Author's response to reviews

Title: The functional magnetic resonance imaging (fMRI) procedure as experienced by healthy participants and stroke patients

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Author's response to reviews: see over
Dear Dr Anderson,
Dear Dr Krestin,

Please find attached a revised version of the above manuscript submitted to BMC Medical Imaging.

We would like to thank the reviewers who helped to improve the manuscript considerably. We addressed all issues raised by the reviewers. In particular, we now provide more methodological details, calculated the requested statistical analyses, and considerably revised the results and discussion section. Please find attached a detailed point-by-point reply to each issue raised.

Yours Sincerely,

Andre Szameitat
Detailed response to the reviewers:

Reviewer: Iris Eshed

Reviewer's report:
The study present results of a questionnaire presented to 70 healthy study participants and 20 post CVA patients all after undergoing fMRI. The questionnaire contained 8 several questions regarding the subjects convenience and personal perception of their MRI experience.

Major Compulsory Revisions

1. The study question though mildly interesting is well presented within the introduction.

2. Methods:
   a. What is the basic for building the questionnaire as it is?
      • The first 2 questions regard the research setting and not the patients' perception of the MRI experience.
      • The 3rd - 5th and the 8th question are the ones regarding the patient's MRI personal experience. More detailed questions could have been asked.
      • The place of the 5th - 7th questions in the questionnaire is not clear. Why did the authors choose to include them and how they imply on the patients' perception is not explained not in the methods or in the discussion.

Originally, the questionnaire was intended for internal quality assurance use only. Accordingly, it was a self-developed questionnaire designed to identify potential problems with the fMRI procedure, which included, among other items concerning e.g. the experimental setup, items about how convenient the procedure was. We agree that this fact imposes a limitation on the current data, and have noted this information now in the methods section.

However, in our everyday research work in the UK we continuously had to face problems with ethical review boards, since they questioned the ethicality of fMRI. In our attempts to bolster our claim that fMRI, if conducted properly, is a safe and ethical
procedure, we realised that there is, to our knowledge, virtually no evidence on the perception of functional MRI in the research context. This made it much harder for us to support our ethics applications, since a direct transfer from the findings of clinical MRI to functional MRI in the basic research context is sometimes questionable. Thus, we saw a need for such data, even if based on a questionnaire initially developed for a different purpose.

With this background, we decided to publish the data from our quality assurance questionnaire, since we already had collected a sizeable sample. Due to the limitations pointed out by the reviewer (and mostly shared by us) we see the present data as initial pilot data. These pilot data should be supported by follow-up studies which are specifically designed to test the question of convenience, acceptance, and compliance of healthy research volunteers in fMRI research. In our view, until such data is available our data will be a useful first source of information.

However, please note that we are not able to conduct further follow-up studies. Thus, if the reviewer still thinks that the methodological shortcomings are too severe to grant publication of the manuscript, we will have to retract it.

In combination with feedback of the other reviewers and during revision of the manuscript, we decided to remove all questions not directly related to the perception of the MRI procedure. This leaves four questions (“felt something strange”, “how comfortable”, “was the scanning too long”, and “would you like to participate again”). The results and discussion sections have been adjusted accordingly.

• How was the questionnaire presented? Did the patients" fill it themselves or was it posed and filled by the researchers? 

It was a paper-and-pencil version of the questionnaire and was filled out by the participants themselves, except for patients who could not write because of their motor deficits. Here, the experimenter filled in the questionnaire. We added this information to the manuscript.
b. Patients:

- The healthy cohorts' age is only approximate. The authors have no knowledge on all patients age and no statistical SD is given.
- The age range of the 20 patients is not given at all.
- No gender is described, while of course it has implication on the questionnaire analysis and the discussion.

The demographic details of the healthy participants and patients are now described in detail. Furthermore, we statistically analysed the effects of demographic details such as gender and age on the questionnaire responses.

- The authors mention in few words that some of the participating cohort have already undergone MRI before. This has of course implication on the questionnaire analysis and needs to be detailed.

Unfortunately, we do not have these data available, and we see no possibility to gather them. Previously we already tried to contact participants of a past study (for another reason) and virtually no one replied / could be contacted. One of the main reasons for this is that most volunteers are students and that most of them have left university by now.

We agree that the fact whether a person has previously undergone fMRI probably affects the outcome of the questionnaire. In our view, the most likely effect is that such participants will (on average) judge the fMRI procedure more positive than a sample of participants without prior experience. Thus, our results may be slightly biased.

However, we would like to note that our sample may reflect a rather typical sample in a research setting, since in basic research participants take part repeatedly (e.g. because they are affiliated with the research institution or because they would like to earn money). Actually, we know of a couple of fMRI research sites which use volunteer lists and try to create subsets of participants who are scanned repeatedly. Therefore, we think that our findings are of interest for the situation of a typical research setting.

We added a paragraph to the discussion section to discuss this point.
c. MRI procedure:
• No time range and average total duration of the MRI procedure is given.
We now provide details for each study and an average scanning time across all studies.

3. Results and discussion:

a. The presentation of the results in this way is not clear. The results presentation is not concise. A summarizing table would have helped.
The result section is now fundamentally revised. Among other things, we now use a more classical result section (not combined with the discussion), present statistical tests on the comparison of groups, provide further statistical analyses (e.g. correlation with study duration, gender, etc.), and present a summarizing table.

b. Discussion is not satisfactory. The authors mainly discuss their assumptions on the results but do not relate to other works previously done on the subject. No validation of the authors’ assumption is given based on previous work.
We revised the discussion section and now relate our work more extensively to previous findings.

c. The difference between the two groups is not discussed.
d. Correlation between patients demographics (i.e. Age, gender) to the results is not discussed.
f. The authors need to correlate between answers in one question to another. For example the questions that complain on a long procedure also perceived it as most disturbing, etc…
We now provide a number of additional analyses, including the ones requested by the reviewer.

e. Not all questions were answered. Why? The authors do not discuss that altogether and not correlate that to the acceptable response rate in the literature.
Participants typically filled out the questionnaire by themselves after the fMRI scan. We did not always check immediately whether participants filled out all items, or whether
they left one or more items open. When participants did not answer an item, we cannot decide whether they just missed it, or whether it was left unanswered deliberately. In general, the response rate was quite high: Question 1 (“felt something strange”): 68/70 participants (97.1%) and 21/22 patients (95.5%); Question 2 (“how comfortable”): 68/70 participants (97.1%) and 22/22 patients (100%); Question 3 (“scanning too long?”): 66/70 participants (94.3%) and 22/22 patients (100%). The only exception was question 4 (“participate again”) with 61/70 participants (87.1%; not presented to patients). The reason for this is unclear, but may found in the fact that the question was at the bottom of the questionnaire sheet (and, thus, rather easily missed), or that participants were undecided whether to take part again. This information is now given in the manuscript as well (new heading “response rates” in the results section).

g. I see no reason for putting the questions on the head moving in the questionnaire. But since they were done, the authors should regard and discuss it. For example: was there any correlation between the way the patients describe their head movement to the MRI images perceived? If not it could be all subjective feelings.

We indeed included a couple of questions not directly related to the research question. To focus the manuscript more clearly, we removed these unrelated questions. In this context, the questions regarding head movements were removed as well.

4. Conclusions:

a. The conclusions has no sound basic from the discussion. They infer the patients felt comfortable though a high percentage described uneasy sensations. They find no difference between the two groups though no comparison was performed and so forth.

We revised the conclusion and based it more closely on the results of the new statistical analyses.
Abstract

There are no facts given about the findings in that study. Figures and statistical analyses would be good. The conclusion is rather long and at least in part, especially the last sentence, not supported by findings in the study.

We now include more detailed results and a more restricted conclusion section.

Introduction

OK.

Papers on MR safety such as the ACR white paper should be included.

In addition to Marshall et al. (2007; A comprehensive analysis of MRI research risks) which was cited in the original version of the manuscript we now also included the ACR white paper (Kanal et al., AJR: 178, 2002).

Methods

Established questionnaires about perception of MR imaging, especially including claustrophobia such as the CLQ, were unfortunately not used.

An eight-item questionnaire of which actually 3 questions are related to the issue discussed is used instead. In contrast to the statement in the introduction, there is no question asking for how stressful or convenient the MR was. There is only one unspecific question (“how was the scanning procedure?”).

Originally, the questionnaire was intended for internal quality assurance use only. Accordingly, it was a self-developed questionnaire designed to identify potential problems with the fMRI procedure, which included, among other items concerning e.g.
the experimental setup, items about how convenient the procedure was. We agree that this fact imposes a limitation on the current data, and have noted this information now in the methods section.

However, in our everyday research work in the UK we continuously had to face problems with ethical review boards, since they questioned the ethicality of fMRI. In our attempts to bolster our claim that fMRI, if conducted properly, is a safe and ethical procedure, we realised that there is, to our knowledge, virtually no evidence on the perception of functional MRI in the research context. This made it much harder for us to support our ethics applications, since a direct transfer from the findings of clinical MRI to functional MRI in the basic research context is sometimes questionable. Thus, we saw a need for such data, even if based on a questionnaire initially developed for a different purpose.

With this background, we decided to publish the data from our quality assurance questionnaire, since we already had collected a sizeable sample. Due to the limitations pointed out by the reviewer (and mostly shared by us) we see the present data as initial pilot data. These pilot data should be supported by follow-up studies which are specifically designed to test the question of convenience, acceptance, and compliance of healthy research volunteers in fMRI research. In our view, until such data is available our data will be a useful first source of information.

However, please note that we are not able to conduct further follow-up studies. Thus, if the reviewer still thinks that the methodological shortcomings are too severe to grant publication of the manuscript, we will have to retract it.

*No statistics paragraph is given.*

We now report statistical analyses.

*How many patients had to be excluded for absolute contraindications to MR imaging? For what reason?*

48% (20/42) of the patients who participated in the behavioral therapy did not participate in the MRI scanning. The major reason was that the persons were not suitable for MRI scans due to either ferromagnetic metal in their body, or due to other conditions which we took as contraindication for MRI scans in the research context (e.g. diabetes or heart
diseases). Occasionally, patients were not tested simply because the MRI scan did not fit into their schedule. This information is now added to the manuscript.

*No results should be given here, especially nothing speculative (such as “approximately one third of the subjects participated …”).*

Since we did not ask for prior experience with MRI (for a more detailed discussion of this point please see reply to reviewer Iris Eshed), this information is not a real result, but rather a description of the sample. Therefore, we would like to keep it in this paragraph of the methods section.

*Was written informed consent for this questionnaire study obtained? Was approval by the IRB in regards to this questionnaire study obtained?*

We would like to thank the reviewer for pointing out that we have forgotten to include this information. Yes, the study was approved and participants/patients gave written informed consent. We added this information to the manuscript.

*More information about the scanner (width, length, dB) would be helpful.*

We now provide more details in the methods section.

*Please explain abbreviations at first use (TR, TE, MPRAGE, FOV).*

Abbreviations are now explained.

*It appears that many of the studies involving volunteers had not the same set-up leading to nonuniformity of the MR imaging experience.*

Indeed there were slight differences in the set-up of the studies. These differences were solely due to the requirements of the experimental paradigms investigated, such that in some studies participants had to squeeze force sensitive grips and in others they did not hold anything in their hands. We think that these differences are rather small and should not affect the scanning experience fundamentally. In line with this a one-way Analysis of Variance (ANOVA) with the factor study and the item “how comfortable” was not significant, indicating that the study had no effect. Please refer also to the results section for more details.
Results

It is unusual to have the results and discussion in one paragraph. This is very hard to read. No statistical analyses are performed.

We revised the results section considerably and changed it to a more standard format (separate results and discussion). In addition we now report a number of statistical analyses of the data.

Some information that belongs to the methods is given here (earplugs, type of studies).

We revised the results section and either removed (unnecessary) methodological information or moved it to the methods section.

Having one out of 70 volunteers being claustrophobic does not appear to be much less than the average of 2.1 to 2.3% found in previous summary analyses of claustrophobic events. Also the number of patients included appears to be too small to comment on reduction of claustrophobic events by selecting only those who are not in fear of narrow spaces.

Indeed, we observed a rate of claustrophobia of 1.4% (1/70), which is not fundamentally different e.g. from the 1.97% reported by Eshel et al. (2007) or the 2.1% reported by Dewey et al. (2007). We changed our interpretation accordingly.

How often did head movements result in relevant artifacts?

We removed this question from the manuscript, as it is not directly related to the research question (see also comment of reviewer Iris Eshel).

Average imaging times should be given.

The methods section now contains detailed information about the scanning times of each study and an average for all studies.
Why were patients imaged twice? Should this be explained in the methods?
Patients participated in a motor rehabilitation program in our lab and were tested twice: Once before the therapy onset and once after therapy had been finished. This was designed to test for reorganisation in the motor cortex. The questionnaires presented here were filled out after the first scanning session. Although we have some questionnaires also from the second session, the data are too sparse to conduct a proper test-retest reliability analysis. This is now detailed in the methods section (subheading “Sample”).

Conclusions
There is no statistical comparison of results in patients and volunteers.
Major strains or stress were also not included in the questionnaire.
There is no comparison with other psychology studies performed. Thus, it might be not on solid grounds to draw comparisons here.
A strong and well-founded closing sentence would be good.
We rewrote the discussion considerably and hope that all aspects have been addressed.

Figures
No comparison of the results shown in Figure 2 is performed.
We now provide statistical analyses of the data.

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Reviewer: Frank MacMaster
Reviewer's report:
This is a report on the subjective experience of participating in an fMRI research study. This is a novel and compelling idea for a research report that is of
importance to those conducting neuroimaging research. That said, there are some concerns that need to be addressed.

**Major Compulsory Revisions**

1. Not knowing if this is a first experience or not is a large limitation. If 1/3 of subjects had experienced an fMRI Study before, you have a larger selection bias (willing to comeback) that may obscure what the experience is like for a first time participant in research. You need to determine exactly who participated in a scan before and use that in a sub-analysis of ‘experienced’ vs. ‘first-time’. That is extremely compelling information to have.

   We agree with the reviewer, but unfortunately, we do not have these data available, and we see no possibility to gather them. Previously we already tried to contact participants of a past study (for another reason) and virtually no one replied / could be contacted. One of the main reasons for this is that most volunteers are students and that most of them have left university by now.

   We agree that the fact whether a person has previously undergone fMRI probably affects the outcome of the questionnaire. In our view, the most likely effect is that such participants will (on average) judge the fMRI procedure more positive than a sample of participants without prior experience. Thus, our results may be slightly biased.

   However, we would like to note that our sample may reflect a rather typical sample in a research setting, since in basic research participants take part repeatedly (e.g. because they are affiliated with the research institution or because they would like to earn money). Actually, we know of a couple of fMRI research sites which use volunteer lists and try to create subsets of participants who are scanned repeatedly. Therefore, we think that our findings are of interest for the situation of a typical research setting.

   We added a paragraph to the discussion section to discuss this point.
2. For the results section, please start with the answer to the main question first, rather than a point-by-point overview of the questionnaire. A small summary paragraph would be most helpful to the reader. Then a more in depth exploration of the responses.

The results section is fundamentally revised: Firstly, we now only report the four questions directly related to the research question of the manuscript and removed the questions not directly related (e.g. head movement). Secondly, we now present the results in a more traditional format, i.e. separate results and discussion sections.

3. In addition, a direct group statistical comparison between the control and clinical group would be of interest.

We now provide a number of statistical analyses, among them the one suggested by the reviewer.

4. “uncomfortabilities” is not a real word. Please rephrase.

We replaced it by “discomfort”

5. Why were some items not asked of some subjects? Please clarify in the text.

The questionnaire was presented as a paper copy and the participants and patients filled out the questionnaire by themselves. We did not always check immediately whether all questions were answered. Unfortunately, we cannot decide whether some items were just missed, or whether they were not answered deliberately.

6. Depending on sample size and data available, an fMRI vs. DTI comparison would be compelling as well (is there a type of imaging effect?).

We conducted a number of further analyses and one of them is the type of imaging. Based on our findings, the inclusion of a DTI scan in the MRI scanning session does not change the perception of the MRI procedure.
Minor Essential Revisions

7. A pre vs. post questionnaire would have been more telling (expectations vs. experience). This should be acknowledged as a limitation.
Since we did not aim to assess the convergence or divergence of expectations and actual experience, but were interested only in the experience, we do not consider this as a real limitation of the study. However, we think it is a valuable suggestion and included an additional paragraph on this issue in the discussion section.

8. When discussing how a research scan differs from a clinical scan (“In addition to the selection bias...” paragraph) you need to mention time. Most clinical scan times are short (less than 1 hour) while most research scans are longer (1 hour plus).
We agree that research scans tend to be longer than clinical scans and incorporated this as an additional argument in the introduction section. However, we would like to point out that our particular sample of studies also included rather short research studies, with total durations of approx. 30 min, so that duration is not always a difference between clinical and research studies.

We apologize, but we do not know what the reviewer might refer to. We proofread the manuscript but did not find stand-alone sentences. Thus, we would like to ask the reviewer to point out more specifically the sentences in question, so that we are able to revise them.

10. Please watch out for typos – “vibration of the scanner’, ‘strange”.
We are not quite sure what the reviewer is referring to, but we’ve exchanged the simple quotes (‘) with double quotes (“) for quotations of participants (i.e. ...vibration of the scanner”, “strange – ...)

Discretionary Revisions

11. The opening sentence is a bit clumsy. Booking scanner time or buying one is totally off point. A simple statement of “There has been a boom in human
neuroscience studies using magnetic resonance imaging (MRI) techniques” is more on point and sets up the paper in a clear manner.
We would like to thank the reviewer for this suggestion and revised the introductory sentence.

Other Comments
A large unexplored question is motivation. The authors touch upon this briefly, but it is a key for a next step study of this type. Indeed, a more telling comparison would be between a research group and a clinical scan group. The author should consider this as a compelling next step.
This is a very interesting suggestion. Should we be able to collect such data, we surely will conduct such a comparison.

**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.

Reviewer: Claire A Hale
**Reviewer's report:**
Major compulsory revisions
1. **Study design**
It is not clear if this study is meant to be a survey of a group of people all of whom had an MRI scan or a comparison of two particular groups of volunteers who had the scan; the young and healthy and the elderly post stroke. This needs to be clarified

The main purpose of the study was to assess the perception of the fMRI procedure in the setting of basic research. The two most prominent populations investigated in basic research are young healthy volunteers, or (usually older) patients suffering from brain damage. We present data for both populations in the context of basic research. While a comparison of both groups is interesting (and now presented), this is only a minor goal
of the study. The main goal is the description of both groups in a rather independent fashion. We revised the end of the introduction section to clarify this point.

2. Study Sample
   
a. More information is needed about the study sample, how they were recruited and the recruitment criteria. It seems strange to be comparing 2 groups who are completely different; one young and healthy the other elderly and post stroke – if that was the intention. If there was a reason for choosing these two groups then it should be stated. Presumably the subjects were all taking part in some other research studies that involved the use of MRI scans and were not just recruited for a study which looked at how acceptable it was. In which case it the authors should give some details about these studies as well as justify the rather peculiar sample distribution and constitution. Two samples matched, at the very least, for size would have improved the study

We now provide more detailed information about the samples, such as more demographic details. The participants were indeed recruited for studies with different purposes, and this is clarified now.

b. The importance of the need to make specific comments about ‘left handedness’ needs to be explained – if it is important. If it is not. then it should not be commented on, and removed. Since about 1 person in 7 is left handed, a sample of 70 healthy people would be expected to have about 10 people who were left handed. Therefore to state that virtually all the healthy sample were right handed is rather unnecessary. Similarly with the 22 post stroke group – one would expect the group to be mixed right and left handed- in fact one would expect about 3 people in the group to be left handed unless of course left handed people are more prone to strokes than right handed people.

Since the information on handedness is indeed not relevant for the present research question, we removed it from the manuscript.
The questionnaire

A copy of the questionnaire should have been included with the article
We now appended a copy of the questionnaire as supplementary material. We leave it to the discretion of the editor whether the questionnaire should appear as an appendix in a future version of the manuscript.

Analysis

The analysis is very simplistic and used descriptive statistics only. There did seem to be some differences between the responses of the two groups and this could have been tested for statistical significance. It would certainly have improved the interest and rigour of the paper when carrying out a comparative analysis.

We conducted a number of further statistical analyses and revised the results section considerably.

Further analysis could have been carried out such as test/retest to check if the subjects still felt the same after a short time period.

Although some patients who participated twice filled out the questionnaire on both scannings, there are unfortunately not enough data to calculate a proper test-retest validity statistics. However, in future studies we will consider this suggestion.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.