Author's response to reviews

Title: Brain regions essential for improved lexical access in an aged aphasic patient: A case report

Authors:

Marcus Meinzer (marcus.meinzer@uni-konstanz.de)
Tobias Flaisch (tobias.flaisch@uni-konstanz.de)
Jonas Obleser (j.obleser@ucl.ac.uk)
Ramin Assadollahi (ramin.assadollahi@uni-konstanz.de)
Daniela Djundja (daniela.djundja@uni-konstanz.de)
Gabriela Barthel (gabriela.barthel@uni-konstanz.de)
Brigitte Rockstroh (brigitte.rockstroh@uni-konstanz.de)

Version: 4 Date: 26 May 2006

Author's response to reviews: see over
Dear Sir or Madam,

attached please find our revised manuscript entitled, "Brain regions essential for improved lexical access in an aged aphasic patient: A case report" by Marcus Meinzer et al. We wish to thank the reviewers for their helpful comments on our paper which are reflected in the revised manuscript. We have addressed each of the comments on the attached pages, which were incorporated in the revised manuscript.

We appreciate the opportunity to revise the paper and believe that the manuscript now has been improved substantially compared to the initial submission.

Sincerely, yours

Dr. Marcus Meinzer

Reviewer 1: Professor Crosson

1. The most ubiquitous activation for correct-response compared to error trials was right inferior frontal gyrus (Brodmann's areas 45, 47). Yet, when activity for correct responses was compared to baseline visual fixation, this area showed no activity. This pattern calls into question the stability of the correct-response vs. error comparisons. Thus, it should be addressed in the discussion. Is it possible that activity actually falls below baseline in this area during error trials, accentuating an otherwise non-significant increase in activity during correct response trials?

In Table 2 we only reported maximally activated voxels in significant clusters. The strongest activation in the cluster that includes the right IFG (k=218) was located in BA 13; see Table 2: coordinates 39, 27, 7; Z=5.1). Closer inspection of the cluster revealed additional activations in BA 45 (29,26,4; Z=5.0), BA 46 (42, 30, 10; Z=4.8) and BA 47 (42,26,1; Z=4.4). Overall 148 voxels in this cluster were located in the right IFG (BA13: 31 voxels; BA 45: 33 voxels; BA46: 38 voxels; BA 47: 46 voxels), the remaining voxels were located in the insula (BA: 22 voxels), the middle frontal gyrus (45 voxels) and the superior temporal gyrus (BA22: 3 voxels).

Therefore, a substantial part of Brodmann's Areas 45/47 are activated above baseline. Rather than including this information into the discussion it has been added to the caption of Table 2.

2. The most critical analysis (correct-response trials for post-treatment imaging where the items produced errors on pre-treatment imaging) was done on the basis of 10 items, which raises further concerns about stability. Can the authors provide evidence that an analysis based upon this small of a number of trials will provide stable results?

We entirely agree with the reviewer that a comparison of 10 trials per condition is a comparably weak data basis, even for functional imaging. However, it has been shown
convincingly that especially in temporal sparse sampling fewer trials are necessary to achieve the same power in brain activation (cf. Hall et al., 1999; Gaab, Gabrieli, & Glover, Hum Brain Mapp, in press). With respect to that, we were optimistic to achieve a reliable activation pattern even with 10 trials per condition. In auditory fMRI, a recent study published in Cerebral Cortex (Narain et al., 2003) actually replicated the now well-established finding of left anterior STS activation with intelligible over unintelligible speech material (cf. Scott et al., 2000; Binder et al.; 2000; Davis & Johnsrude, 2003; Obleser, Wise, Dresner, & Scott, in prep.) on the basis of a mere 10 trials per condition. Therefore we feel that it was both justified and conclusive to use even a comparably sparse data basis in performing this revealing contrast of error trials which have been corrected in post-testing.

These points have now been included into the discussion of the results.

3. The area activated on correct-response trials as opposed to error trials includes right pars triangularis, the very area that Naeser sought to inactivate using rTMS. This point deserves some discussion. Could it be that differences in the current case (Wernicke's aphasia) vs. Naeser's cases (nonfluent aphasias) account for this discrepancy? There is some evidence that this region in the left hemisphere of normal subjects is more involved in semantic than phonological processes (Devlin et al., Journal of Cognitive Neuroscience, 2003). Could this have any bearing on why this area appears to be active in this particular patient?

The role of the function of the contralesional IFG is controversially discussed in the literature. In particular, right hemispheric activation following stroke has been attributed to “...the loss of active inhibition or competitive interaction from the homologous left frontal area, or an inefficient dead-end strategy (c.f. Naeser et al. 2005).

A recent study by Winhuisen et al. (2005) directly addressed the contribution of the left and right IFG in aphasic patients during a semantic task using PET. Left or right IFG function was inhibited by rTMS and language functions were assessed by a verb generation task. The authors found disruption of verb generation in 8/11 patients following rTMS to the left IFG and in 5/11 patients after rTMS to the right IFG. Therefore right IFG function might be essential for task performance in a subset of patients. In general, patients who responded to right hemispheric rTMS were lower functioning than “non-responders”. This points to a hierarchy of recovery, with a better outcome in patients where there is no essential activation of the contralesional IFG homologue.

In the present case the IFG lesion was only small and located in the white matter. Moreover, functional activation of the left IFG was substantiated (Tab.2 baseline contrasts of correct responses vs. fixation and semantic paraphasias vs. fixation), therefore a bilateral activation pattern could be observed. Language performance (in particular naming performance) in this patient in general was low and even though performance improved, the overall naming capacity is still severely disturbed, which in some way points to a dysfunctional compensatory activation pattern. We can only speculate about the effect of rTMS to the right IFG in this patient, it might be possible that inhibition of this area might facilitate naming performance as well.

On the other hand, the results of the present study show that gradual involvement of the right IFG contributes to improved language functions in this patient, which makes the previous assumption unlikely. These points have now been discussed.
4. Evidence suggests there is considerable variability in areas responsible for recovery of language function in aphasia. The authors should caution readers that findings from this case might not generalize widely. Replication would be needed to assess this issue.

We totally agree with this query and the readers are now cautioned that results of the present single case study cannot be generalized and replication in a larger sample is necessary (see also answer to query 1 of reviewer 2).

5. The authors neglected to cite a number of important studies on aphasia and neuroplasticity. Pulvermuller's original paper on Constraint-Induced Aphasia Therapy (Stroke, 2001) should be cited. Musso and colleagues' (Brain, 1999) paper supports the importance of the right hemisphere in aphasia therapy for patients with Wernicke’s aphasia. Crosson and colleagues' (Journal of Cognitive Neuroscience, 2005) paper supports the importance of right frontal cortex in successful naming therapy. Cornelissen and colleagues' (Journal of Cognitive Neuroscience, 2003) and Belin and colleagues' (Neurology, 1996) papers present somewhat different viewpoints.

All the requested citations have now been included and a discussion of the right/left controversy has been included.

Reviewer 2: Professor Knecht

1) The motivation of this case report with an 80 year old patient remains unclear. Prior fMRI aphasia studies already showed that there is recovery potential for patients older than 70 years (e.g. Rosen et al., 2000). Overall, the novel aspect of this study is the combination of fMRI with an intervention (pre and post therapy assessment). To this end, only few studies with major methodological caveats were conducted in this area (e.g. Peck et al., 2004). However, a single case study is insufficient to draw general conclusions about “the neural substrate of lexical access”. The authors should include more aphasia patients with anomia.

The motivation for this report was not to draw conclusions about the role of right hemispheric areas in lexical access in aphasic patients in general (!) but rather to show on a single case basis that it is possible to localize brain regions areas differentially engaged during correct and erroneous naming performance. This has never been done before using functional imaging and no study investigated whether such areas are related to functional recovery of functions after treatment as well. This can only be done on an individual basis, and, of course, results can’t be used to infer the role of the right IFG during recovery of aphasic patients in general. We did not intend do this claim and therefore the full title reads “...in an aged aphasic patient: A case report”.

Based on the promising results in this aged patient a larger group study is forthcoming. In this sample the design will be modified and will include more stimuli. Furthermore fMRI will be complemented by MEG slow wave analysis to localize individual pathology and to assess whether changes in fMRI activation/differences between correct/erroneous namings are located in areas with individually determined dysfunctionaltity.
Nonetheless, since reviewer 1 also asked us to caution the reader that results can’t be generalized we did so in the discussion.

2) Page 5: In the results section, the authors focus on the observed activity increase in the right inferior frontal gyrus for correctly named objects. However, they also found activated clusters in left frontal regions for correctly named objects compared to incorrectly named objects (cf. Table 1, coordinates -50, -3, 47 and – 50, -4, 44). The perilesional activations may functionally at least be as important as the right hemisphere activation.

It has been shown in patients with primary progresssive aphasia (Sonty et al. 2003, Annals of Neurology) that activation in precentral (and other) areas is negatively correlated with performance during a naming task using fMRI. Activation of precentral areas in this study was interpreted as “a compensatory spread of language-related neural activity or a failure to suppress activity in areas normally inhibited during language tasks”. While to our knowledge no studies found associations between precentral activations and semantic tasks, activation of the right IFG has been implicated with semantic decisions by a number of studies (Winhuisen et al. 2005, Blasi et al. 2002), which points to its potential importance during recovery of naming performance aphasic patients.

Moreover, left precentral areas were not activated when we compared correct trials vs. former errors, which provides additional evidence for the importance of the right hemispheric IFG for improved task performance in this particular patient rather than that of the left precentral activation pattern.

These 2 points have now been included in the discussion.

3) Cf. Table 1: The right hemispheric IFG activation for the contrast “Words>Semantic Errors” (coordinates 59, 18, 18) differs with regard to localisation extensively from the right sided activity increase for the contrast “Correct Trials>Former Errors (T2>T1)” (coordinates 42, 28, -17). This location difference is not discussed.

Actually, the contrast correct>errors (42,28,-17) includes 7 neologisms and 3 semantic paraphasias (this has already been mentioned in the methods section). When comparing the right sided activity in the IFG of this contrast to that of correct>neologisms (Table 2: 42,28,-19) they almost match perfectly. Therefore this pattern is most probably “dominated” by the 7 neologisms rather than the 3 semantic errors. This information has been included in the caption of Table 1.

4) Several functional imaging studies on naming in aphasic patients showed no correlation between right hemispheric (frontal) activation and speech recovery (e.g. Cao et al., 1999; Rosen et al., 2000; Perani et al., 2003; Zahn et al., 2004). Functionally more important was the perilesional activation. This inconsistency is not addressed by Meinzer et al..

Even though a number of functional imaging studies showed correlations of performance with increased activation in perilesional areas there also reports that emphasize the importance of right hemispheric areas in the recovery of language functions as well (e.g. Musso et al. 1999, Brain, supports the importance of the right hemisphere in aphasia
therapy for patients with Wernicke's aphasia; Crosson et al. 2005, Journal of Cognitive Neuroscience, supports the importance of right frontal cortex in successful naming therapy, Winhuisen et al. 2005 reported increased latencies and error rates after rTMS in aphasic patients after right IFG stimulation indicating its importance during semantic tasks).

We have now addressed this point in the discussion.

5) The behavioral data for trained and untrained object names are based upon a single baseline assessment. Aphasic patients generally fluctuate in their language performance. For this reason, multiple baseline investigations are essential for the interpretation of therapy induced effects.

We totally agree with the reviewer that multiple baseline data would be the best way to assess stability of language functions and activation patterns before therapy. Still, the patient presented here is in the late chronic stage of aphasia where major fluctuations or even major spontaneous improvements within short time intervals are not to be expected (Robey et al. 1998; J Speech Lang Hear Res.). This would be different for the acute or post acute stage, where spontaneous recovery and stronger fluctuations of behavioral performance would call for multiple baselines in any case.

Furthermore, there is evidence that repeated scanning (without intervention in between) produces stable activation patterns even in severe chronic aphasia (e.g. Kurland et al. 2004; Behav Neurol). Furthermore, repeated scanning in this study yielded a decrement of activation, supposedly related to task familiarity, rather than an increase of activation. Therefore, the increase of activation found in the present report is unlikely to be interpreted as the effect of the repeated measurement.

From a more pragmatic viewpoint we chose not to assess stability in this 80-year old patient for the following reasons:
(1) Since we used the same pictures for pre-post assessment repeated measures would have familiarized the patient with the test materials.
(2) Three or even more fMRI-scans would have increased the stress that accompanies every fMRI scan, this was especially important in this 80-year old lady.
(3) We included a gender and age-matched control group that evidenced no increased activation. This shows stability of the activation pattern induced by the paradigm across time (at least in healthy subjects). Of course we can’t preclude a different pattern in chronic aphasic patients, but we had no chance to find a group of matched aphasic patients willing to be scanned within the same time frame without treatment, which would have been the best test...

These issues have now been included in the discussion.

6) The naming performance for trained and untrained objects improves comparably from pre- to post-assessments (from 8 to 14 for trained and from 5 to 9 for untrained object names). Therefore, the fMRI results cannot be interpreted as a training effect. Additionally, an improvement from 8 (pre) to 14 (post) correct trials (out of 40) can hardly be considered a “training success”.

I agree with Professor Knecht in that an increase of 10 correctly named objects is not much. Still, the results of this patient were obtained under rigorous time constraints. Naming of the
pictures had to be performed within 3 seconds. This might be a reason for the relatively low number of improved namings. Moreover, taking into account the relatively low number of correctly named pictures at the first investigation (13/80) and increase by 10 equals an improvement of 77%. By the way, not only the number of correct namings increased, rather the number of neologisms almost halved (2/14 – this number has been corrected in table 1, there was a typing error - 4 instead of 14) and the number of semantic paraphasias increased (which means, there were more semantically related namings than before treatment). Therefore a closer look at the behavioral data during fMRI (obtained under rigorous time constraints) reveals an overall increase of semantically more correct namings after treatment.

Furthermore, a naming test outside of the scanner without time restrictions was performed before and after treatment including only untrained items. We found an increase of correct naming responses of 83% (24/44), when we allowed self-corrections this increase was even more pronounced (31/63). Therefore, we are confident that there was an actual improvement of naming performance due to the treatment and that this was not merely a specific effects of the training of the 40 pictures, but rather due to a general facilitation of lexical access.

These points have been stressed in the discussion.

7) The control subjects’ naming performances was well below 100%, indicating that the name agreement for the selected objects was low. Consequently, the difference in activity for correctly and incorrectly named objects could merely reflect differences in (working memory) effort to correctly identify the presented objects (cf. Kan et al., 2004).

The objects that were used for the naming task were taken from an internet database (Szekely et al. 2004). Data about name agreement is included in this database and objects were chosen because of their high name agreement scores. The average name agreement of the stimuli we used was actually very high (average .92 with a standard deviation of .09.). This information has now been included into the methods section.

Moreover, most of the “incorrect trials” in the healthy control subjects were omissions and the subjects stated that the 3 seconds were quite fast for them to come up the correct name for some of the pictures. Especially since they were instructed not to utter the name of the picture after it disappeared. The relatively high rate of omissions might be explained by the fact that the average age of the control subjects was 80 years and the well known fact that processing speed might decrease at this age. Interestingly, in an unpublished pilot study of our workgroup 12 younger subjects (~25 years on average) completed the same design with almost no omissions or misnamed pictures.