclusion, it is quite informative how the different instructions influence visuospatial attention even in depressive patients. The manuscript addresses this point in the discussion section (p.13, ll.12-14). An exclusion of this test from the analysis would hardly influence the results of the study as a whole; the Bonferroni correction would lead to less conservative thresholds. The validity of the results, however, would be reduced, because of the post-hoc exclusion of the test. When designing the study, the test was chosen as a measure for visuospatial deficits in the current study, because of the clinical experience with this test in the diagnostic of residual symptoms of neglect in stroke patients. The test is able to measure subtle impairments in the capture of a visual scene and was used to assess deficits in attentional orienting before (e.g. M. Thimm, G.R. Fink, J. Küst, H. Karbe, W. Sturm, Impact of alertness training on spatial neglect: A behavioural and fMRI study, Neuropsychologia 2006, 44: 1230–1246; K. Finke, P. Bublak, J. Krummenacher, S. Kyllingsbæk, H.J. Müller, W.X. Schneider, Usability of a theory of visual attention (TVA) for parameter-based measurement of attention I: Evidence from normal subjects, Journal of the International Neuropsychological Society 2005, 11: 832–842).

3) In task 3 (WAF Extinction-Neglect) what was the stimulus duration and the interstimulus interval?
The manuscript was complemented accordingly (p.7, l.15; p.8, ll.8-9).

3) It is not clear whether the depressed group still met criteria for acute major depression episode at the moment of testing. Given that all patients were medicated at the time of testing, it would be important to know whether a number of patients were clinically remitted at the time of testing, or if they did not meet criteria for major depression episode. Do you have symptom ratings at the time of testing or Hamilton scores? Also, it would be important to report the medications the patients were on.

According to the Beck Depression Inventory (BDI) and Hamilton depression scale (HAMD) scores, the depressive group met criteria for a mild to moderate depression at the time of testing (p.12, l.1). This was also mentioned in the discussion concerning the lack of more pronounced cognitive deficits in the present sample. HAMD scores were added to table 1 (p.5, l.6; p.18, ll.4-5; Table1, p.20). Furthermore, information about medication of the patients was added to the methods section (p.5, ll.10-13).

4) Given that previous studies have addressed a gender difference in the manifestation of VF differences associated to depression or sad mood, it would
be useful to run an additional set of analyses adding gender as a co-variate.
We added an analysis to explore the influence of gender on the attention measures.
No significant effect emerged (p.9, ll.2-3; p.10, ll.15-18).

5) Page 2 (Background. It would be useful to include references of studies reporting visuospatial deficits in depression (e.g., Freeman et al, 1985; Kronfol et al, 1978, etc).
The manuscript has been changed accordingly (p.2, ll.19; p.15, ll.8-15).

6) Page 3, line 6. Replace "approaches" with "interpretations".
The manuscript has been changed accordingly (p.3, l.8).

7) Page 3, third paragraph. Prolonged RT and omissions in the LVF are observed in laboratory settings and are really not clinical manifestations of hemineglect.
This sentence should more clearly describe the clinical symptoms of hemi-inattention and then introduce the evidence on laboratory measures of neglect/extinction.
We appreciate the suggestion and changed the manuscript accordingly (p.3, ll.21-25).

8) Please specify if the neuropsychological measures used here are sensitive to detect neglect/extinction in clinical populations and whether normative data are published for control population. Since these measures are not particularly well-known -at least to an North American audience- it would be useful to add what components of the attentional system they are meant to tap into.
Information about reliability, validity and normative data was added in the methods section for all four tests (p.6, ll.18-21; p.7, ll.6-9; p.7, l.22 – p.8, l.1; p.8, ll.10-13; p.18, l.16 – p.19, l.8).

9) Check spelling of the word "extent" spelled a few times "extend".
Due to contentual changes, the word “extent” is not used in the manuscript any more.

10) In the Conclusion, I would say that depression leads to abnormal left-sided attention rather then more rightward attention (for which a different, less straightforward mechanism may need to be invoked).
We agree with the reviewer that this expression may be ambiguous. We are talking about a rightward bias, which results from a difference value of omissions in the left and right visual field. Such a bias expresses an imbalance of omissions in both visual fields in consequence of the chosen method, but – in our opinion – does not necessarily implicate a different attention mechanism. Therefore, we clarified the expression in our hypotheses (p.4, ll.18-22) and kept the wording through the whole manuscript.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.