

JoVE Revision: Response to Reviewers' comments

1) some of the paragraphs have several topics of information (e.g., 83 to 96) that might be separated into separate paragraphs. For example, perhaps all the information about structural and fMRI could be in one paragraph (description, strengths, weaknesses), one with EEG, and one with source analysis. Following this, one could then make comparative judgements better.

The structure of the article and the content of the section was revised

2) Second, perhaps a slight bit more could be said about the models used for source analysis. The procedure introduces the BEM method, and MNE; but little information is given about what these are, why alternative models (FEM; LORETA; sLORETA) might be useful. The paper also states that BEM methods only show activity on the cortical surface. The BEM method describes the head model and forward/inverse lead-field matrices for the biophysical properties of the head. However, the sources for the BEM model need to be specified and can include any elements inside the inner compartment (e.g. gray matter voxels inside the inner compartment).

A section with a short overview of the most commonly used models and inverse solution algorithms was added to the introduction. References are provided for reviews and technical notes that discuss the topic in more detail.

3) Third, one missing component in the introduction is the application of these methods to children. Whereas there is sufficient information to show

the motivation for using EEG rather than fMRI, one wonders if there are special considerations for children with the source analysis methods (conductivity of elements different? Head size effects? Electrode placement?).

a section was added to the discussion that addresses the limitation of the technique and applicability to children

4) Is there a need for exact sensor positions on the head?

Standard electrode positions can be used for source reconstruction when the fit is adjusted using age-appropriate or individual anatomical scans (see step 3.5.5). However, we observed in our lab that the fit of electrode nets is quite variable. For instance, the participant's head circumference may be at the lower or upper cut-off for a particular net size, which leads to a tight or loose fit. Digitisation systems help to quantify this variability and build it into the model. We are not aware of any study that compared source solutions using adjusted standard positions and positions based on digitisation, but agree that a study like this would be a very useful addition to the literature.

5) The paper mentions spatial digitization systems, perhaps should give examples. (e.g., Polhemus; EGI GPS system; average age-appropriate electrode maps).

A note with reference to different digitisation systems was added to step 2.5 following the reviewer's suggestion.

5) In 3.2.8 the paper says to select a channel position file from the mfr or EEGLab www site. However, there is no information given about how this will

fit on the MRI scan that is used to do the BEM model. In source analysis the positions of the electrodes must be specified in the source model (lead-field matrix). How is this done with mfr / EEGLab locations? Do you need locations specified for the exact MRI that is being used? (either individual, or age-appropriate avg). incidentally, mfrs and EEGLab have adult head position electrode maps. What about child maps?

All processing steps up to section 3.4 describe transformations on the channel level. The independent component analysis algorithm that is used for pre-processing does not take anatomical information into consideration. Instead, differences in channel statistics are used to separate the data. Step 3.5.5 described how channel location information is aligned with the MRI. Briefly, the nasion, and left and right preauricular point need to be identified on the anatomical scan. The remaining channels are warped to the skull surface accordingly. Because of space constraints, we refer to the website of the analysis software developers that covers this topic in some detail.

6) 2.1 to 2.9 Perhaps refer to the EGI instructions for net preparation and application.

A reference to the EGI instructions was added. We think that the net application and general testing procedures are particularly well suited for the video format of the Journal of Visualized Experiments, because many of the testing practices for young participants are hard to convey in writing.

7) Perhaps describe the BEM (and other models) in the introduction. Also, perhaps it should be mentioned that most of the available source analysis tools do BEM (BESA, Curry, EMSE, EEGLab). Also, perhaps lay out the case why BEM models are sufficient, when some literature suggest some improvement with FEM methods. Also, CURRY, EMSE, and BESA, allow the calculation of the head model via GUI-driven segmenting methods. They do this for individual participants, or for average MRIs, and then analyses are based on the head model for that MRI rather than for an adult average head model.

A section discussing different head models was added to the introduction.

8) 3.4 A brief note is stated about using age-appropriate MRI templates, or individual MRIs. I believe there is no literature that compares the efficacy of individual MRIs with children vs age-appropriate MRIs; or even age-appropriate vs adult MRIs. I agree with the authors about the need for individual/age-appropriate MRIs, but perhaps this issue should be addressed in the introduction and/or discussion. A paper comparing the age-appropriate with adult-head models, vis-à-vis cortical source analysis, would be a useful addition to the literature.

A study by Brodbeck and colleagues (Brodbeck et al., 2011) compared sensitivity and specificity for detecting sources of focal epileptic activity in a sample of 152 children using individual and template standard head models. They report high sensitivity and specificity when individual MRI are used for the source models (84%,88%) for source reconstruction of hdEEG and lower values when template models are

used (76%,55%). We are not aware of any study that compares individual, age-appropriate, and adult template head models. A possible reason for this gap in the literature is that average MRIs for developmental populations only become available relatively recently (see Sanchez et al. 2012). Using BEMs, it is reasonable to assume that the accuracy of age-appropriate templates is closer to head models based on individual MRIs than adult templates. We agree that a comparative study as suggested by the reviewer would be a very useful addition to the literature.

Brodbeck, V., Spinelli, L., Lascano, A. M., Wissmeier, M., Vargas, M. I., Vulliemoz, S., et al. (2011). Electroencephalographic source imaging: A prospective study of 152 operated epileptic patients. *Brain*, 134(10), 2887-2897. doi:10.1093/brain/awr243

Sanchez, C. E., Richards, J. E., & Almli, C. R. (2012). Age-specific MRI templates for pediatric neuroimaging. *Developmental Neuropsychology*, 37(5), 379-399. doi:10.1080/87565641.2012.688900

Reviewer #2:

Minor Concerns:

Introduction:

1) P4, Lines 133-135: Please explain this sentence (provide an example).

The section was rephrased and expanded

2) The authors should introduce an overview on some of the currently and more used available source localization algorithms (see Michel et al., 2004),

with an empirical example for each: in terms of the most common application of each specific method.

An overview of the most commonly used inverse solution algorithms was added to the introduction.

Analysis:

3) I believe that could it be better say that ICA isn't a mandatory step before source localization analysis: If the data collected are enough clean it is possible avoiding this procedure, how it has been done recently (see Berchio et al. 2013).

An introductory note was added to section 3.2 to clarify that pre-processing with ICA is optional and maybe skipped or replaced with other approaches.

4) Are there any bibliographic references that can sustain these % thresholds?

The percentage thresholds are ball-park figures that were adjusted from processing recommendations for adults to account for the higher amount of artefact in child data. We clarified that researchers may adjust these thresholds for their data.

Bibliographic references for percentage thresholds cannot be supplied, because the exact procedure for data preprocessing is not usually described in ERP papers.

5) This sentence needs to be clarified. The idea that as a rule 'the necessary number of repetitions should be doubled compared to adult studies', it is partially in contradiction to the view that is difficult make EEG experiments

with children. The Authors should suggest more convincing strategies: for example, increase the sample, planning easy task....

The paragraph was revised and extended

6) An important message of the present work it is that in children 'the accuracy of EEG source analysis with standard head models is limited'. It would be useful to include an additional figure: a standard MNI template, with the same contrast analysis (faces vs scrambled faces). The Authors should add some comments in the discussion section and describe any differences in the cortical source responses.

A figure showing the difference between an adult head model and an age appropriated head model for a recording of a 6 year old was added.

Reviewer #3:

1) The Introduction meanders and is repetitive.

The discussion introduction was revised

2) What is the link between Figure 2 at L451 and Figure 4 at L516? Did anyone proofread this?

The figure numbering and references in the text were revised to accommodate the added figures

3) The first para in the Discussion belongs only in the Intro - it's repetitive here.

The discussion was revised according to the reviewers' comments

4) The second sentence in the Short Abstract doesn't make sense.

Line 96: "distant to"?

Line 98: "to take advantages".

Line 166/7: repeat of "for the purposes".

The sentences were changed

5) The EEG reference is not specified - how to replicate?

A note about the reference channel used for recording was added to step 3.1.5

6) Line 244: "Calculate the average reference by...". No, this should be "Re-reference to the average reference by....".

The wording of step 3.1.5 was changed following the reviewer's comment

7) Line 281: I have never seen published data which combines channels as suggested.

The channel selection for channel-level analysis was based on commonly used channels in studies investigating N170 responses to emotional facial expressions {Sherbondy:2008fo}. The exact selection of channels varies between EEG systems and also depends on the preferences of the research group.

We use the channel-level analysis of N170 responses only as an example to illustrate that additional information can be obtained by applying source reconstruction.